

An Observational, Multicenter, Parallel-Cohort Study Evaluating the Association of Clinical Manifestations and Patient-Reported Outcomes in Patients with *Demodex* Blepharitis

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Purpose: This study aimed to evaluate the clinical manifestations and patient-reported outcomes related to *Demodex* blepharitis.

Patients and Methods: In this observational, multicenter, cross-sectional, parallel-cohort study conducted at 7 sites in the United States, adult participants were assigned to study cohorts based on collarette grade: Control Cohort (no collarettes), Cohort 1 (1–10 collarettes), or Cohort 2 (>10 collarettes). Key outcome measures included collarette grading, lid margin erythema, ocular symptoms (itching, fluctuating vision, irritation, redness, and burning) measured on a visual analog scale (VAS), and the location of ocular itching when present.

Results: A total of 147 participants were enrolled and completed the study: 47 in the Control Cohort, 46 in Cohort 1, and 54 in Cohort 2 (a total of 100 participants with ≥ 1 collarette, identified as having *Demodex* blepharitis). Eighty-five percent of patients with *Demodex* blepharitis were symptomatic, reporting at least 1 ocular symptom. Mean VAS scores were statistically significantly worse (higher) in participants with *Demodex* blepharitis for itching (24.5 vs 15.1, $p = 0.025$), fluctuating vision (24.2 vs 9.8, $p = 0.0005$), irritation (27.6 vs 17.3, $p = 0.021$), and redness (19.8 vs 9.9, $p = 0.0128$) compared to those without *Demodex* blepharitis. Mean VAS scores for burning were similar between cohorts. The lid margin was the most common location for ocular itching in patients with *Demodex* blepharitis compared to the corner(s) of the eye in patients without collarettes.

Conclusion: This study demonstrated the vast majority (85%) of patients with *Demodex* blepharitis were symptomatic, reporting at least 1 ocular symptom, and an association between increasing collarette severity in participants with *Demodex* blepharitis and ocular symptoms (itching, fluctuating vision, irritation, and redness), as well as increased lid margin erythema.

Keywords: blepharitis, *Demodex*, collarettes, patient-reported outcomes, visual analog scale, ocular symptoms, fluctuating vision

Introduction

Blepharitis is a common pathologic condition involving inflammation of the eyelids, primarily the eyelid margin. Both the anterior and posterior eyelid margin can be involved, including the skin, lashes, lash follicles, and the meibomian glands.¹ Signs and symptoms associated with blepharitis include ocular itching, fluctuating vision, irritation, redness, burning, tearing, contact lens intolerance, debris at the bases of the lashes, and lash anomalies.²

While the pathophysiology for all types of blepharitis is not well understood, causative factors have been identified for specific types of blepharitis, including infestation of the lid margin with *Demodex* mites. *Demodex* blepharitis is estimated to account for more than two-thirds of all blepharitis cases in the United States and affects up to 25 million



Americans.^{3,4} *Demodex* blepharitis was reported to affect 58% of adults visiting eye care clinics in the United States.³ *Demodex* mites (*Demodex folliculorum* and *Demodex brevis*) are the most common ectoparasites on humans. *Demodex folliculorum* is often present in clusters around the lash follicle and lash root, while *Demodex brevis* are typically associated with infestation of the sebaceous glands.⁴ The infestation of *Demodex* mites in the eyelash follicles, meibomian glands, and sebaceous glands is associated with chronic inflammation known as *Demodex* blepharitis.^{2,5-8}

The overlap of symptoms associated with *Demodex* blepharitis and other common conditions affecting the ocular surface, such as dry eye disease, has created challenges in determining the extent of the contribution of the infestation of *Demodex* mites on the lid margin to ocular outcomes. The presence of collarettes, appearing as cylindrical dandruff at the base of the lashes that is the combination of waste from the mites, mite eggs, epithelial cells, and keratin, is a pathognomonic sign for *Demodex* blepharitis.^{3,4,9-14} *Demodex* blepharitis can be simply diagnosed by identifying the presence of collarettes by instructing the patient to look down under conventional slit lamp examination.¹⁵

Demodex blepharitis is often overlooked or misdiagnosed even after the presence of collarettes is confirmed. Patients often report experiencing one or more ocular symptoms for ≥ 2 years prior to being diagnosed with *Demodex* blepharitis, despite having multiple eyecare visits while symptomatic.¹⁶⁻¹⁸ An observational study evaluating the impact of *Demodex* blepharitis on patient symptoms and daily life found a significant negative impact on patient's daily activities, with eyes that itch, dry eyes, and ocular foreign body sensation ranked as the most bothersome symptoms.¹⁶ The purpose of the present study was to determine if there was an association between clinical manifestations and patient-reported ocular outcomes related to *Demodex* blepharitis.

