PRESUMED HYPOSECRETORY/HYPEREVAPORATIVE KCS: TEAR CHARACTERISTICS

BY ***James P. McCulley MD,**** *Ward E. Shine PhD, Joel Aronowicz MD, Deniz Oral MD,* AND *Jose Vargas MD*

ABSTRACT

Purpose: To characterize patients with ocular surface drying and a diagnosis of keratoconjunctivitis sicca (KCS).

Methods: Patients with a prior diagnosis of KCS and symptoms of dryness or foreign-body sensation who also had vital staining of the interpalpebral fissure ocular surface in the absence of lid and ocular surface inflammation were entered into the study along with normal controls. Patients were segregated into those with "classic" KCS, who did not have concomitant meibomian gland dysfunction (MGD), and those with KCS and MGD. The latter had slit-lamp evidence of difficult-to-express or turbid meibomian secretions upon expression. Patients and normal controls were evaluated for tear volume, flow, and turnover using fluorophotometry; meibomian gland dropout by meibography; evaporation by evaporometry; and tear production by the Schirmer 1 test.

Results: All patients with KCS had decreased tear volume, flow, and Schirmer 1 values as well as increased meibomian gland dropout. None of the patient groups were found to have increased tear evaporation compared with normals or other disease subgroups. No correlation between degree of meibomian gland dropout and evaporation was found. The degree of total vital staining or presence of corneal staining correlated with a more severe aqueous deficiency.

Conclusions: Patients with ocular surface drying in the absence of inflammation have decreased tear volume, flow, and Schirmer 1 values as well as increased meibomian gland dropout. The role of meibomian gland dropout or slit-lamp MGD in disease is unclear and in our study specifically did not correlate with increased tear evaporation.

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INTRODUCTION

Keratoconjunctivitis sicca (KCS) is a common disease with numerous manifestations.[1] In recent years, the concept of two types of KCS has emerged: (1) dry eye due to deficient aqueous tear production (hyposecretory) and (2) evaporative dry eye (hyperevaporative).[2] Dry eye due to deficient aqueous tear production is primarily caused by decreased tear production by the main and accessory lacrimal glands. Evaporative dry eye is thought to be the result of a defective tear film lipid layer—either insufficient lipids or abnormal composition resulting in excessive evaporation from the tear film. These lipids are produced by the meibomian glands of the eyelids. KCS occurs in 25% to 50% of patients with blepharitis of all types.[2] A lipid abnormality (ie, decreased phosphatidylethanolamine and sphingomyelin) in the blepharitis patients with associated KCS has been reported.[3] Noninflammatory meibomian gland dysfunction (MGD) has been reported to be associated with evaporative dry eye, which in turn can be associated (up to 40%) with aqueous tear–deficient dry eye (ie, combined mechanism).[2] However, it is not clear to date that MGD represents a form of meibomian gland disease or that it has a mechanistic role in expression of aqueous tear–deficient dry eye disease.

There are numerous methods to characterize each dry eye type. Tear volume, turnover, and flow can be characterized by fluorescein dilution or clearance rate from the aqueous layer. Tear flow can also be determined by the Schirmer test.[1,4] Tear evaporation can be determined by use of evaporometry.[5,6] Meibomian gland dysfunction has been diagnosed and characterized either by difficulty of expression of turbid meibomian gland secretions as observed at the slit lamp or by meibomian gland dropout as determined by transillumination meibography.[5] Through a survey of the literature, we noted that a thorough clinical evaluation including vital

From the Department of Ophthalmology, University of Texas Southwestern Medical Center at Dallas. Supported by grant EY 12430 from the National Institutes of Health and by Research to Prevent Blindness, New York, NY.
*Presenter.
Bold type indicates AOS member.

staining for dry eye signs, together with evaluations of tear function including meibography, was lacking in patients with noninflamed ocular surface drying. We therefore undertook to thoroughly characterize these patients with dry eyes by using all available clinical approaches and tests.

