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A Clinical Scoring System for Diagnosis of Ocular Demodicosis

Authors' Contribution:
Study Design A
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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABEF 1 Oktay Alver
ABCDEF 2 Sertaç Argun Kıvanç
ABDEF 2 Berna Akova Budak
BE 1 Nazmiye Ülkü Tüzemen
EF 1 Beyza Ener
EF 2 Ahmet Tuncer Özmen

1 Department of Medical Microbiology, Uludag University School of Medicine, Bursa, Turkey
2 Department of Ophthalmology, Uludag University School of Medicine, Bursa, Turkey

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Corresponding Author: Berna Akova-Budak, e-mail: bernaakova@hotmail.com

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Background: Demodex may cause chronic and refractory blepharitis with associated ocular surface problems, and its diagnosis and treatment can be quite challenging. In this study, our aim was to assess the efficacy of tea tree oil in *Demodex* treatment on caucasian patients in an industrialized region of Turkey, and to develop a systematic scoring system for extremely accurate diagnosis in the absence of advanced facilities.

Material/Methods: Charts of 412 patients with blepharitis were reviewed. A group of 39 out of 412 cases were identified as chronic and treatment-refractory, and therefore were enrolled in this study. Eyelashes from each of the lower and upper eyelids of both eyes were evaluated at ×40 and ×100 magnification using light microscopy. Treatment was started with 4% tea tree oil eyelid gel and 10% eyelash shampoo. Symptoms and findings were scored according to the most common complaints.

Results: The mean age of the patients was 54.1±15.4 years. Seventeen (43.5%) patients were male and 22 (56.5%) patients were female. In 30 out of the 39 patients (76.9%) *D. folliculorum* was detected. Symptoms disappeared in 25 patients. The mean score of patients who were *Demodex*-negative was 2.7±1.0, and the mean score of patients who were *Demodex*-positive was 3.8±1.6 (p=0.047). Ninety-four percent of those with a score of 4 and over were found to be *Demodex*-positive (p=0.025).

Conclusions: Treatment with tea tree oil can be successful. If there is no facility to identify *Demodex* under light microscopy, we recommend starting treatment for patients who have scores of 4 and over using the scoring chart developed in this study.

MeSH Keywords: Dry Eye Syndromes • Keratitis • Mite Infestations • Ocular Surface • Score • Tea Tree Oil

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Background

Demodex spp. are mites in the subclass of Acariformes of the Arachnida class, which constitute an important group of Arthropoda. *Demodex folliculorum* is an obligate parasite in human hair follicles, and *Demodex brevis* is localized in the pilosebaceous unit [1,2]. These mites are transmitted through close person-to-person contact, but the pathogenic mechanism is not fully understood [3]. *D. folliculorum* and *D. brevis* are more often found in the eyelashes and ears, and may also be found in other sites, especially in the forehead and nose region [2,4–7]. Although many recent studies suggest that these parasites play a role in the etiopathogenesis of disorders such as skin diseases and facial blepharitis, others regard the presence of mites in the pilosebaceous follicles as harmless [8].

D. folliculorum mites cause tension and plugs as mites multiply in the follicles, and the penetration of parasite antigen into the dermal structure can cause allergic reactions and facilitate the development of infection by carrying microorganisms [5]. Ophthalmic complaints such as blepharitis and blurred vision associated with *Demodex* infestation can cause dry eye, erythematous eye lid, eye itching, burning, and irritation [6]. Chronic and treatment-refractory blepharitis is a common disorder, and the diagnosis of the *Demodex* infestation is difficult, usually requiring an experienced parasitologist or use of an expensive device such as an *in vivo* confocal microscope.

In the present study, we assessed the ocular surface problems associated with chronic and treatment-refractory blepharitis, the frequency of *Demodex,* and the effectiveness of tea tree oil (TTO) in *Demodex* treatment in white patients living in an industrialized region of Turkey. Based on our findings, we developed a systematic scoring method for accurate diagnosis of *Demodex* infestation.