Materials and Methods

This was an observational, multicenter, cross-sectional (single visit), parallel-cohort study. Participants were enrolled at 7 study centers located in the United States. All study participants signed an informed consent prior to any study specific procedures being performed. The study was conducted in compliance with the study protocol and in accordance with the principles of the Declaration of Helsinki. Advarra Independent Review Board (Columbia, MD, USA) reviewed and approved (approval # Pro00072904) the study protocol and other study-related subject-facing materials prior to use to ensure ethical conduct of the study.

Study Design

This study consisted of a single visit (Day 1). The study schematic is presented in Figure 1. Each study participant provided written informed consent on the Day 1 visit, prior to any study specific procedures being conducted. Patient's demographic information and any information regarding ocular signs and symptoms was collected. Eligibility for participation was determined based on the study inclusion and exclusion criteria. Participants were assigned to a study cohort based on their clinical assessment of the presence and number of collarettes: Control Cohort = no collarettes; Cohort 1 = 1–10 collarettes; Cohort 2 = >10 collarettes. Participants presented with ≥ 1 collarette (combination of Cohort 1 and Cohort 2) were identified as having *Demodex* blepharitis. Participants exited the study following the completion of the study assessments and procedures on the Day 1 visit.

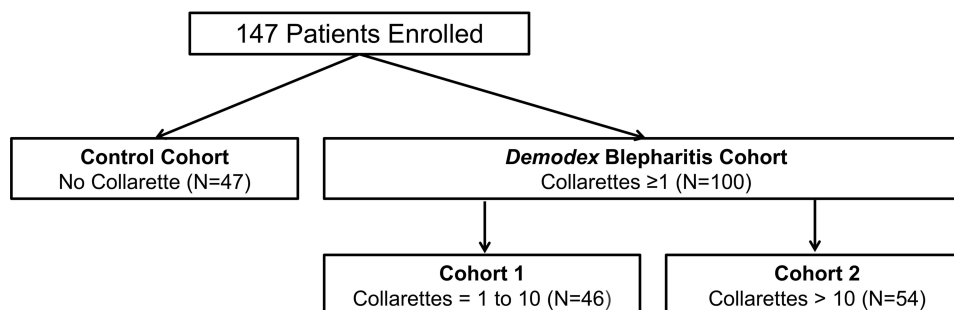


Figure 1 Study schematic and patient disposition.
Note: All enrolled patients completed the study.

Eligibility Criteria

Patients were determined to be eligible for participation in the study if they met all of the inclusion criteria and none of the exclusion criteria. The inclusion criteria required the study population to be male or female with ≥ 18 years of age, have a corrected distance visual acuity of 20/100 or better in each eye, be willing and able to sign informed consent, and have at least one eye meeting both criteria (in same eye) of an average non-invasive fluorescein tear break-up time (TBUT) of >7 seconds and a Schirmer 1 test (without anesthesia) of ≥ 10 mm.

Patients were excluded from participating in the study if they were currently taking or had taken any prescription antibacterial, antiparasitic, or anti-inflammatory corticosteroid treatment (regardless of the route of administration, eg, systemic, drug delivery implant, ocular or topical) within 14 days of the Day 1 visit. Use of lotilaner 0.25% ophthalmic solution (XDEMVY[®] [previously TP-03], Tarsus Pharmaceuticals, Inc., Irvine, CA) within 12 months of the Day 1 visit, or TP-03 in a previous clinical study (unless study drug administration was completed at least 12 months prior to the Day 1 visit) was exclusionary. Patients were also excluded if they had received active treatment for blepharitis (eg, tea tree oil-based products, hypochlorous acid-based products, commercial eyelid foams, eyelid wipes, lid scrubs) or used varenicline nasal spray or perfluorohexyloctane ophthalmic solution within 14 days of the Day 1 visit. Patients were not allowed to participate if they had an active ocular infection or inflammation other than blepharitis, used artificial eyelashes or eyelash extensions on Day 1, if the lid margin could not be accurately evaluated, had worn contact lenses within 24 hours of the Day 1 visit, had abnormal eyelid anatomy (eg, ectropion, entropion), had used an artificial tear product on the day of Visit 1, or were currently enrolled in an investigational drug or device study.

