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Dry Eye Profiles in Patients with a Positive Elevated Surface Matrix Metalloproteinase 9 Point-of-Care Test Versus Negative Patients

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Abstract

Purpose—To compare dry eye (DE) symptoms and signs in subjects who tested positive versus those who tested negative for ocular surface matrix metalloproteinase 9 (**MMP-9**) using the InflammaDry point of care test (RPS, Sarasota, FL).

Methods—In this cross-sectional study, individuals seen in the Miami Veterans Affairs eye clinic with DE symptoms, as evidenced by DE questionnaire 5 (**DEQ5**) ≥6, were given standardized questionnaires to assess DE symptoms and ocular and non-ocular pain complaints. Also, a complete evaluation was conducted to measure ocular surface signs of DE. MMP-9 testing was performed using the InflammaDry once in each eye, per the manufacturer's instructions. The main outcome measure was a comparison of DE symptoms and signs in MMP-9 positive versus negative subjects.

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Results—Of 128 subjects, 50 (39%) were positive for MMP-9 for InflammaDry testing in either eye. No statistically significant differences in mental health indices, DE symptoms, or ocular surface signs were seen in subjects based on MMP-9 status.

Conclusion—In our population, there was no difference in the DE profile by both symptoms and signs between those testing positive versus negative for MMP-9 on the ocular surface. This suggests that clinical exam alone cannot predict patients with clinically significant inflammation.

Keywords

dry eye; InflammaDry; matrix metalloproteinase-9

I. Introduction

Dry eye (**DE**) is defined by the Definition and Classification Subcommittee of the International Dry Eye Workshop (DEWS) as a "multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface."[1] DE is an extremely common disease in the United States and abroad, affecting 5 to 30% of the population aged 50 years and older.[2–5] Its symptoms, which include visual disturbances and pain/dysesthesias, have been found to negatively impact quality of life.[6–8] Due to the multifactorial etiology of DE and its varied pathophysiologic mechanisms, it has been difficult to identify specific biomarkers that can aid in the diagnosis of DE and help predict treatment efficacy. For example, only two-thirds of patients with DE symptoms have been found to test positive for DE with existing confirmatory tests.[9]

Inflammation is understood to play an important role in the initiation and propagation of DE.[10,11] However, several studies have demonstrated that not all patients with DE symptoms respond to topical anti-inflammatory therapies. For example, Prabhasawat et al evaluated 70 patients with delayed tear clearance and found that 83% of patients (n=58) demonstrated improvement in symptoms (defined as irritation) after 3 weeks of 1% non-preserved methylprednisolone.[12,13] In a similar manner, Sall et al evaluated 293 patients with moderate to severe DE disease and found that 39% of patients (n=115) demonstrated at least a moderate response to treatment according to physician assessment after 6 months of 0.1% topical cyclosporine therapy.[14] The fact that not all patients respond to different anti-inflammatories suggests that not all patients with DE symptoms have significant ocular surface inflammation.

In the current investigation, we considered InflammaDry, a novel test for DE that has been shown to correlate better with DE symptoms than existing confirmatory tests.[15] The test measures the presence of matrix metalloproteinase-9 (**MMP-9**), a nonspecific biomarker for inflammation.[16] Tear samples are collected from the palpebral conjunctiva with the sample collector, which is then placed within the test cassette with the addition of buffer solution. Within 10 minutes, if there is an MMP-9 antibody-antigen interaction on the immunoassay test strip, the result window will read positive (MMP-9 >40 ng/mL) with two lines (one blue and one red). According to the manufacturer, the intensity of the red line is directly related to the amount of MMP-9 present.