METHODS

SELECTION OF PATIENTS

The study protocol and data accumulation methods have been approved by the university's institutional review board. The criteria for patients entering the study were a prior diagnosis of dry eyes with symptoms of foreign-body sensation or dryness. On clinical examination the patients had uninflamed lids and ocular surfaces, interpalpebral fissure vital staining, and an apparent decrease in tear meniscus. Patients who had normal-appearing meibomian secretions (ie, easily expressed and clear) were considered to have hyposecretion, or pure aqueous tear deficiency. Patients who had either difficult-to-express meibomian secretions or turbid secretions were considered to have MGD as a contributing factor. The first group of patients, with normal-appearing meibomian secretions, were categorized as having "classic" KCS; patients who had associated meibomian secretion changes at the slit lamp were categorized as having KCS with MGD. Age- and sex-matched patients with no symptoms or signs of ocular disease served as normal controls.

METHODS/INSTRUMENTS USED

Vital Staining: Lissamine Green

Vital staining was performed at the entry examination before instrument evaluations. Staining scores were based on the van Bjisterveld system.[2] Scored points ranged from 1 to 9. Patients were grouped into three subgroups according to their staining score: group 1, 1 to 3 points; group 2, 4 to 6 points; and group 3, 7 to 9 points. Patients were also subgrouped on the basis of the presence or absence of corneal staining.

Tear Volume, Flow, and Turnover

Determination of background fluorescence was done prior to instillation of 0.5 µL of 0.5% sodium fluorescein onto the ocular surface, where it was mixed by blinking (Fluorotron Master, OcuMetrics, Mountain View, Calif). Repeated measurements to determine tear fluorescence were done after the first minute and every 3 minutes thereafter until completion at 19 minutes.[7] This data was used for calculating tear flow, tear volume, and tear turnover as previously reported by Mathers[4,8] and others.[9]

Tear Surface Evaporation

An evaporometer (Oxdata, Portland, Ore) utilized a pump to direct air through a drying tube into an eye goggle.[10] The goggle, placed firmly over the eye, contained a water vapor detector and a temperature monitor. The pumped air passed into the goggle reduced the humidity to 15%, at which time the pump was turned off. The increase in humidity from evaporating tears was measured and stored in a computer. The process was done first with the lids closed and then with them open; the difference was calculated to be the tear evaporation rate.[4] The area of the interpalpebral ocular surface was used to calculate evaporation per unit area. This area was determined in two ways: First, the open-eye vertical interpalpebral aperture (PA) was measured; the area was then calculated using a published formula.[10,11] Alternately, the area was captured with the use of a digital camera (TA) and calculated directly with the aid of PhotoShop software (ADOBE 6.0.1.2001, ADOBE Systems, San Jose, Calif). In addition to these two methods of determining evaporation rate per unit area, evaporation was calculated as a percentage of available tear volume and as a percentage of tear turnover.

Meibomian Gland Dropout: Meibography

A frame grabber was matched to a Hitachi, KP-F2A progressive scan, near infrared camera that was mounted to a slit lamp. Imaging Studio software allowed the capture of images and storage in a computer. With the aid of a small hand-held lamp (muscle light) with a short fiber optic cable and tip to disperse a small band of light, the inverted lower eyelid was transilluminated and photographed. The digital picture of the meibomian glands was further processed, and the degree of dropout of individual meibomian glands was noted. Dropout was calculated based on seven central glands of each lower lid. The seven glands were graded from 0 (no dropout) to 4 (complete dropout). The score of each of the seven lower-lid glands was then summed and taken as a percentage of 28, the maximum possible.

Patients were also stratified by degree of dropout, either less than or more than 50% dropout, or less than or more than 20% dropout.

Tear production: Schirmer 1 Test

A Schirmer strip was placed over the lower-lid margin at the junction of the middle and temporal third without use of anesthetic. Patients were instructed to gently close their lids and not move their eyes. After 5 minutes, the strip was removed and tear wetting distance was measured.

Statistical analyses

Analyses (Statistica for Windows, StatSoft, Tulsa, Okla) included analysis of variance (one-way ANOVA), *t* test for independent samples, and correlations (Pearson *r* coefficient).

