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ORIGINAL ARTICLE – OPEN ACCESS

Evaluation of the Relationship Between Rosacea Cutaneous Subtype and Meibography Findings

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ABSTRACT

Objective: Acne rosacea (AR) is a chronic inflammatory skin disease that can cause serious ocular complications. This study was designed to evaluate dry eye disease (DED) and meibomian gland dysfunction (MGD) in AR patients and to investigate the relationship between the cutaneous subtype of AR and ocular involvement.

Materials and Methods: This study included 67 participants with AR and 50 healthy individuals. Patients diagnosed with 3 cutaneous subtypes were examined: erythematotelangiectatic rosacea (ETR), papulopustular rosacea (PPR), and phymatous rosacea (PR). An ophthalmatological examination was performed that included an evaluation of lid margin alterations due to meibomian gland (MG) obstruction, Ocular Surface Disease Index assessment, tear film break-up time testing, Schirmer testing, and a corneal conjunctival fluorescein staining assessment. Meibography was used to evaluate the upper and lower lids for MG loss.

Results: Findings in the AR group revealed MGD in 45.5% and DED in 28.1%. The meibomian gland loss rate (MGLR) was 38.7±16.9% and the meibomian gland loss grade (MGLG) was 1.57±0.82%. The rate of MGLR and MGLG was significantly greater in the AR group than in the control group ($p<0.001$). PPR was seen in 59.7% of the 67 patients, ETR in 29.9%, and PR in 13.4%. A comparison of the MGD, MGLR, MGLG, and presence of DED in the 3 cutaneous subtype groups yielded statistically insignificant results.

Conclusion: AR can affect MG morphology, which may result in MGD or DED. Though we did not find a significant difference in the ocular findings by subgroup, ocular involvement is a recognized risk in AR. Ophthalmologists and dermatologists should cooperate in the evaluation of AR patients. Additional studies to further examine the effects in subtype groups are recommended.

Keywords: Dry eye disease, meibography, meibomian gland dysfunction, ocular surface diseases, rosacea

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INTRODUCTION

Acne rosacea (AR) is a common, chronic, inflammatory skin disorder with multifactorial causes characterized by redness, inflammatory papules and plaques, telangiectases, and phyma on the mid-facial region, such as the cheeks, nose, chin, and forehead. The disease is known to have relapsing and remitting periods; trigger factors can include exposure to heat, spicy foods, or ultraviolet radiation (1, 2). AR has been classified into 4 subtypes based on specific clinical findings: erythematotelangiectatic rosacea (ETR), papulopustular rosacea (PPR), phymatous rosacea (PR), and ocular rosacea (OR) (3).

According to previous studies in the literature, the incidence of ocular involvement in AR is 6% to 72% (4). Studies have suggested that most ocular involvement is in the form of ocular surface abnormalities and impaired tear function. OR often includes meibomian gland dysfunction (MGD), chronic conjunctivitis, and recurrent chalazions.

MGD is an ocular disease with clinicopathological findings of terminal duct obstruction and quantitative-qualitative changes in secretions (5). The reported prevalence of MGD ranges from 3.5% to 74.5% (6–8). Meibomian gland (MG) obstruction or secretions, telangiectasia, gland loss, and a combination of some of these parameters have been used to diagnose MGD (7, 8). A significant relationship has been found between AR and MGD, and meibography, a recent, noninvasive, objective observational approach, is now widely preferred for clinical use to provide a comprehensive assessment (9).

Though it can have a considerably negative psychosocial effect on patients and may cause blindness if left untreated, OR is frequently overlooked by clinicians, both dermatologists and ophthalmologists. This study was designed to compare ocular involvement according to cutaneous subtype using meibography, which represents a new contribution to AR studies.

This research was designed to evaluate the relationship between dry eye disease (DED) and MGD, the most common manifestations of OR, in other cutaneous subtypes of AR.

MATERIALS and METHODS

The single-center, cross-sectional, controlled study was conducted at Aksaray University Research and Training Hospital after receiving approval from the Clinical and Laboratory Research Ethics Committee of Aksaray University on April 19, 2019 (no:2019/03-60). A total of 67 patients aged 18-65 years who had been clinically diagnosed with AR by a single dermatologist using standard diagnostic criteria (10) in the dermatology outpatient clinic between June and August 2019, and 50 healthy control individuals were enrolled. Patients with other inflammatory skin diseases, autoimmune diseases, other systemic diseases that can cause ocular involvement and those who used medications were not included. Additionally, participants with an ocular infection, allergy, ocular surface disorder, anamnesis of eye surgery or trauma, current topical or systemic treatment that could affect the ocular surface, and users of contact lenses were excluded from the study.