Material and Methods

The files of patients who attended our clinic between January 2016 and August 2017 and who were diagnosed with blepharitis were reviewed. We included 39 of 412 patients diagnosed with chronic and treatment-resistant blepharitis and who were older than 18 years of age. Age, sex, complaints on admission, examination findings, additional systemic diseases, and *Demodex* examination findings from the patient records were recorded.

Microscopic *Demodex* examination

The diagnosis of ocular demodicosis was made at the Microbiology Department of Uludag University. Three eyelashes from each of the lower and upper eyelids of both eyes were epilated (6 eyelashes from each side), made into a preparation with glycerin-type separation, and evaluated at ×40 and ×100 magnification under light microscopy [2,9] (Figure 1). Type separation was carried out by the same expert as soon as all samples were taken [10,11]. Measurements were made oculometrically (CHWK, Olympus, Japan).

Treatments of ocular demodicosis

In the patients diagnosed with *Demodex* infestation, treatment was started with 4% TTO eyelid gel (Blefatitto Gel, Jeomed, Turkey) and 10% TTO eyelash shampoo (Blefaritto Shampoo, Jeomed, Turkey), as these were the commercially available

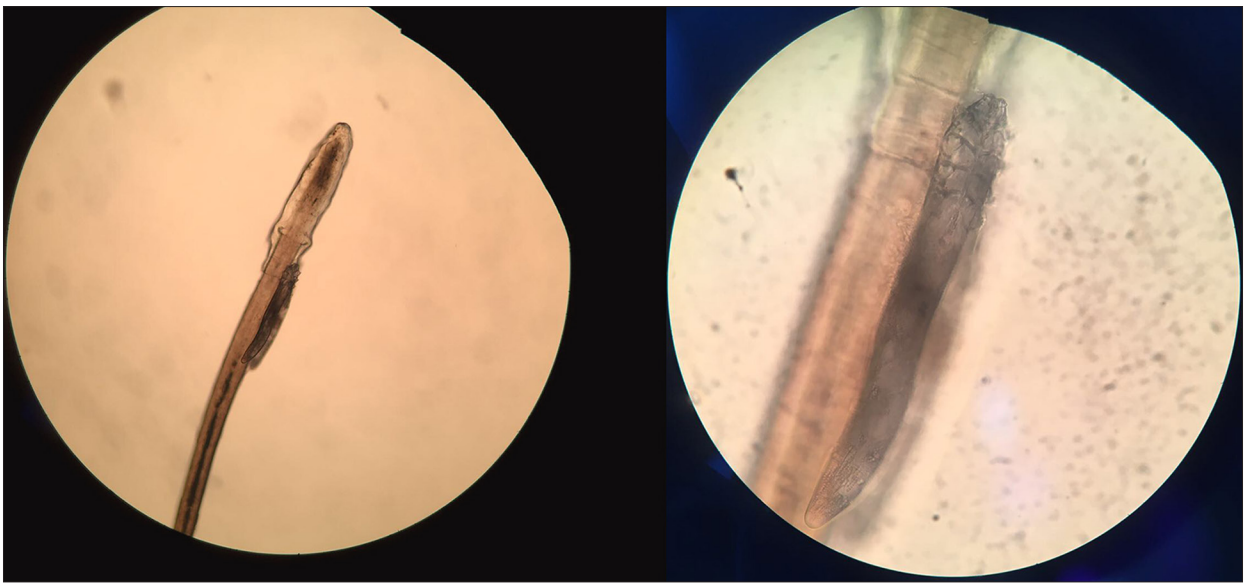

Figure 1. A view of *Demodex folliculorum* under light microscope.

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Table 1. Uludag ocular demodicosis clinic scoring.