TABLE I: ALL KCS PATIENTS

TABLE IA. ALL KCS PATIENTS

		VITAL STAINING	TURNOVER (%/MIN)	VOLUME (μL)	FLOW (μL/MIN)	SCHIRMER 1 (MM)	DROPOUT (%)	EVAP PA (G/CM²/S) ×10⁻⁷	EVAP TA (G/CM²/S) ×10⁻⁷	% EVAP (%/MIN)	THICKNESS (μM)
n = 35 eyes	**Mean:**	**4.61***	**13.5**	**2.69**	**0.36**	**14.6***	**52.8***	**7.03**	**9.36**	**4.10**	**16.79**
	SD:	1.97	9.3	2.72	0.48	11.0	30.6	4.03	5.77	3.19	15.61

TABLE IB. NORMAL CONTROLS

		VITAL STAINING	TURNOVER (%/MIN)	VOLUME (μL)	FLOW (μL/MIN)	SCHIRMER 1 (MM)	DROPOUT (%)	EVAP PA (G/CM²/S) ×10-7	EVAP TA (G/CM²/S) ×10⁻⁷	% EVAP (%/MIN)	THICKNESS (μM)
n = 22 eyes	**Mean:**	**0.00**	**16.3**	**2.06**	**0.31**	**24.7**	**15.1**	**7.29**	**10.92**	**7.43**	**12.31**
	SD:	0.00	7.3	1.54	0.24	7.0	10.8	2.19	4.28	5.15	8.80

Evap TA = Evaporation true area of the ocular surface.
Evap PA = Evaporation ocular surface area calculated from measured palpebral aperture.
% Evap = (volume evaporated per second) / (tear volume) × 100%.

*Significantly different from normal controls ($P<.05$).

TABLE II: ALL KCS PATIENTS STRATIFIED BY VITAL STAINING CHARACTERISTICS

TABLE IIA. ALL KCS PATIENTS IN LGS GROUP 1

		VITAL STAINING	TURNOVER (%/MIN)	VOLUME (μL)	FLOW (μL/MIN)	SCHIRMER 1 (MM)	DROPOUT (%)	EVAP PA (G/CM²/S) ×10⁻⁷	EVAP TA (G/CM²/S) ×10⁻⁷	% EVAP (%/MIN)	THICKNESS (μM)
n = 9 eyes	**Mean:**	**2.33***	**13.1**	**4.05**	**0.38**	**15.6**	**57.4***	**5.45**	**7.96**	**3.81**	**22.33**
	SD:	0.87	10.3	4.70	0.38	10.8	34.5	2.43	3.70	2.15	23.87

TABLE IIB. ALL KCS PATIENTS IN LGS GROUP 2

		VITAL STAINING	TURNOVER (%/MIN)	VOLUME (μL)	FLOW (μL/MIN)	SCHIRMER 1 (MM)	DROPOUT (%)	EVAP PA (G/CM²/S) ×10-7	EVAP TA (G/CM²/S) ×10⁻⁷	% EVAP (%/MIN)	THICKNESS (μM)
n = 18 eyes	**Mean:**	**4.47*†**	**14.7**	**2.73**	**0.46**	**15.9**	**59.5***	**8.24**	**10.29**	**3.52**	**15.75**
	SD:	0.78	10.5	1.79	0.59	9.8	28.4	4.12	6.98	2.35	10.69

TABLE IIC. ALL KCS PATIENTS IN LGS GROUP 3

		VITAL STAINING	TURNOVER (%/MIN)	VOLUME (μL)	FLOW (μL/MIN)	SCHIRMER 1 (MM)	DROPOUT (%)	EVAP PA (G/CM²/S) ×10-7	EVAP TA (G/CM²/S) ×10⁻⁷	% EVAP (%/MIN)	THICKNESS (μM)
n = 8 eyes	**Mean:**	**7.50*†‡**	**11.1**	**1.27**	**0.12**	**11.1***	**29.8**	**5.52**	**9.42**	**6.11**	**9.04**
	SD:	0.53	5.4	0.68	0.04	13.9	22.8	3.28	5.96	6.10	4.39