MMP-9 is an important enzyme for tissue remodeling in normal physiological processes like wound healing and bone development.[17] MMP-9 is also understood to play a pathological role in inflammatory disease, responsible for disrupting epithelial layers by cleaving tight junction proteins occludin and zonula occludens-1.[18] Tear fluid hyperosmolarity, which is seen in some patients with DE, has been shown to trigger the release of MMP-9, thus initiating a cycle of progressive inflammation.[18–22] The mitogen-activated protein kinase (**MAPK**) cascade is stimulated by corneal epithelial surface hyperosmolarity and inflammatory factors interleukin (**IL**)-1B and tumor necrosis factor (**TNF**)-α. Activated kinases switch on nuclear transcription factors such as NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells), AP-1 (activated protein-1), and activating transcription factor (**ATF**), which in turn stimulate the expression of inflammatory cytokines such as IL-8 and MMPs.[23] MMP-9 activity is regulated by cytokines binding to the mmp-9 gene promotor region of local neutrophils, where MMP-9 is constitutively stored in vesicles. MMP-9 is then secreted in its proenzyme form bound to endogenous tissue inhibitors of metalloproteinases (**TIMP**s) and activated extracellularly by other proteinases.[24] MMP-9 is an early marker of inflammation and is known to become elevated within 2 hours of inflammatory stimuli.[25] T-cell recruitment and subsequent secretion of additional cytokines initiate a self-perpetuating cycle of inflammation, secretory dysfunction, and worsening ocular surface disruption.[26,27]

Similar to its role in non-ocular processes, MMP-9 is likely important in the normal physiological processes of the eye, as the ocular surface epithelia normally express low levels of MMP-9.[28] An aggregate of studies measuring MMP-9 levels by Sambursky and O'Brian shows that normal human tears contain 3 to 41 ng/mL of MMP-9 or a mean of 13.2 ng/mL.[29] Typical diagnostic tests determine cutoff levels for a positive result by taking the average multiplied by 2–3 times the standard deviation. Using this criterion and in the context of the results of studies on normal MMP-9 levels, 40 ng/mL is a reasonable cutoff level for the InflammaDry test.

MMP-9 also likely has a pathological role in DE. DE patients (defined by an ocular surface disease index (**OSDI**) score >20, and one or more of the following: tear film breakup time (**TFBUT**)≤7 seconds, corneal staining, or Schirmer I score <10 mm) had higher mean MMP-9 activity levels than 19 asymptomatic control subjects, with a positive correlation noted between MMP-9 activity levels and symptom severity.[17] Furthermore, patients with meibomian gland disease (**MGD**; n=13) and Sjogren syndrome (n=9) have also been found to have increased tear fluid MMP-9 activity levels compared to controls without DE (n=17).[30] From a therapeutic perspective, corticosteroids and tetracycline derivatives, agents known to reduce MMP-9 levels,[31] have been shown to reduce the severity of DE symptoms and/or signs in mice and humans.[26,32–34]

Interestingly, on pilot testing, it has been reported that not all patients with DE symptoms test positive for MMP-9 via InflammaDry testing.[9] However, it is not known whether patients with DE symptoms and negative InflammaDry test results represent a different DE population from those with a positive test. To clarify this, in this study we investigate differences in the DE profile of patients who test positive versus negative for MMP-9 on the ocular surface via InflammaDry.

II. Materials and Methods

A. Study Population

Patients with DE symptoms (dry eye questionnaire 5 score ≥6) were prospectively recruited from the Miami Veterans Affairs (**VA**) Healthcare System eye clinic between May 2014 and July 2015 and underwent a complete ocular surface examination. Patients were excluded from participation if they wore contact lenses; had undergone refractive surgery; were undergoing cancer therapy; used ocular medications such as steroids with the exception of artificial tears; had HIV, sarcoidosis, graft-versus host disease, or a collagen vascular disease; had an active external ocular process; had had cataract surgery within the last 6 months; or had previously undergone any glaucoma or retinal surgery. The Miami VA Institution Review Board approval was obtained to allow the prospective evaluation of patients. The study was conducted in accordance to the principles of the Declaration of Helsinki.

B. Data Collected

For each individual, demographic information, past ocular and medical history, and medication information were collected. Subjects also filled out two standardized questionnaires regarding posttraumatic stress disorder (**PTSD**) checklist – Military Version (PCL-M [score 17–85]) and depression (patient health questionnaire 9 (PHQ9 [score 0–27])).

1. Dry Eye Symptoms and Ocular Pain—Subjects filled out standardized questionnaires regarding ocular complaints, including:

1. DE questionnaire 5 (DEQ5 [scale 0–22])[35];
2. OSDI (scale 0–100);
3. Numerical rating scale (**NRS**) for ocular pain. (Subjects were asked to rate the intensity of their average eye pain over a 1-week recall period using a numerical rating scale anchored at “0” for “no pain sensation” and at “10” for “the most intense eye pain imaginable”);
4. Neuropathic ocular pain features, including dysesthesias (eye pain characterized as burning) and sensitivity to wind and/or light (is your eye pain provoked or increased by wind or light), all rated on a scale of 0–10.