For all cohorts, if only one eye of a participant qualified, that eye was designated as the analysis eye. For the Control Cohort, if both eyes of a participant qualified, the right eye was designated as the analysis eye. For Cohort 1 and Cohort 2, if both eyes of a participant qualified, the eye with the higher collarette grade was designated as the analysis eye. If both eyes had an equal collarette grade, then the right eye was designated as the analysis eye.

Outcome Measures

Patient-reported ocular outcomes (ocular itching, fluctuating vision, irritation, redness, and burning) were assessed using a visual analog scale (VAS). The participant's level of discomfort in these ocular symptoms was measured on a 0 to 100 VAS scale (no discomfort/issue to maximal discomfort/issue). The participant self-recorded the discomfort level experienced for each ocular symptom for the 1-week period prior to visit day. Additionally, participants were queried regarding their most bothersome ocular symptoms.

Collarette grading was based on an assessment of the number of lashes per eyelid that had collarettes present upon examination. The scale for the collarette score ranged from 0 to 4 for each eyelid in whole-unit increments, with Grade 0 = 0 to 2 lashes had collarettes per eyelid, Grade 1 = 3 to 10 lashes had collarettes per eyelid, Grade 2 = more than 10 but less than 1/3 of lashes had collarettes per eyelid, Grade 3 = 1/3 or more but less than 2/3 of lashes had collarettes per eyelid, and Grade 4 = 2/3 or more of lashes had collarettes per eyelid.

The grading for erythema severity of each eyelid margin ranged from 0 (normal) to 3 (severe) in whole-unit increments. The scoring and severity levels were defined as follows: Grade 0 (normal) = normal age-related lid coloration, Grade 1 (mild) = pink capillary involvement along the lid edge with no patches of confluent capillary redness throughout the lid edge, Grade 2 (moderate) = deep pink or red confluent capillary redness present locally along the lid edge, and Grade 3 (severe) = deep red, diffuse confluent capillary redness present along the lid edge.

Statistical Analysis

Categorical variables were summarized by the frequency counts and percentages for each response category, while continuous variables were summarized using the sample size, mean, median, standard deviation (SD), minimum, and maximum values for the data collected at the study visit. Statistical tests were 2-sided with an alpha level of 0.05.

Collarette grades and lid margin erythema grades were summarized separately by cohort. The assessments were compared separately between cohorts using the Cochran-Mantel-Haenszel row mean score test. The patient-reported ocular outcomes included continuous variables measured on VAS scales ranging from 0 to 100 for ocular itching,

fluctuating vision, irritation, redness, and burning. In addition, ocular patient-reported outcomes included the following categorical variables: location of ocular itching, most bothersome symptom, symptom(s) that led to participant's first visit to an eye care practitioner, and symptom(s) that led to the participant's first treatment by an eye care practitioner. Descriptive analyses were performed to characterize the assessments for each cohort and evaluate the association of each clinical assessment with each ocular patient-reported outcome.

Results

A total of 147 patients across 7 study sites in the United States met the eligibility criteria and enrolled in the study, with 47 (32.0%) participants assigned to the Control Cohort (no collarettes), 46 (31.3%) participants to Study Cohort 1 (1–10 collarettes), and 54 (36.7%) participants to Study Cohort 2 (>10 collarettes). A total of 100 patients (Cohort 1 and Cohort 2 combined) presented with ≥ 1 collarette and were identified as having *Demodex* blepharitis. All enrolled participants completed this single-visit study. The participant disposition for the study is presented in Figure 1.

The mean (SD) age of the full study population was 46.7 (17.9) years. The majority of participants were female (63.3%), not Hispanic or Latino ethnicity (85.7%), and White race (85.7%). The demographics for the study population by group and total are presented in Table 1. The ocular characteristics for mean (SD) TBUT and Schirmer I scores are also listed in Table 1.

Collarette Grades

All 47 participants in the Control Cohort had no collarettes present on any eyelashes of the study eye. The majority of participants in Cohort 1, 43 of 46 (93.5%) had Grade 1 collarettes on eyelashes of the study eye. All 54 participants in Cohort 2 had collarettes of at least Grade 2 on the eyelashes of the study eye. A summary of the worst collarette grade by cohort for the study eye is presented in Table 2.