Diagnosis and Assessment of Acne Rosacea

All of the participants were examined by a single dermatologist and demographic features were recorded. The cases studied were patients diagnosed with 3 cutaneous subtypes of AR: erythematotelangiectatic rosacea (ETR), papulopustular rosacea (PPR), phymatous rosacea (PR) (3).

Diagnosis and Assessment of Eye Disease

The upper and lower eyelids were evaluated with a microscope for obstruction, telangiectasia, notching, and mucocutaneous junction shift. After the examination, fluorescent staining of the ocular surface was performed and a tear break-up time (TBUT) test, the Schirmer test, and a meibography test were administered.

The diagnosis of MGD was made according to the diagnostic criteria recommended by an MGD working group in Japan (6). MGD was diagnosed when the MG was occluded and there were lid margin abnormalities. The BG-4M non-contact meibography system (Topcon Corp., Tokyo, Japan) was used to visualize the morphology of meibomian glands (MGs). MG examination was performed with a slit lamp and an infrared video camera. The ratio of the MGL area to the total area of the gland was calculated using the device software. The examiner marked the total area and loss of area, and the percentage of MGL was calculated. The MGL was categorized as grade 0 (no loss of MG), grade 1 (0–1/3 of the total MG), grade 2 (1/3–2/3 of the total MG), or grade 3 (>2/3 of the total MG) (11). The grading of MGL was performed blindly by a single researcher. MG distortion was classified as 0 (<50%) or 1 (>50%). The meiboscore and MG distortion of the lower/upper eyelids were evaluated in the right eye.

DED was diagnosed using the modified Tear Film & Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) Criteria: An Ocular Surface Disease Index (OSDI) value of >13 and at least 1 of the following: TBUT <10 seconds, Schirmer test score <10 mm, or conjunctival and corneal staining >0 (12). The TBUT, Schirmer test, and conjunctival and corneal staining evaluations were performed on the right eye.

Statistical Analysis

IBM SPSS Statistics for Windows, Version 23.0 software (IBM Corp., Armonk, NY, USA) was used to perform the statistical analysis. The Shapiro-Wilk test was used to evaluate the normality of the distribution of the numerical data.

Table 1. Demographic features of the participants

	Rosacea group	Control group	p
Age (years)	41.31±12.63	40.21±8.85	>0.05
Gender			>0.05
Female, n (%)	43 (64.2)	30 (60)	
Male, n (%)	24 (35.8)	20 (40)	

Table 2. Comparison of the ocular involvement in the rosacea and control groups

	Rosacea group	Control group	p
MGD, n (%)	30 (45.5)	6 (11.5)	<0.001
MGLR	38.7±16.9	12.9±11.3	<0.001
MGLG	1.57±0.82	0.40±0.57	<0.001
DED, n (%)	18 (28.1)	3 (5.8)	=0.004

DED: Dry eye disease; MGD: Meibomian gland dysfunction; MGLG: Meibomian gland loss grade; MGLR: Meibomian gland loss rate

An independent sample t-test was used to compare the means of numerical variables between the 2 groups. A chi-squared test was used to compare the means of categorical variables between the 2 groups. Binary logistic regression analysis was used to compute the odds ratio for associations between explanatory variables. A p value of <0.05 was considered statistically significant.

RESULTS

In all, 67 patients who were diagnosed with AR were enrolled in this study; the group comprised 43 (64.2%) females and 24 (35.8%) males. The mean patient age was 41.31±12.63 years. In the control group of 50 individuals, 40% (n=20) of the participants were male, while 60% (n=30) were female. The mean age in the control group was 40.21±8.85 years. There was no significant difference between the patient and control groups in age or gender (p>0.05). Demographic features of the participants are presented in Table 1.

According to the clinical anamnesis of the patients, 16 of the 67 patients (23.8%) had subjective ocular symptoms, such as itching, burning, or stinging.

The frequency of MGD was 45.5% (n=30) in the rosacea group, and 11.5% (n=6) in the control group (p<0.001). There was a statistically significant difference between the AR and the control groups in the MGLR and the MGLG values (p<0.001) (Table 2).

The frequency of DED in the rosacea group was 28.1% (n=18), whereas it was 5.8% (n=3) in the control group (p=0.044) (Table 2).

The relationship between MGD and age, gender, duration of AR, and the cutaneous subtype of AR was assessed using a binomial logistic regression test. No significant relationship was observed between MGD and any of these variables (p>0.05) (Table 3).