	Yes	No	Total
Symptom			
At least one of the symptoms			
that mentioned below is positive			
burning, sting, itching, pain	☐	☐	.....
Finding			
Anterior blefaritis	☐	☐	.....
Posterior blefaritis	☐	☐	.....
Additional points			
Lashes			
Cylindrical dandruff (If yes add 2 points)	☐	☐	.....
Ocular surface			
Chronic user of an eye drop that contains preservative (If yes add 1 point)	☐	☐	.....
Systemic or local any cause of dry eye diseases except blepharitis (If yes add 2 points)	☐	☐	.....
Cornea			
Epithelial defect (If yes add 1 point)	☐	☐	.....
Keratitis (If yes add 2 points)	☐	☐	.....
Total Score	.....		

products at the time of the study. Apart from that, if keratitis was present when the patient was first examined, keratitis treatment was started. Artificial tear treatment was started if there were other factors that could cause dry-eye disease. Patients were re-examined 1 month after the initial treatment. Patients whose symptoms and signs did not resolve were re-examined for *Demodex spp*.

Assessment of patients and scoring

Symptoms and findings were scored from 1 and 10 according to the most common complaints and findings of the patients, in comparison with the most common complaints and findings in international publications by Dr. Kivanc and Dr. Akova-Budak. This scoring system is referred to as "Uludag Ocular Demodicosis Clinical Scoring (UODS)". The chart based on this scoring is illustrated in Table 1. If there was at least 1 complaint of stinging sensation and/or burning, itching, and pain, 1 point was given; otherwise, a score of 0 points was given. Based on to the emerging findings, 1 point each was given for anterior or posterior blepharitis, and 2 points were given if both were present. Apart from that, cases that may have compromised ocular surface were also included in the scoring. If the long-term use of drops containing a preservative (e.g., glaucoma medications) was in question, it was given 1 point; if there was a systemic or local disease other than blepharitis that would cause dry eye, it was given 2 points. If there was an epithelial defect, 1 point was given, and if the patient was admitted with keratitis, 2 points were given. The presence of cylindrical dandruff (CD) was given 2 points (Figure 2). With this scoring system, the rate of *Demodex*-positivity was assessed (Table 1).

Statistical analysis

For the statistical analysis, SPSS 23 statistical analysis software was used. Descriptive statistical methods were used for age, sex, symptoms, and findings. Relations between *Demodex* infestation and symptoms, findings, and scores were assessed with the Pearson chi-square test. The Wilcoxon signed rank test was used for evaluating the change in OSDI score and tear film break-up time. The Mann-Whitney test was used to compare the mean UODS of *Demodex*-positive and -negative patients.

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Figure 2. A *Demodex*-positive patient with cylindrical dandruff before and 2 weeks after TTO treatment.

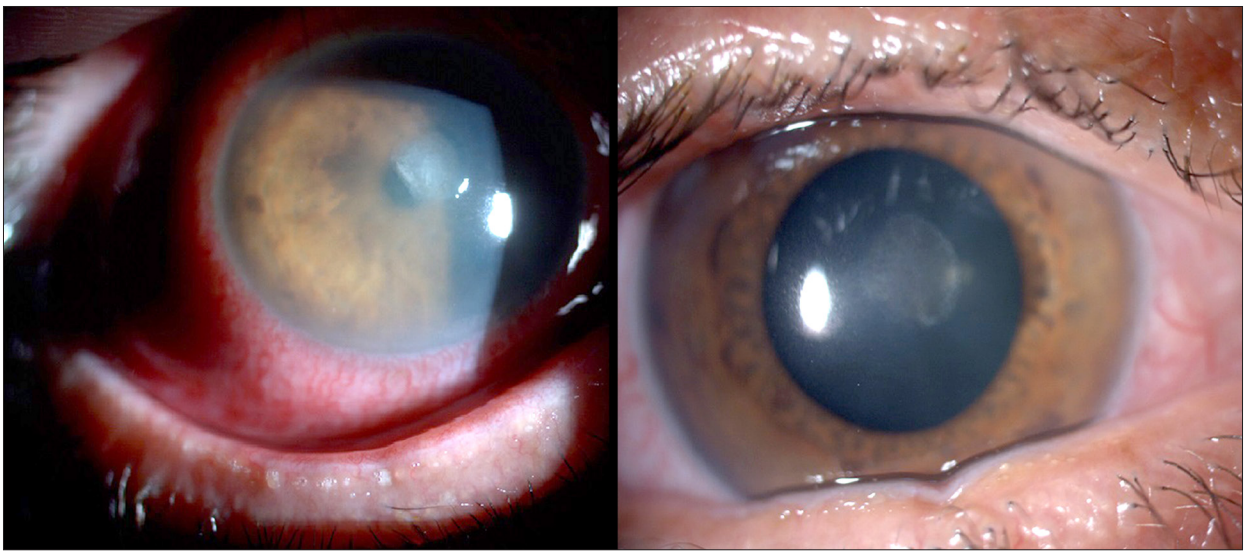

Figure 3. A *Demodex*-positive patient with keratitis and blepharitis before and 1 week after TTO treatment.