Table 1 Participant Demographics and Ocular Characteristics

Demographics and Ocular Characteristics		Control (N = 47)	Cohort 1 (N = 46)	Cohort 2 (N = 54)	Total (N = 147)
Age (years)	Mean (SD)	38.0 (15.9)	47.0 (17.7)	53.9 (16.7)	46.7 (17.9)
Sex [N, (%)]	Female	39 (83.0)	29 (63.0)	25 (46.3)	93 (63.3)
	Male	8 (17.0)	17 (37.0)	29 (53.7)	54 (36.7)
Race [N, (%)]	African American/Black	2 (4.3)	3 (6.5)	5 (9.3)	10 (6.8)
	Asian	4 (8.5)	3 (6.5)	1 (1.9)	8 (5.4)
	Mixed	0 (0.0)	0 (0.0)	1 (1.9)	1 (0.7)
	White	40 (85.1)	39 (84.8)	47 (87.0)	126 (85.7)
	Unknown	1 (2.1)	1 (2.2)	0 (0.0)	2 (1.4)
Ethnicity [N, (%)]	Hispanic or Latino	8 (17.0)	6 (13.0)	7 (13.0)	21 (14.3)
	Not Hispanic or Latino	39 (83.0)	40 (87.0)	47 (87.0)	126 (85.7)
Tear Break-Up Time (seconds)	Study Eye Mean (SD)	9.6 (2.3)	9.2 (1.8)	10.9 (3.7)	10.0 (2.9)
Schirmer I (mm)	Study Eye Mean (SD)	20.7 (8.9)	20.1 (10.0)	20.2 (8.1)	20.3 (8.9)

Abbreviations: mm, millimeters; SD, standard deviation.

Table 2 Collarette Grade by Cohort for the Study Eye

Collarette Grade	Control (N = 47)	Cohort 1 (N = 46)	Cohort 2 (N = 54)	Total (N = 147)
Grade 0: 0 to 2 lashes with collarettes per eyelid [N, (%)]	47 (100.0)	3 (6.5)	0 (0.0)	50 (34.0)
Grade 1: 3–10 lashes with collarettes per eyelid [N, (%)]	0 (0.0)	43 (93.5)	0 (0.0)	43 (29.3)
Grade 2: >10, < 1/3 of lashes with collarettes per eyelid [N, (%)]	0 (0.0)	0 (0.0)	16 (29.6)	16 (10.9)
Grade 3: 1/3 to 2/3 of lashes with collarettes per eyelid [N, (%)]	0 (0.0)	0 (0.0)	19 (35.2)	19 (12.9)
Grade 4: >2/3 of lashes with collarettes per eyelid [N, (%)]	0 (0.0)	0 (0.0)	19 (35.2)	19 (12.9)

Note: Collarette assessment was performed in each eyelid of the study eye. Data showed the worst collarette grade between the upper and lower eyelids of the study eye.

Eyelid Margin Erythema

The percentage of participants with eyelid margin erythema increased with higher collarette grades and therefore by cohort. The majority of participants in the Control Cohort (80.9%) did not exhibit any lid margin erythema, while the proportion of participants with mild and moderate erythema increased in Cohort 1 and Cohort 2, respectively. Severe eyelid margin erythema was only observed in Cohort 2 (1.9%). A higher severity of eyelid margin erythema was observed with increasing collarette grade. The proportion of participants with normal, mild, moderate, and severe lid margin erythema is presented by cohort for the study eye in [Figure 2](#).

Ocular Patient-Reported Outcomes

Eighty-five of 100 (85.0%) patients with *Demodex* blepharitis reported at least one ocular symptom, while 26 of 47 (55.3%) patients in the Control cohort reported at least one ocular symptom. The mean VAS scores for itching, fluctuating vision, irritation, and redness were statistically significantly higher (indicating greater discomfort) in participants with *Demodex* blepharitis (combined data for Cohort 1 and Cohort 2) compared to the Control Cohort ($p < 0.05$) ([Figure 3](#)). The difference between two groups remained statistically significant for itching, fluctuating vision, irritation, and redness, after adjusting for age and sex.