TABLE IID. ALL KCS PATIENTS WITHOUT CORNEAL STAINING

		VITAL STAINING	TURNOVER (%/MIN)	VOLUME (μL)	FLOW (μL/MIN)	SCHIRMER 1 (MM)	DROPOUT (%)	EVAP PA (G/CM²/S) ×10-7	EVAP TA (G/CM²/S) ×10⁻⁷	% EVAP (%/MIN)	THICKNESS (μM)
n = 18 eyes	**Mean:**	**3.39***	**13.6**	**3.24**	**0.40**	**20.2**	**55.9***	**7.56**	**10.36**	**3.33**	**19.59**
	SD:	1.14	11.9	3.31	0.53	8.5	28.3	3.86	6.12	1.76	17.71

TABLE IIE. ALL KCS PATIENTS WITH CORNEAL STAINING

		VITAL STAINING	TURNOVER (%/MIN)	VOLUME (μL)	FLOW (μL/MIN)	SCHIRMER 1 (MM)	DROPOUT (%)	EVAP PA (G/CM²/S) ×10-7	EVAP TA (G/CM²/S) ×10⁻⁷	% EVAP (%/MIN)	THICKNESS (μM)
n = 17 eyes	**Mean:**	**5.91*§**	**13.4**	**2.08**	**0.32**	**9.41*§**	**48.9***	**6.20**	**7.90**	**5.19**	**12.31**
	SD:	1.84	5.6	1.76	0.43	10.6	34.0	3.61	5.15	4.45	10.86

LGS, lissamine green staining.
*Significantly different from normal controls ($P<.05$).
†Significantly different from LGS Group 1 ($P<.05$).
‡Significantly different from LGS Group 2 ($P<.05$).
§Significantly different from patients without corneal staining ($P<.05$).

TABLE III: ALL KCS PATIENTS STRATIFIED BY DEGREE OF MEIBOMIAN GLAND DROPOUT

TABLE IIIA. ALL KCS PATIENTS WITH LESS THAN 50% DROPOUT

		VITAL STAINING	TURNOVER (%/MIN)	VOLUME (µL)	FLOW (µL/MIN)	SCHIRMER 1 (MM)	DROPOUT (%)	EVAP PA (G/CM²/S) ×10⁻⁷	EVAP TA (G/CM²/S) ×10⁻⁷	% EVAP (%/MIN)	THICKNESS (µM)
n = 13 eyes	**Mean:**	**4.92***	**15.2**	**3.08**	**0.32**	**20.6**	**24.6**	**7.31**	**9.65**	**4.95**	**20.76**
	SD:	2.25	9.7	3.83	0.27	12.3	15.9	3.78	5.00	4.98	23.52

TABLE IIIB. ALL KCS PATIENTS WITH GREATER THAN 50% DROPOUT

		VITAL STAINING	TURNOVER (%/MIN)	VOLUME (µL)	FLOW (µL/MIN)	SCHIRMER 1 (MM)	DROPOUT (%)	EVAP PA (G/CM²/S) ×10-7	EVAP TA (G/CM²/S) ×10⁻⁷	% EVAP (%/MIN)	THICKNESS (µM)
n = 16 eyes	**Mean:**	**4.06***	**13.8**	**2.33**	**0.43**	**10.3*†**	**75.7*†**	**7.15**	**9.88**	**3.48**	**15.87**
	SD:	1.69	10.4	1.90	0.67	8.8	17.4	4.87	6.95	1.71	10.63

TABLE IIIC. ALL KCS PATIENTS WITH LESS THAN 20% DROPOUT

		VITAL STAINING	TURNOVER (%/MIN)	VOLUME (µL)	FLOW (µL/MIN)	SCHIRMER 1 (MM)	DROPOUT (%)	EVAP PA (G/CM²/S) ×10-7	EVAP TA (G/CM²/S) ×10⁻⁷	% EVAP (%/MIN)	THICKNESS (µM)
n = 7 eyes	**Mean:**	**5.57***	**12.3**	**4.11**	**0.33**	**16.9**	**11.0**	**7.15**	**11.61**	**3.87**	**28.74**
	SD:	2.64	5.1	5.14	0.32	13.7	4.7	3.59	5.10	3.91	30.05