Results

We reviewed the charts of 412 patients who were seen at the Ophthalmology Department of Uludag University between January 2016 and August 2017 and who were diagnosed with blepharitis. Blepharitis was chronic and treatment-refractory in 39 (9.5%) of the adult patients. The mean age of the patients was 54.1±15.4 years. Seventeen (43.5%) patients were male and 22 (56.5%) were female. Twenty-two patients (56.4%) had stinging and/or burning as an initial complaint, 6 patients had (15.4%) itching, and 5 patients had pain (12.8%). While eyelid edema, loss of eyelash, irritation, and frequent chalazion were present in each patient, 2 patients had only complained of dandruff on their eyelids. Biomicroscopic examination revealed anterior blepharitis in 19 patients (48.7%), posterior blepharitis in 7 patients (17.9%), and both anterior and posterior blepharitis in 13 patients (33.3%). Fourteen (35.9%) patients had foamy secretions. In addition to blepharitis, keratitis was present in 4 patients (Figure 3) and epithelial defect was present in 3 patients (Figure 4). In cultures taken from the patients with keratitis, *Enterobacter aerogenes* grew in the culture of 1 patient and *Staphylococcus epidermidis* grew in the other. There was no culture growth in 2 patients.

Six patients were reported to have been receiving topical glaucoma medication; and 7 patients had systemic or ocular condition other than blepharitis, causing dry-eye disease. Two patients had Sjögren's syndrome, 1 had ectropion, 1 had uncontrolled diabetes, 1 had acne rosacea, 1 had keratoplasty, and 1 had ocular surface lesion secondary to trauma.

In 30 of the 39 patients (76.9%) *D. folliculorum* was detected. In 1 patient, *D. brevis* was detected together with *D. folliculorum*. No *Demodex spp.* was detected in 9 patients (Table 2).

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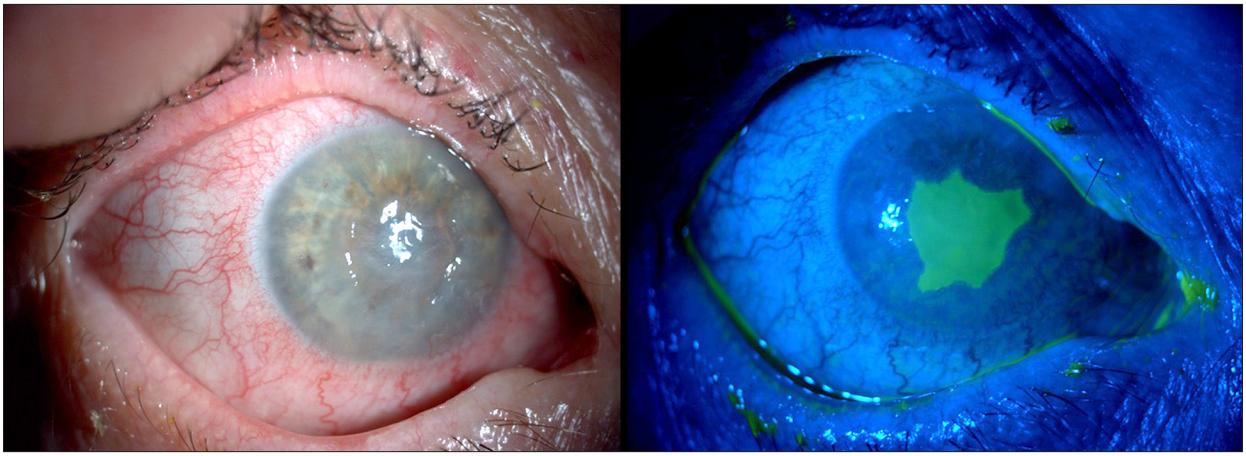

Figure 4. A *Demodex*-positive patient with epithelial defect.