The mean VAS scores for each ocular symptom (itching, fluctuating vision, irritation, redness, and burning) were consistently worse (higher) in Cohort 1 and Cohort 2 compared with the Control Cohort. The mean VAS scores (SD) are presented by ocular outcome and cohort in [Table 3](#). Significantly higher VAS scores were reported by participants in Cohort 1 compared to the Control Cohort for redness ($p = 0.0224$) and fluctuation of vision ($p = 0.0131$). The mean VAS

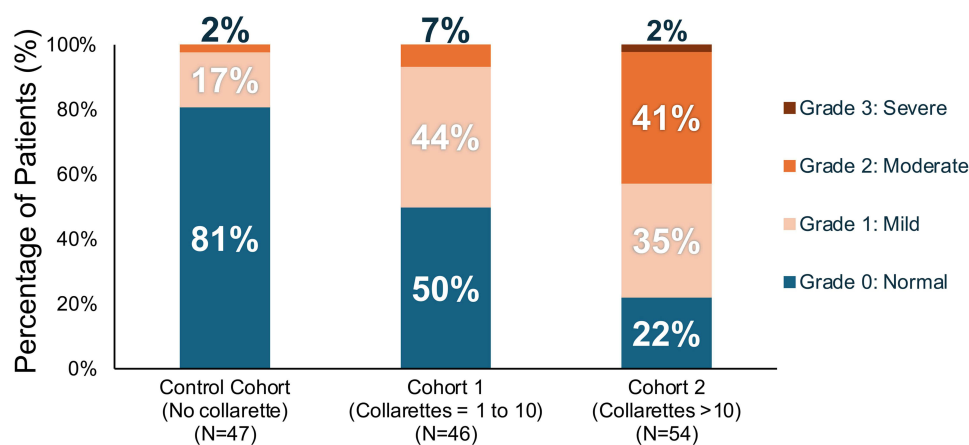


Figure 2 Percentage of eyelid margin erythema by grade and cohort for the study eye.

Note: Assessment of eyelid margin erythema was performed in each eyelid of the study eye. Data showed the worst erythema grade between the upper and lower eyelids of the study eye.

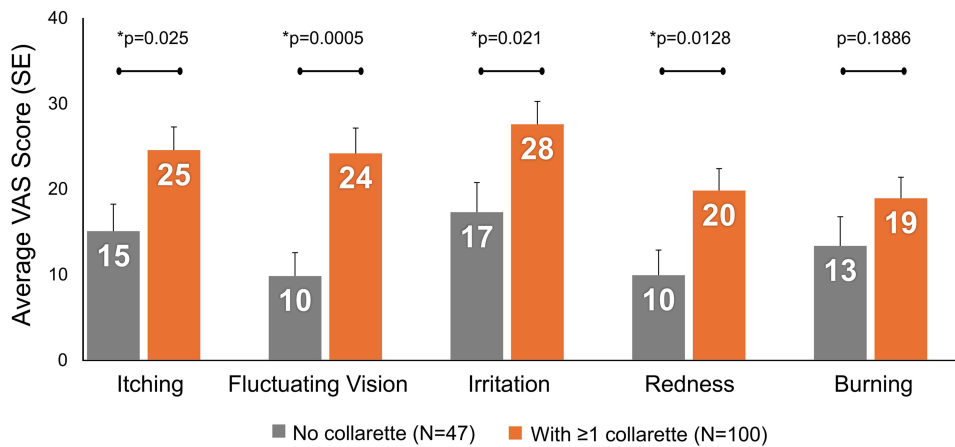


Figure 3 Mean (SE) VAS score for patient-reported ocular outcomes for participants with no collarettes (Control Cohort) and with ≥1 collarette (combination of Cohort 1 and Cohort 2).

Note: *Statistically significant p-value.

Abbreviations: SE, standard error; VAS, visual analog scale.

scores in Cohort 2 were statistically higher than in the Control Cohort for itching ($p = 0.0319$), irritation ($p = 0.0189$), and fluctuation of vision ($p = 0.0023$). Mean VAS scores for itching, irritation and fluctuation of vision were numerically higher in Cohort 2 than Cohort 1, but no statistically significant differences were observed. The mean VAS scores for burning were similar between the Control and study Cohorts.