TABLE IIID. ALL KCS PATIENTS WITH GREATER THAN 20% DROPOUT

		VITAL STAINING	TURNOVER (%/MIN)	VOLUME (µL)	FLOW (µL/MIN)	SCHIRMER 1 (MM)	DROPOUT (%)	EVAP PA (G/CM²/S) ×10-7	EVAP TA (G/CM²/S) ×10⁻⁷	% EVAP (%/MIN)	THICKNESS (µM)
n = 22 eyes	Mean:	4.09*	15.1	2.21	0.40	14.7*	66.1*‡	7.25	9.29	4.21	14.68
	SD:	1.63	11.1	1.63	0.58	11.2	21.9	4.63	6.43	3.54	9.79

*Significantly different from normal controls ($P<.05$).
†Significantly different from less than 50% dropout group ($P<.05$).
‡Significantly different from less than 20% dropout group ($P<.05$).

TABLE IV: "CLASSIC" KCS PATIENTS STRATIFIED BY VITAL STAINING CHARACTERISTICS

TABLE IVA. ALL "CLASSIC" KCS PATIENTS

		VITAL STAINING	TURNOVER (%/MIN)	VOLUME (μL)	FLOW (μL/MIN)	SCHIRMER 1 (MM)	DROPOUT (%)	EVAP PA (G/CM²/S) ×10⁻⁷	EVAP TA (G/CM²/S) ×10⁻⁷	% EVAP (%/MIN)	THICKNESS (μM)
n = 14 eyes	**Mean:**	**5.14***	**12.8**	**1.89**	**0.25**	**12.9***	**45.8***	**7.58**	**11.67**	**5.52**	**13.50**
	SD:	2.80	8.1	1.95	0.32	11.9	29.2	4.38	6.13	4.24	11.77

TABLE IVB. "CLASSIC" KCS PATIENTS IN LGS GROUP 1

		VITAL STAINING	TURNOVER (%/MIN)	VOLUME (μL)	FLOW (μL/MIN)	SCHIRMER 1 (MM)	DROPOUT (%)	EVAP PA (G/CM²/S) ×10⁻⁷	EVAP TA (G/CM²/S) ×10⁻⁷	% EVAP (%/MIN)	THICKNESS (μM)
n = 6 eyes	**Mean:**	**2.33***	**14.8**	**2.84**	**0.43**	**14.2**	**58.3***	**8.01**	**12.65**	**4.46**	**17.38**
	SD:	1.51	10.9	2.71	0.44	10.3	27.1	3.16	6.23	1.97	14.01

TABLE IVC. "CLASSIC" KCS PATIENTS IN LGS GROUP 3

		VITAL STAINING	TURNOVER (%/MIN)	VOLUME (μL)	FLOW (μL/MIN)	SCHIRMER 1 (MM)	DROPOUT (%)	EVAP PA (G/CM²/S) ×10⁻⁷	EVAP TA (G/CM²/S) ×10⁻⁷	% EVAP (%/MIN)	THICKNESS (μM)
n = 8 eyes	**Mean:**	**7.25***	**11.3**	**1.18**	**0.11**	**11.9***	**33.3†**	**7.25**	**10.21**	**7.28**	**7.68**
	SD:	1.04	5.5	0.70	0.03	13.5	27.7	5.31	6.57	6.90	3.66

TABLE IVD. "CLASSIC" KCS PATIENTS WITHOUT CORNEAL STAINING

		VITAL STAINING	TURNOVER (%/MIN)	VOLUME (μL)	FLOW (μL/MIN)	SCHIRMER 1 (MM)	DROPOUT (%)	EVAP PA (G/CM²/S) ×10⁻⁷	EVAP TA (G/CM²/S) ×10⁻⁷	% EVAP (%/MIN)	THICKNESS (μM)
n = 5 eyes	**Mean:**	**2.20***	**15.8**	**3.15**	**0.49**	**16.0**	**53.6***	**8.57**	**13.62**	**4.19**	**19.16**
	SD:	1.64	11.9	2.90	0.46	10.3	27.3	3.19	6.44	2.16	14.88