Table 2. Demographics, symptoms and findings of the patients.

	N	Age	Gender (F/M)	Anterior blepharitis (Yes/No)	Posterior blepharitis (Yes/No)	Burning, staining, itching, pain*** (%)
Demodex positive	30	54.1±14.6	16/14	24/6	15/15	83
Demodex negative	9	56.3±18.7	6/3	8/1	5/4	89
		0.741*	0.704**	0.480**	0.535**	0.575**

* Mann-Whitney test; ** Fisher's exact test (1-sided); ***One of those findings was positive. F – Female; M – Male.

Table 3. Ocular surface findings at initial and 1 month examination in demodex positive patients.

	N	Initial examination	1 month examination	P value
OSDI score#	12	39.6±10.1	33.0±2.7	0.002*
TBUT##	10	8.3±4.0	10.1±3.3	0.042*
Keratitis	4	4	0	–
Epithelial defect	2	2	0	–
Blepharitis	30	30	5	–

Ocular surface disease index; ## Tear film break up time; * Wilcoxon signed rank test.

The ocular surface disease index (OSDI) scores of the patients at presentation and in the first month, as well as the tear film break-up time (BUT) values, are illustrated in Table 3. Only 12 patients had OSDI score for both visits and 10 patients had BUT values. The patients who were detected to have *D. folliculorum* were started on eyelash cleaning twice a day with TTO shampoo and TTO eyelid gel twice a day. Additionally, artificial tear treatment was initiated. Patients came in for re-examination after applying this treatment for 1 month; 28 of 30 patients were re-examined 1 month later. Complaints disappeared in 25 patients (89.2%) and blepharitis findings disappeared in 23 (82.1%) patients. The blepharitis symptoms disappeared in 3 patients whose complaints did not resolve. While 2 of these patients had Sjögren's syndrome, 1 patient had seasonal allergy symptoms. At the end of the first month, we found that *D. folliculorum* was positive in 5 of the patients who continued to have blepharitis. Antibiotic and steroid fixed-combination medicine was added to the TTO treatment. At the end of the third month, 3 of 5 patients had blepharitis. *Demodex* positivity was detected again in the re-examination of these 3 patients. The distribution of symptoms and indications in the patients who did not improve with treatment was similar to the symptoms and indications in the patients who improved with treatment. The mean age of the patients who did not recover with the treatment was 60.4±12.2 years, while the mean age of the patients who benefited from the treatment was 51.9±15.1 years. There was no statistically significant relationship between the positivity for *Demodex*

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mites and indications and symptoms of the patients. However, *Demodex* was found to be positive in all patients who had CD on eye lashes and systemic and ocular predisposing factors that could cause dry eyes, except for blepharitis.

The mean UODS of patients who were *Demodex*-negative was 2.7±1.0, while the mean UODS in those who were *Demodex*-positive was 3.8±1.6 (p=0.047). Ninety-four percent (94%) of those with a score of 4 and over were found to be *Demodex*-positive (p=0.025). However, scores of only 54% of the *Demodex*-positive patients were 4 or higher. Eighty-three percent of those with scores of 3 and above were *Demodex*-positive, but it was found that 72% of all *Demodex*-positive patients had a score of 3 or more (p=0.140). The score of all of the patients who did not recover from blepharitis with 1-month treatment was 3 and above and 80% of the patients had a score of 4 and above. In this group, 28.6% of the patients did not recover with the TTO treatment. While none of the patients complained of the TTO use, 1 patient with nasolacrimal duct obstruction had acute dacryocystitis 1 month after TTO was started, and was then treated with oral antibiotic therapy.