Among all participants, ocular itching was reported at the highest frequency as being the most bothersome symptom (20.4%), the most common reason leading to a participant’s first visit to an eye care practitioner (32.0%), and the most common reason leading to a participant’s first treatment (30.6%). Evaluation of the participant responses with respect to the location of itching revealed differences between the study groups. Itching in the corner(s) of the eye was reported by 19.1%, 19.6%, and 14.8% of the participants, respectively, in the Control Cohort, Cohort 1, and Cohort 2 participants. In contrast, itching at the eyelid margin occurred in 2.1%, 8.7%, and 25.9% of the participants in the Control Cohort, Cohort 1, and Cohort 2. The responses from Cohort 2 participants and Control Cohort participants regarding the location of itching for participants that reported this symptom is presented in Figure 4.

Table 3 Mean (SD) VAS Scores for Participants by Ocular Outcome and Cohort

Ocular Outcome	Control (N = 47)	Cohort 1 (N = 46)		Cohort 2 (N = 54)		Cohort 1 + Cohort 2 (N = 100)	
	Mean (SD)	Mean (SD)	p-value vs Control	Mean (SD)	p-value vs Control	Mean (SD)	p-value vs Control
Itching	15.1 (21.7)	23.0 (26.3)	0.1164	25.9 (28.0)	0.0319*	24.5 (27.1)	0.0250*
Fluctuating Vision	9.8 (18.8)	22.4 (28.1)	0.0131*	25.6 (31.0)	0.0023*	24.2 (29.6)	0.0005**
Irritation	17.3 (23.8)	25.3 (26.1)	0.1230	29.4 (27.4)	0.0189*	27.6 (26.8)	0.0210*
Redness	9.9 (20.2)	21.0 (25.3)	0.0224*	18.8 (26.2)	0.0572	19.8 (25.7)	0.0128*
Burning	13.3 (23.4)	18.7 (24.3)	0.2855	19.1 (25.1)	0.2331	18.9 (24.6)	0.1886

Note: *p-value vs Control < 0.05; **p-value vs Control < 0.001.

Abbreviations: SD, standard deviation; VAS, visual analog scale.

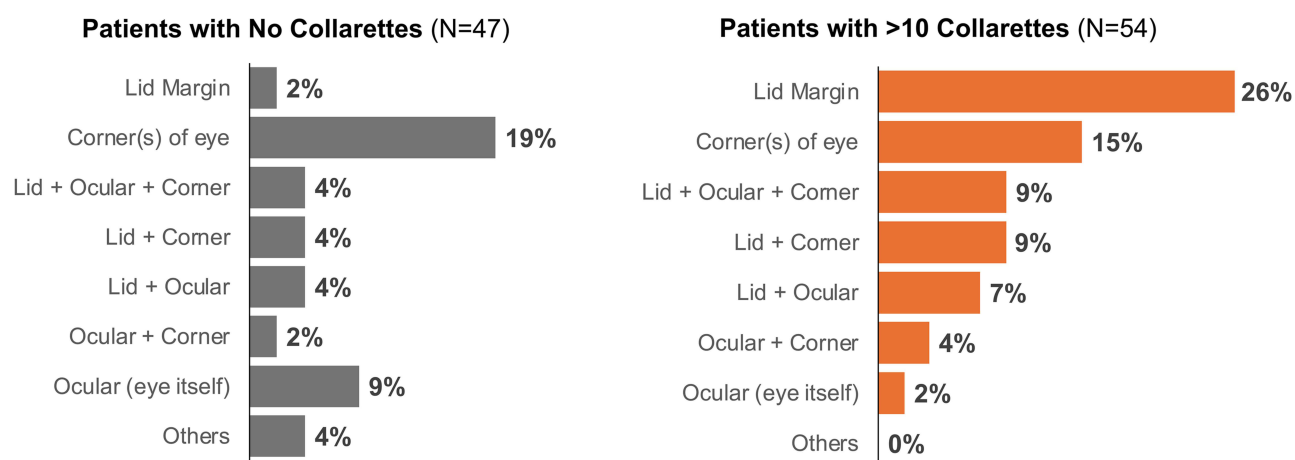


Figure 4 Summary of participant responses regarding the location of ocular itching for participants with no collarettes (Control Cohort) and with >10 collarettes (Cohort 2).