2. Ocular Surface Evaluation—All subjects underwent tear film assessment that included, in the order performed:

1. Tear osmolarity (TearLAB, San Diego, CA) (once in each eye);
2. TFBUT (5 μL fluorescein placed, 3 measurements taken in each eye and averaged);
3. Corneal staining (National Eye Institute (NEI) scale, 5 areas of cornea assessed; score 0–3 in each, total 15; significant staining defined as score ≥ 2);
4. Schirmer strips with anesthesia, and;

5. Meibomian gland assessment. Eyelid vascularity was graded on a scale of 0 to 3 (0 none; 1 mild engorgement; 2 moderate engorgement; 3 severe engorgement) and meibum quality on a scale of 0 to 4 (0 = clear; 1 = cloudy; 2 = granular; 3 = toothpaste; 4 = no meibum extracted).

3. Determination of Eyelid Laxity—The presence of lower eyelid laxity was determined by the snap-back test. A grade of 0 indicated laxity within normal limits, and a grade of 1 indicated a delay of 2–5 seconds for the lower lid to return to its native state. A grade of 2 indicated persistent separation necessitating a blink to return to the normal state. Upper eyelid laxity was determined by pulling on the forehead skin and evaluating movement of the upper eyelids. A grade of 0 indicated laxity within normal limits. A grade of 1 indicated rotation of the upper eyelid up to 50% or an elevation by 6–10 mm; a grade of 2 indicated rotation between 50–100% or an elevation greater than 10 mm.[36]

4. Determination of Conjunctivochalasis—Conjunctivochalasis was graded as absent or present in each area of the lower eyelid (temporal, central, nasal) based on the obliteration of the tear film by conjunctivae in the region of interest.

5. Determination of Corneal Sensitivity—Mechanical detection and pain thresholds of the central cornea were assessed with a modified Belmonte non-contact aesthesiometer, which was developed based on the original Belmonte instrument.[37] The tip of the aesthesiometer (0.5 mm in diameter) was placed perpendicular to and 4 mm from the surface of the cornea of the right eye. Stimulation consisted of pulses of air at room temperature (approximately 23 to 26°C)[38] applied to the corneal surface. The method of limits, using ascending series only, was used to measure threshold.

For corneal detection threshold measurements, subjects were presented with a stimulus immediately following a blink and asked to indicate by pressing a button whether they felt the stimulus. The initial flow rate was set at a level below threshold (50 mL/min for most individuals) and increased by 10 mL/min (with 15 second intervals between stimuli) until the subject stated that they felt the stimulus or the maximum allowable flow rate (400 mL/min) was reached. Two ascending series were conducted, and detection threshold was defined as the arithmetic mean of the value at which the subject pressed the button across the two series. To estimate ocular pain threshold, the flow rate was further increased beyond the detection threshold in 10 mL/min increments until the subject reported the stimulus as painful, or the maximum allowable flow rate (400 mL/min) was reached. Two ascending series were conducted in this way, and pain threshold was defined as a mean of the two series. All threshold measures were performed during the morning hours by the same operator, with room temperature varying between 73°F and 83°F, and humidity ranging between 38% and 53%.

6. InflammaDry Testing—All subjects underwent InflammaDry testing (RPS, Sarasota FL) once in each eye. In brief, a tear sample was collected prior to instillation of anesthetic or fluorescein by exposing the lower palpebral conjunctiva and gently dabbing the fleece of the sample collector temporally to nasally approximately 6–8 times, allowing the patient to blink between dabs to ensure saturation. The sampling fleece glistened or turned pink when

an adequate sample was collected and was then snapped into the test cassette prior to immersion of the absorbent tip into the buffering solution for approximately 20 seconds or until a purple wave appeared in the cassette window. The cap was then replaced over the absorbent tip, and the applicator was laid flat for 10 minutes before interpretation of test results. Individuals were instructed not to use any eyedrops for at least 2 hours prior to InflammaDry testing.

C. Main Outcome Measure

The main outcome measure was a comparison of symptoms and signs of DE in subjects who tested positive versus negative for MMP-9 by InflammaDry testing.