Discussion

Demodicosis etiopathogenesis in patients with blepharitis has been the subject of intensive research in the years 2000 to 2010, showing it was present at high rates in chronic blepharitis patients. The present study was carried out in a tertiary hospital in the most industrialized region of Turkey. We found that *Demodex* ratio was approximately 77% in chronic and treatment-refractory patients. In Tasmania, which is more of an agricultural and forestry region, *Demodex* positivity was found in 99% of patients with chronic ocular surface disease [12]. A study conducted in Seoul, one of the most developed cities in Korea, found that the *Demodex* ratio in the routine examination of eye disease in outpatient clinics was 70% [13]. However, we believe that the comparison of these studies will be scientifically problematic since the groups of patients included in the majority of studies were quite different.

Treatment is another challenging issue. In the literature, different treatments were tried for *Demodex*. Fulk et al. [14] showed, in a study conducted in 1996, that pilocarpine reduced the number of *Demodex*, but this treatment was not very popular. Hirsch-Hoffmann et al. [15] found that while the average number of *Demodex* was 13 after 2 months of 5% TTO treatment, this number was 13 with ivermectin, 22 with oral metronidazole, 12 with 0.02% TTO, and 9 with metronidazole ointment. Holzchuh et al. [16] found that the 28-day oral ivermectin treatment managed to reduce the number of mites with *D. folliculorum* treatment, reducing them from 5 mites to 0.5 on average. Salem et al. [17] reported that they compared the oral ivermectin alone, and oral ivermectin and metronidazole treatment, and concluded that at the end of 4 weeks, combined treatment in blepharitis patients was more beneficial than ivermectin treatment alone. However, patients prefer topical medication to oral medication. The most popular and successful topical treatment is the application of tea tree oil eyelid gel after the cleaning of eyelashes. In a study conducted in Tasmania, it was reported that symptoms decreased in 91% of patients with 5% TTO use. In the same study, it was revealed that the patients who recovered the least were those who had underlying dry-eye disease [12]. Gao et al. [18] found that weekly eye lid cleaning with 50% TTO and daily eye lid cleaning with 5% TTO were effective. However, it was also revealed that daily eye lid cleaning with 50% TTO and massage with 5% gel were effective [19,20]. A Korean study compared patients who did weekly 50% TTO, 10% daily TTO, and only saline cleaning, reporting that while the average number of mites in patients who cleaned with TTO decreased from 4.0 to 3.2, cleaning with saline did not lead to any decrease in number of mites [21]. In the present study, patients were told to wash with 10% TTO eye shampoo and to massage with 4% gel. With this particular treatment, complaints were reduced in 89% of patients and findings disappeared in 82%. Despite the fact that the findings of 3 patients disappeared, their complaints continued. Two of these patients had Sjögren's syndrome, and the other had seasonal allergy symptoms. Similarly, other studies [22,23] also pointed out that the changes in objective ocular symptoms did not always lead to recovery. However, since this was a retrospective study and the patients did not report any complaints, the parasitologic examination, which is a relatively invasive procedure, was not repeated. However, we found that the OSDI scores of the patients who had TTO treatment and their BUT values were improved with the decrease of patients' subjective complaints. In a previous study, it was revealed that the patients with high OSDI but low BUT score had high numbers of *Demodex* mites, but the effect of treatment on these scores was not evaluated [13]. It was reported that the number of *Demodex* mites was correlated with the OSDI score. In their study in Korea, Koo et al. found that 85% of patients with ocular disease had *Demodex* [21]. They found that while the OSDI score of the patients who cleaned with TTO decreased from 35 to 24, there was a statistically significant improvement in OSDI scores of those who washed with saline. In their study utilizing *in vivo* confocal microscopy, Randon et al. [24] reported that *Demodex* was found in 60% of the dry-eye patients who did not have anterior blepharitis.