Discussion

This observational study was designed to understand the association between clinical manifestations and ocular patient-reported outcomes related to *Demodex* blepharitis. In the current study, 85.0% of participants with *Demodex* blepharitis were symptomatic, reporting at least 1 ocular symptom, consistent with previous studies that noted that nearly all patients with *Demodex* blepharitis were symptomatic.^{16,18} The magnitude of the difference in symptom scores on the VAS scales used to measure patient-reported discomfort with respect to itching, fluctuating vision, irritation, and redness in this study between the participants with collarettes and the participants with no collarettes helps to elucidate the importance of increasing symptomology in the development of *Demodex* blepharitis. The mean differences in VAS scores for itching, fluctuating vision, irritation, and redness were significantly worse for participants with collarettes compared to the control participants without collarettes. The mean differences between the participants with *Demodex* blepharitis and control participants for itching, fluctuating vision, irritation and redness VAS scores ranged from approximately 10–14 points on the VAS scale, exceeding the 7-point difference that has been established for clinically meaningful differences.^{19,20}

Consistent with previous findings, this study identified itching as a common symptom in patients with *Demodex* blepharitis.^{16,17} Additionally, eyelid itching has been noted as a factor in the diagnosis of *Demodex* blepharitis.^{18,21,22} Notably, the location of itching provided valuable insights in the present study. Itching, specifically at the eyelid margin, was significantly more prevalent among patients with *Demodex* blepharitis, particularly those with higher collarette counts. In Cohort 2, 25.9% of participants reported itching at the eyelid margin, compared to 2.1% of control participants. In contrast, the rates of itching in the corners of the eyes were similar across all groups. This observation supports the role of lid margin inflammation in *Demodex* infestation and suggests that the lid margin may be a distinguishing location of itching in patients with *Demodex* blepharitis, differentiating it from other ocular surface diseases.

In addition, fluctuating vision emerged as a significant and clinically relevant symptom in patients with *Demodex* blepharitis. Participants with collarettes reported significantly worse VAS scores for fluctuating vision compared to those without ($p = 0.0005$), indicating a strong association between disease severity and its impact on tear film and visual instability. These fluctuations likely reflect tear film disruption and eyelid inflammation caused by *Demodex* mites.^{4,23} These findings are especially important in the context of ocular surgery success, where tear film irregularity is a known contributor to less precise presurgical biometry measurement and postoperative visual fluctuations.^{24,25} As such, it could be beneficial for clinicians to examine patients for collarettes and treat *Demodex* infestations prior to surgical procedures, such as cataract surgery, to minimize potential *Demodex*-induced fluctuating vision post-operatively.

The results of the present study also highlight that as the severity of collarette grade increases, the lid margin erythema grade increases as well. Improving clinician awareness of collarettes as the pathognomonic sign for *Demodex* blepharitis may benefit patients with respect to understanding the common combination of signs and symptoms that

present with this condition. Despite *Demodex* blepharitis being a common eyelid disease, with estimates of the condition occurring in approximately 58% of adults visiting eye clinics in the US,³ additional efforts to increase awareness may be beneficial as the condition is often underdiagnosed, misdiagnosed, untreated, and is not self-remitting. Patients with *Demodex* blepharitis often experience symptoms for multiple years, and the condition is associated with increased anxiety, depression, and psychosocial impact.^{17,26} Early recognition and treatment have the potential to improve quality of life for patients with *Demodex* blepharitis.

Limitations of the current study include the observational nature of the study design and sample size. Increasing the sample size and stratification by cohort may provide additional insight into the correlation of clinical outcomes and patient-reported outcomes in patients with *Demodex* blepharitis. *Demodex* mite count was not performed in this study; however, *Demodex* blepharitis was accurately determined based on the presence of collarettes. Additionally, while collarettes are a pathognomonic sign of *Demodex* blepharitis, some of the signs and symptoms associated with *Demodex* blepharitis frequently overlap with other common conditions affecting the ocular surface, such as dry eye disease, meibomian gland disease, and different forms of conjunctivitis and keratitis. The eligibility requirements regarding TBUT and the Schirmer I test were intended to limit the participation of patients with current dry eye disease, but incorporating more stringent eligibility criteria may be useful in future studies.

Conclusion

In this observational, multicenter, single-visit study, patients with *Demodex* blepharitis, identified by the presence of collarettes, reported worse ocular symptom outcomes including itching, fluctuating vision, irritation, and redness compared to patients without collarettes. Furthermore, the vast majority (85%) of patients with *Demodex* blepharitis are symptomatic.

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Disclosure

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