D. Statistical Analysis

Data were entered into a standardized database. Statistical analyses were performed using the SPSS 22.0 (SPSS Inc, Chicago, IL) statistical package. Descriptive statistics were used to summarize patient demographic and clinical information. Chi-square, Fisher exact, t-test, and Mann-Whitney U analyses were used, as appropriate, to evaluate for differences in symptoms and signs of DE between groups (MMP positive versus negative).

III. Results

A. Study Population

A total of 128 individuals participated in the study (mean age of 62 ± 10 years, 90% men). Demographic data of the study population, stratified by MMP-9 positivity, are presented in Table 1. Of the 128 subjects, all of whom had DE symptoms, 50 (39%) were positive for MMP-9 in at least one eye (19 in one eye only; 31 in both eyes). MMP-9-positive subjects had a higher mean age, but this demographic feature failed to reach statistical significance. MMP-9-positive subjects were also more likely to be non-Hispanic (16% vs 33%, P=.03), more frequently carried a diagnosis of hypertension (84% vs 68%, P=.04), and more frequently reported multivitamin use (58% vs 36%, P=.01). No other demographic characteristics, comorbidities, or systemic medications were significantly different between MMP-9 positive versus negative subjects. Though nonsteroidal anti-inflammatory drugs (**NSAIDs**), fish oil supplements, and tetracycline derivatives are known to reduce tear levels of MMP-9, no statistically significant difference in MMP-9 status was noted between those who did and did not take these medications.

B. Comparisons between MMP Status and Dry Eye Symptoms

Overall there were no differences in DE symptoms by MMP positivity in either eye. This included traditionally assessed symptoms via DE questionnaires (DEQ5, OSDI) and questions focusing specifically on ocular pain (Table 2). In a subgroup analysis, subjects in whom InflammaDry testing was positive in both eyes (n=31, 24% of total population) had a degree of DE symptoms similar to that of patients in whom InflammaDry testing was positive in only one eye (n=19, 15% of total population [mean DEQ5 12.6, SD 4.0 versus 13.9, SD 3.6, P=.25; mean OSDI 33, SD 23, versus 45, SD 27, P=.11]). Tear osmolarity and corneal staining were slightly elevated in subjects with bilateral InflammaDry positivity compared to those in whom the test was positive in one eye only. These differences,

however, were not significant (311, SD 19.5 versus 309, SD 16.9, P=.71; 2.1, SD 2.5 versus 1.3, SD 2.2, P=.27, respectively).

C. Comparisons between MMP Status and Dry Eye Signs and Anatomical Abnormalities

Subjects in whom InflammaDry testing was positive in either eye had a similar ocular surface profile (DE signs and anatomic abnormalities) compared to those in whom InflammaDry testing was negative in both eyes (Table 3). Considering the eyes separately, subjects in whom MMP 9 was positive in the left eye more frequently had abnormal meibum quality in that eye compared to those with a negative MMP 9. In the right eye, all signs and anatomic abnormalities, including meibum quality, were similar between the two groups (data not shown). Additionally, when symptomatic subjects with signs of DE (either staining >2, TFBUT < 8, or Schirmer < 8, n=69) were compared to symptomatic subjects without signs of DE (staining ≤ 2, TFBUT ≥ 8, and Schirmer ≥ 8, n=57), there was no difference in the frequency of MMP-9 positivity (any eye) between the groups (n=26, 38% vs n=23, 40%, P=.82).

IV. Discussion

Our study underscores the fact that DE symptoms develop as a result of multifactorial etiologies that at any given timepoint may or may not be associated with clinically significant inflammation. In our population of individuals with DE symptoms, almost half tested positive for MMP-9 (via InflammaDry) in either eye, and no differences in the DE profile were noted by MMP-9 status. Our results confirm the findings of others that not all patients with DE symptoms test positive for MMP-9[15] and may explain why not all patients with DE symptoms respond to anti-inflammatory therapies.

There are several explanations as to why clinically measured DE parameters did not differ by MMP status in our study.