Meibomitis secondary keratitis or keratoconjunctivitis development has been reported in many studies [25,26], but they do not mention if any search for the presence of *Demodex* were carried out on patients. *Demodex* has been shown to cause many different corneal findings [27]. *Demodex*-related corneal findings can be encountered and may lead to visual loss. In our

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study, 18% of patients had keratitis or corneal epithelial defect, and 86% of these patients were *Demodex*-positive. While *D. brevis* was positive in the majority of patients with corneal manifestation [15], in our study *D. folliculorum* was detected in all patients except in 1 patient who had *D. brevis* and *D. folliculorum* together. Previous studies reported that *Bacillus oleronius* proteins were found in the *Demodex* mite, and emphasized that these *Bacillus* proteins delay healing of wounds, which may hence cause inflammation, non-healing keratitis, and scar formation in the demodulated patients [28,29]. In their study of corneal abnormalities in *Demodex* patients, Kheirkah et al. [27] found that while *D. folliculorum* was detected in all of the 6 patients who were found to have anterior blepharitis and CD, *D. brevis* was detected only in 3 patients. In the same study, 5 of 6 patients had meibomian gland disfunction and 4 patients had rosacea. It was reported that there was marginal corneal inflammation in 2 eyes and a phlyctenule-like lesion in 1 patient, superficial corneal opacity in 1 patient, and nodular corneal scar in 2 patients. In our study, we found that 20% of the *Demodex*-positives had corneal findings and *Demodex* was positive in 86% of the patients with chronic and treatment-refractory blepharitis and corneal findings. Among the 39, 7 patients had corneal findings, of which 5 were diagnosed with *D. folliculorum* and 1 was diagnosed with *D. folliculorum* and *D. brevis*. In 4 of these 6 patients, keratitis was diagnosed and the patients were treated with TTO. Three patients of the 4 recovered from keratitis, but persistent epithelial defect developed in the other, and healed with in a month. In the other 2 patients, epithelial defects were present.

In many studies, the presence of CD in ocular demodicosis was regarded as pathognomonic. In the present study, we found that *Demodex sp.* was positive in all the patients with CD. In another study, CD was found to be positive in 31% of the patients who were *Demodex*-positive [19].

In vivo confocal microscopy has been used along with microbiological methods. It is not possible to perform *Demodex* diagnosis when there is no confocal microscope and when microbiological examinations are not available, or when the patient refuses to have eyelashes pulled out. However, different methods were also proposed in the literature to diagnose *Demodex* sp. from eyelashes [24,27,30]. Even though it is claimed that CD is diagnostic, it is not possible to detect in every patient. In this paper, we introduce a clinical scoring system based on the most common complaints and symptoms encountered in our work as well as in studies by other groups. With this scoring method, which we developed for correct diagnosis adequate treatment of patients, *Demodex* was detected in 94% of patients with a UODS of 4 or above. We recommend initiation of TTO treatment for the patients in this group. We found that this rate was 85% in the patients with a score of 3 or above. We have started to use this scoring successfully in our own current practice.

In our study, the most common complaints from patients with *Demodex* were stinging, burning, and itching, in line with the results reported by Gao et al. [20]. It was also proved that there was a relationship between stinging, burning, and itching, and *Demodex* [20]. However, since none of them is a single pathognomonic finding and there is no chance for all physicians to demonstrate *Demodex* positivity, we have introduced a new scoring system. In the years since the relationship between blepharitis and *Demodex* was first described in 1960s [31,32], approximately 60 original studies on *Demodex* blepharitis or ocular demodicosis were found in PubMed in the English literature. When we look at the number of studies, while it is expected that there should have been more studies conducted on a common disease related to blepharitis, we think that the relatively small number of studies may be attributed to the difficulty in diagnosis. In order to make a diagnosis, an experienced microbiologist in the field of parasitology or an expensive instrument such as an *in vivo* confocal microscope are needed. Therefore, the number of studies on easily performed diagnostic tests have been increasing in recent years. We also set up a scoring algorithm in our study and used a scoring that would allow us to start treatment without delay based on symptoms and clinical findings, particularly where there was no experienced parasitologist or no confocal microscope. It is also important to note that this scoring system should be verified by prospective studies before it is implemented in large populations of patients.

Conclusions

Demodex infestation is a common disorder in adult patients with chronic and refractory blepharitis in an industrialized region of Turkey. TTO treatment was found to be effective. Patients with *Demodex* infestation had many ocular surface and corneal findings. Therefore, this scoring system should be useful in making accurate diagnosis when advanced investigation techniques are not available.

Conflict of interest

None.

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