Table 3. The relationship between MGD and age, gender, duration of rosacea, and cutaneous subtype of rosacea

	Sig.	Odds ratio
ETR	0.406	0.448
PPR	0.500	0.538
PR	0.675	0.697
Duration	0.979	1.001
Age	0.339	1.022
Gender	0.295	1.909

ETR: Erythematotelangiectatic rosacea; MGD: Meibomian gland dysfunction; PPR: Papulopustular rosacea; PR: Phymatous rosacea

Table 4. The relationship between DED and age, gender, duration of rosacea, and cutaneous subtype of rosacea

	Sig.	Odds ratio
ETR	0.396	0.338
PPR	0.420	0.372
PR	0.613	0.685
Duration	0.376	0.933
Age	**0.038**	**1.535**
Gender	0.461	0.572

DED: Dry eye disease; ETR: Erythematotelangiectatic rosacea; PPR: Papulopustular rosacea; PR: Phymatous rosacea

Table 5. Comparison of ocular involvement in rosacea cutaneous subtypes and controls

	ETR n (%) 20 (29.9)		**PPR n (%) 40 (59.7)**		**PR n (%) 7 (13.4)**		**Controls n (%) 50 (100)**
MGD, n (%)	10 (50)	p<0.001	18 (45)	p<0.001	3 (42.9)	p=0.033	6 (11.5)
MGLR	39.6±16.9	p<0.001	38.1±16.6	p<0.001	38.7±16.6	p<0.001	12.9±1.3
MGLG	1.10±1.17	p=0.012	1.00±1.02	p=0.001	1.17±1.33	p=0.005	0.40±0.57
DED, n (%)	6 (30)	p=0.005	11 (28.2)	p=0.004	1 (16.7)	p=0.293	3 (5.8)

DED: Dry eye disease; ETR: Erythematotelangiectatic rosacea; MGD: Meibomian gland dysfunction; MGLG: Meibomian gland loss grade; MGLR: Meibomian gland loss rate; PPR: Papulopustular rosacea; PR: Phymatous rosacea

The relationship between DED and age, gender, duration of AR, and the cutaneous subtype of AR was evaluated with a binomial logistic regression test. A significant relationship was found between DED and age (p=0.038). No significant relationship was observed between DED and gender, duration of AR, or the cutaneous subtype of AR (p>0.05) (Table 4).

PPR was the subtype classification of 59.7% of the 67 patients, while 29.9% were classified as ETR, and 13.4% as PR. When the 3 groups were compared in terms of MGD, MGLR, MGLG, and DED, the difference was insignificant (p>0.05) (Table 5).

DISCUSSION

The prevalence of AR is estimated to be >5% worldwide. Females and males are equally affected (13).

OR, one of the subtypes of AR in the National Rosacea Society classification, is a common condition that can be blinding if inadequately treated (3). This condition is commonly overlooked by clinicians. OR occurs independently of cutaneous findings in about one-third of cases (14, 15). The severity of cutaneous findings has not been related to ocular involvement. It has been suggested that ocular involvement is more likely to be seen in the ETR and PPR subtypes of AR, with an estimated risk of ocular inflammation of about 50% (16).

Most ocular involvement is in the form of ocular surface abnormalities and impaired tear function. Marginal corneal infiltrates, ulceration, corneal neovascularization and scarring, scleral perforation, episcleritis, scleritis, and iritis have also been reported in studies (4).

MGD is a common chronic ocular disorder in OR. Eyelid changes, including MGD, have been reported in some 90% of patients with OR (17). The pathophysiology is an immunological mechanism similar to a type IV hypersensitivity reaction: An unknown antigen, such as Staphylococcus aureus, Staphylococcus epidermidis, or Demodex follicularum, reaches the globe via tears from diseased valves, and secretion in the MG is disrupted by mediators released from inflammatory cells (18).

MGs are sebaceous glands located at the edges of the eyelids. The glands secrete lipids, which coat the surface of the eye and keeps the water component of our tears from evaporating, ensuring that the ocular surface is well-lubricated and healthy. The ocular disease of MGD involves terminal duct obstruction and quantitative-qualitative changes in secretions (5). This results in changes to tear film composition and causes clinical signs of ocular irritation (19).

MGD is one of the primary causes of DED. DED can also be the cause of MGD. In a population-based study with 356 participants, it was reported that the rate of MGD and DED coincidence was 12.9% (20). Many risk factors have been identified for MGD and DED. Arita et al. (20) observed that male sex, age, and the use of lipid-lowering agents were significantly associated with MGD, whereas female sex, contact lens wear, and the presence of conjunctivochalasis or lid margin abnormalities were significantly associated with DED. In the current study, MGD was not significantly associated with age or gender. DED was significantly associated with age, but not gender. Differences in findings may be due to the sample size of the respective study.

AR can trigger MGD and DED (21). In our study, the incidence of MGD and DED was high in patients with AR, as reported in similar studies in the literature. Additionally, it was observed that ocular disease (both MGD and DED) was not significantly associated with the duration of AR or the cutaneous subtypes of AR.