1. Changes in the tear film are dynamic, and intermittent episodic exposures to environmental stressors like windy conditions, low humidity, or excessive computer work may lead to transient signs which may not become apparent clinically.[9]
2. Specific tear abnormalities may not directly result in inflammation. For example, an in-vitro study of osmolarity found that concentrations similar to that measured on the ocular surface (~ 300 mOsm/L) did not trigger an inflammatory response. In contrast, an inflammatory response was noted in the setting of higher osmolarity concentrations (400 to 600 mOsm/L).[39]
3. The presence of corneal somatosensory dysfunction may lead to DE symptoms that are dissociated from peripheral ocular surface pathology. Many patients with DE symptoms report features of neuropathic ocular pain, including spontaneous pain, dysesthesias, hyperalgesia, and allodynia.[40,41] Initial ocular surface damage or inflammation may produce peripheral and/or central sensitization, resulting in hypersensitivity and ongoing DE symptoms even once the source of damage and/or inflammation has resolved.[42]

4. Other ocular surface signs not measured in our study may have related more closely to MMP-9 positivity. For example, chronic inflammation of the ocular surface has also been associated with progressive goblet cell loss, a factor not examined in our study.[43]

Regarding treatment response, many studies have evaluated anti-inflammatory therapies in DE (corticosteroids, cyclosporine).[12–14] While these studies had different inclusion criteria and different metrics for treatment success, the fact remains that not all patients with DE respond to anti-inflammatory therapies. As MMP-9 is intimately associated with the other mediators of the inflammatory pathway on the ocular surface,[24–27] MMP-9 is a good marker to detect the presence of inflammation in general. Thus, the InflammaDry test may have the potential to separate patients based on underlying DE etiology (inflammatory versus neuropathic). However, it is still not known whether MMP-9 positivity can predict whether a patient will have a favorable response to anti-inflammatory therapy. If this is found to be the case, InflammaDry testing will allow for physicians to individualize DE therapy by tailoring treatment to a patient's underlying disease pathology. Unfortunately, our cross-sectional methodology does not allow comment on the predictive utility of InflammaDry on treatment success.

The following study limitations must be considered in interpreting our findings. Our subjects were recruited from the Miami VA Medical Center and as such represent a unique patient population consisting of older, mostly male US veterans. In addition, we recruited patients with mild or greater symptoms of DE. Thus, we cannot comment on MMP-9 positivity in those without DE symptoms but with ocular surface signs. Furthermore, the included patients had a wide range of ocular surface findings (none to severe changes in different aspects of DE pathophysiology [decreased production, increased evaporation, ocular surface disruption]). In addition, we collected specific DE metrics at only one point in time and are thus not able to comment on variability in MMP-9 testing in an individual over time. With a larger sample size, some differences between groups may have reached statistical significance. However, clinically there did not appear to be significant differences in most parameters between the groups. Finally, some potential confounders of MMP-9, such as cancer therapeutics and systemic corticosteroids, were not specifically assessed. However, we believe that the frequency of such drug use was very low as our population was generally healthy.

Despite its limitations, our study is the first to investigate differences between populations with DE symptoms by InflammaDry testing. This study reinforces the concept that DE is a heterogeneous condition and that patients with DE symptoms may fall into different categories, including inflammatory, non-inflammatory, and/or neuropathic. We found that clinical tests of osmolarity, Schirmer test values, TFBUT, and MGD could not predict patients with clinically significant inflammation. This suggests that clinical examination alone may not be sufficient to guide therapeutic decision-making or to monitor the impact of treatment. It is not yet known, however, whether a differential effect of anti-inflammatory therapies will be seen in patients with DE symptoms based on initial MMP-9 status. If found, these results could have a profound effect on influencing future treatment recommendations and lead to significant managed care implications.

V. Conclusion

In our population, there was no difference in the DE profile by both symptoms and signs between those testing positive versus negative for MMP-9 on the ocular surface. This suggests that clinical exam alone cannot predict patients with clinically significant inflammation.

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Table 1

Demographics of the study population.