TABLE IVE. "CLASSIC" KCS PATIENTS WITH CORNEAL STAINING

		VITAL STAINING	TURNOVER (%/MIN)	VOLUME (μL)	FLOW (μL/MIN)	SCHIRMER 1 (MM)	DROPOUT (%)	EVAP PA (G/CM²/S) ×10⁻⁷	EVAP TA (G/CM²/S) ×10⁻⁷	% EVAP (%/MIN)	THICKNESS (μM)
n = 9 eyes	**Mean:**	**6.78*‡**	**11.1**	**1.19**	**0.11**	**11.1***	**40.3***	**5.44**	**9.73**	**6.58**	**7.84**
	SD:	1.72	5.1	0.66	0.03	12.9	31.3	3.10	5.79	5.70	3.19

LGS, lissamine green staining.
*Significantly different from normal controls ($P<.05$).
†Significantly different from LGS Group 1 ($P<.05$).
‡Significantly different from patients without corneal staining ($P<.05$).

TABLE V: KCS WITH MGD STRATIFIED BY VITAL STAINING CHARACTERISTICS

TABLE VA. ALL KCS WITH MGD PATIENTS

		VITAL STAINING	TURNOVER (%/MIN)	VOLUME (μL)	FLOW (μL/MIN)	SCHIRMER 1 (MM)	DROPOUT (%)	EVAP PA (G/CM²/S) ×10⁻⁷	EVAP TA (G/CM²/S) ×10⁻⁷	% EVAP (%/MIN)	THICKNESS (μM)
n = 21 eyes	**Mean:**	**4.26***	**14.0**	**3.26**	**0.44**	**16.0**	**57.7**	**6.66**	**7.99**	**3.28**	**18.85**
	SD:	1.09	10.3	3.06	0.56	10.4	31.5	3.85	5.26	2.20	17.64

TABLE VB. KCS WITH MGD PATIENTS IN LGS GROUP 1

		VITAL STAINING	TURNOVER (%/MIN)	VOLUME (μL)	FLOW (μL/MIN)	SCHIRMER 1 (MM)	DROPOUT (%)	EVAP PA (G/CM²/S) ×10⁻⁷	EVAP TA (G/CM²/S) ×10⁻⁷	% EVAP (%/MIN)	THICKNESS (μM)
n = 4 eyes	**Mean:**	**3.00***	**9.0**	**5.61**	**0.21**	**14.5**	**62.5***	**3.71**	**5.20**	**2.72**	**30.89**
	SD:	0.00	6.6	7.36	0.08	13.5	50.3	2.39	3.87	2.35	37.37

TABLE VC. KCS WITH MGD PATIENTS IN LGS GROUP 2

		VITAL STAINING	TURNOVER (%/MIN)	VOLUME (μL)	FLOW (μL/MIN)	SCHIRMER 1 (MM)	DROPOUT (%)	EVAP PA (G/CM²/S) ×10⁻⁷	EVAP TA (G/CM²/S) ×10⁻⁷	% EVAP (%/MIN)	THICKNESS (μM)
n = 17 eyes	**Mean:**	**4.56*†**	**14.8**	**2.84**	**0.48**	**16.3***	**56.6***	**7.35**	**8.85**	**3.43**	**16.07**
	SD:	1.00	10.7	1.78	0.60	10.0	28.8	3.84	5.45	2.25	10.57

TABLE VD. KCS WITH MGD PATIENTS WITHOUT CORNEAL STAINING

		VITAL STAINING	TURNOVER (%/MIN)	VOLUME (μL)	FLOW (μL/MIN)	SCHIRMER 1 (MM)	DROPOUT (%)	EVAP PA (G/CM²/S) ×10⁻⁷	EVAP TA (G/CM²/S) ×10⁻⁷	% EVAP (%/MIN)	THICKNESS (μM)
n = 13 eyes	**Mean:**	**3.85***	**12.7**	**3.27**	**0.37**	**22.1**	**57.0***	**7.17**	**8.87**	**2.95**	**19.79**
	SD:	0.38	12.3	3.56	0.57	7.3	30.0	4.14	5.64	1.53	19.54