Zengin et al. (22) reported that the results of tear function tests (Schirmer, TBUT, and MG function) were significantly lower in patients with OR when compared with patients with only cutaneous involvement and control patients, as in our study. In a study by Evren et al. (23), the signs of DED, lid margin telangiectasia, and metaplasia in the MG orifices were significantly higher in 21 patients with AR (8 used oral doxycycline, 13 did not) compared with a control group. Reduced tear film meniscus height and MG secretion quality were observed when compared with controls. However, no significant difference was observed between patients with AR who received treatment and those who did not. Lipid analysis revealed a significant difference between the untreated group, the treated group, and the control group. Sobrin et al. (24) reported an increase in the level of matrix metalloproteinase 9, tissue inhibitor of metalloproteinase 1, and interleukin 1 in the tears of patients with AR. A high oleic acid level in both meibum triglycerides and free fatty acids in meibomitis patients diagnosed with AR has also been reported, and the authors noted that the presence of high oleic acid could be controlled with minocycline treatment (25).

In a retrospective descriptive study conducted by Akpek et al. (26) with 131 OR patients, cutaneous findings were recorded in 112 patients. However, the relationship between OR and the cutaneous subtype was not evaluated in detail.

The results of a study of 176 AR patients, 88 from dermatology clinics and 88 from ophthalmology clinics indicated that 25% of the dermatology clinic patients had ocular symptoms. The presence of MGD, telangiectasia, interpalpebral conjunctival hyperemia, and anterior blepharitis was statistically significantly higher in the patients from the ophthalmology clinics. There was no significant difference in corneal, episcleral, or lens findings between the 2 patient groups (15). Machalińska et al. (27) noted that among 41 AR patients and 44 controls evaluated with meibography, cutaneous rosacea was associated with ocular erythema and lid margin abnormalities. Their comparison of cutaneous subgroups in terms of lid margin abnormality scores yielded a statistically significant difference. They suggested that ocular signs of rosacea may affect MG morphology, causing MGL, and that OR may be associated with the loss of MG tissue. Palamar et al. (9) evaluated 18 patients with AR and compared meibography results with 19 controls. They suggested that OR may cause DED and significant MGL; however, their research did not include analysis of the patients according to cutaneous group, as in the present study.

The literature includes studies that have examined the cutaneous subtypes of AR in terms of disease severity, progression, and histopathological features (28, 29). However, to the best of our knowledge, no study has evaluated the relationship between OR and the cutaneous subtype of AR in detail.

Our results indicated that the incidence of MGD and DED was high in AR patients, as previously reported. We suggest that AR can cause structural changes by affecting MG morphology, and as a result, may cause MGD and DED. We did not, however, observe a remarkable relationship between ocular findings (MGD, MGLR, MGLG, DED) according to cutaneous subgroup.

Meibography is a relatively new, noninvasive approach for clinicians to evaluate patients with MG disease that has advanced clinical assessment capability as well as research. At the time of writing, our search returned only 2 studies that had evaluated AR patients using meibography (10, 26).

A relatively small study group and the inability to detect changes to the quality of the meibum are limitations of this study.

CONCLUSION

Possibly serious ocular complications in AR patients can be prevented with early diagnosis and treatment based on a carefully coordinated effort of dermatologists and ophthalmologists using clinical findings of MGD and DED. The dermatological literature has generally not adequately addressed these potential complications; however, a thorough understanding and management of ophthalmic involvement is important to provide appropriate and comprehensive care to patients with AR. Ocular involvement is very common; dermatologists and ophthalmologists should be aware of the possibility of MGD and DED accompanying AR. In this study, 16 of 50 patients (23.8%) had ocular symptoms. Therefore, we suggest that periodic ophthalmological examinations should be performed for patients with AR regardless of pre-existing ocular symptoms, since early diagnosis and treatment of the condition will preserve patient quality of life. Although we found no difference between the cutaneous subtypes in terms of MGD and DED in this study group, we think further research with a larger group to more extensively assess the relationship between cutaneous subgroup and ocular involvement is warranted.

Ethics Committee Approval: The Aksaray University Clinical Research Ethics Committee granted approval for this study (date: 19.04.2019, number: 2019/03-60).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – FK, EY; Design – FK, EÇ, EY; Supervision – FK, EÇ, EY, UG; Resource – FK, EY; Materials – FK, EY; Data Collection and/or Processing – FK, EY, UG; Analysis and/or Interpretation – FK, EY, UG; Literature Search – FK, EÇ, EY, UG, GAS; Writing – FK, EY, GS; Critical Reviews – FK, EÇ, EY, UG, GAS.

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