	MMP-9 positive* (n=50)	MMP 9 negative (n=78)	P-value
Demographics			
Age, mean (SD)	64 (10)	61 (10)	.07
Gender, n (%) male	46 (92%)	69 (89%)	.52
Race, n (%) white	24 (48%)	40 (51%)	.72
Ethnicity, n (%) Hispanic	**8 (16%)**	**26 (33%)**	**.03**
Co-Morbidities			
Arthritis, n (%)	25 (50%)	44 (57%)	.43
BPH, n (%)	8 (16%)	13 (17%)	.92
Diabetes mellitus, n (%)	15 (31%)	22 (28%)	.77
Hypertension, n (%)	**42 (84%)**	**53 (68%)**	**.04**
Hypercholesterolemia, n (%)	31 (62%)	48 (62%)	.96
Sleep apnea, n (%)	9 (18%)	16 (21%)	.73
Medications			
Anti-anxiolytic, n (%)	20 (40%)	41 (53%)	.17
Antidepressant, n (%)	20 (40%)	40 (51%)	.21
Anti-histamine, n (%)	8 (16%)	18 (23%)	.33
Analgesics, n (%)	36 (74%)	56 (72%)	.84
NSAID, n (%)	22 (44%)	30 (39%)	.53
Fish oil supplements, n (%)	8 (16%)	7 (9%)	.23
Multivitamin, n (%)	**29 (58%)**	**28 (36%)**	**.01**
Tetracycline derivative†, n (%)	3 (6%)	2 (3%)	.38
Mental health indices			
PTSD questionnaire, mean (SD)	42 (21)	43 (20)	.82
Depression questionnaire (PHQ-9), mean (SD)	11.5 (8.4)	10.0 (7.7)	.28

*Matrix metallopeptidase positive in either eye; SD=standard deviation; n=number in group; PTSD=post traumatic stress disorder; PHQ=patient health questionnaire; BPH=benign prostatic hyperplasia

†doxycycline, tetracycline, minocycline

Table 2

Comparison of dry eye and ocular pain symptoms in MMP-9 positive versus negative dry eye patients.

	MMP-9 positive*	MMP 9 negative	P-value
Dry eye symptoms			
DEQ5, mean (SD)	13 (3.8)	13 (3.5)	.86
OSDI, mean (SD)	38 (25)	40 (25)	.72
Severity of ocular pain			
Ocular pain now (0–10), mean (SD)	3.5 (2.5)	2.9 (2.5)	.22
Ocular pain avg. over 1 week (0–10), mean (SD)	3.7 (2.6)	3.7 (2.4)	.99
Features of neuropathic ocular pain			
Hot-burning, range (0–10) mean (SD)	3.3 (3.2)	3.3 (3.1)	.93
Hot-burning ocular pain, yes, n (%)	35 (70%)	57 (73%)	.71
Sensitivity to wind, range (0–10) mean (SD)	2.8 (3.3)	3.3 (3.3)	.42
Sensitivity to wind, yes, n (%)	29 (58%)	54 (69%)	.19
Sensitivity to light, range (0–10) mean (SD)	3.3 (3.2)	3.6 (3.4)	.65
Sensitivity to light, yes, n (%)	37 (74%)	58 (74%)	.96

*Matrix metallopeptidase positive in either eye; DEQ5=dry eye questionnaire 5; OSDI=ocular surface disease index; SD=standard deviation; avg=average

Table 3

Comparison of dry eye signs and anatomical abnormalities in MMP-9 positive versus negative dry eye patients

	MMP-9 positive*	MMP 9 negative	P-value
Osmolarity†, mOsm/L, mean SD	310 (18)	309 (15)	.61
Tear film breakup time†, second, mean SD	10 (4)	9 (4)	.29
Corneal staining†, ≥2, % (n)	15 (31%)	22 (28%)	.77
Schirmer score†, mm, mean SD	13.6 (6.4)	13.4 (6.9)	.86
Eyelid vascularity†, ≥, % (n)	6 (12%)	9 (12%)	.90
Meibum quality†, ≥2, % (n)	30 (61%)	40 (51%)	.27
Conjunctivochalasis† (any), % (n)	42 (86%)	68 (87%)	.81
Conjunctivochalasis † (nasal), % (n)	20 (41%)	38 (49%)	.38
Eyelid laxity† (any), % (n)	32 (65%)	53 (68%)	.76
Eyelid laxity† (lower eyelid), % (n)	24 (49%)	35 (45%)	.65
Eyelid laxity† (upper eyelid), % (n)	27 (55%)	45 (58%)	.77
Detection thresholds by modified Belmonte aesthesiometer right eye, mL/min, mean (SD)	90 (36)	89 (44)	.90
Pain thresholds by modified Belmonte aesthesiometer right eye, mL/min, mean (SD)	215 (94)	211 (107)	.84

*Matrix metallopeptidase positive in either eye;

†= value in more severely affected eye