TABLE VE. KCS WITH MGD PATIENTS WITH CORNEAL STAINING

		VITAL STAINING	TURNOVER (%/MIN)	VOLUME (μL)	FLOW (μL/MIN)	SCHIRMER 1 (MM)	DROPOUT (%)	EVAP PA (G/CM²/S) ×10⁻⁷	EVAP TA (G/CM²/S) ×10⁻⁷	% EVAP (%/MIN)	THICKNESS (μM)
nn = 8 eyes	**Mean:**	**4.94*‡**	**16.3**	**3.23**	**0.58**	**7.5*‡**	**58.9***	**5.82**	**6.37**	**3.87**	**16.77**
	SD:	1.52	5.1	2.10	0.57	7.9	37.2	3.42	4.48	3.21	14.34

LGS, lissamine green staining.
*Significantly different from normal controls ($P<.05$).
†Significantly different from LGS Group 1 ($P<.05$).
‡Significantly different from patients without corneal staining ($P<.05$).

TABLE VI: COMPARISON OF TEAR FILM PARAMETERS OF NORMAL PATIENTS IN THE LITERATURE

SOURCE	VITAL STAINING	TURNOVER (%/MIN)	VOLUME (μL)	FLOW (μL/MIN)	SCHIRMER 1 (MM)	DROPOUT (%)	EVAP PA ($G/CM^2/S$) $\times 10^{-7}$	EVAP TA ($G/CM^2/S$) $\times 10^{-7}$	TEAR THICKNESS (μM)
Afonso et al[13]		1.89±0.7*			22.25±8.27				
Battat et al[14]					23.95±10.05				
Goto et al[6]							4.4±1.4		
Eter and Gobbels[9]			7.2	3.42					
Goebbels M[15]				1.2±0.5	18±5				
Jordan and Baum[16]	0†			0.9±0.2	17±12				
Macri et al[17]	0†				22.6±7.7	4.8±8.2			
Macri and Pflugfelder[18]					21.7±5.1	2.6±11.5			
Mathers[5]					13±10	0‡	14.8±6		
Mathers and Daley[8]		8.2±4.3	2.23±2.5	0.15±0.12	15.3±10		13±6		
Mathers et al[19]			2.74±2.06	0.19±0.19	16.6±10.12	1.12±3.41‡			
Mathers et al[4]		2.59±1.88	0.16±0.15			2.22±4.33‡			
Mishima et al[20]		18	6.6±2.3						
Rolando et al[30]							4.07±0.4		
Rolando and Refojo[11]							4.07±0.4		
Stolwijk et al[21]		15.5±5.1			11.9±7.8				
Tsubota and Yamada[22]							8.3±1.9§		
Webber et al[23]		14.9±5.6							
Creech et al[24]									10.4
Prydal et al[25]									34 - 45
Mishima[26]									7
King-Smith et al[27]									3
Our Study	**0.00**	**16.3±7.3**	**2.06±1.54**	**0.31±0.24**	**24.7±7.0**	**15.1±10.8**	**7.29±2.19**	**10.92±4.28**	**12.39±8.58**

*Logarithmic tear fluorescein concentration.
†NEI/Industry Workshop scale.
‡Dropout of glands per lower lid.
§Evaporation at 40% ambient humidity.

TABLE VII: COMPARISON OF TEAR FILM PARAMETERS OF ABNORMAL PATIENTS IN THE LITERATURE

TABLE VIIA. TEAR PARAMETERS OF "CLASSIC" KCS PATIENTS

SOURCE	VITAL STAINING	TURNOVER (%/MIN)	VOLUME (µL)	FLOW (µL/MIN)	SCHIRMER 1 (MM)	DROPOUT (%)	EVAP PA ($G/CM^2/S) \times 10^{-7}$	EVAP TA ($G/CM^2/S) \times 10^{-7}$	TEAR THICKNESS (µM)
Eter and Gobbels[9]			7	2.48					
Keping Xu et al[29]		3.43±1.14†			7.12±6.2§				
Macri et al[17]	0.6±0.9*				2.7±1.7	24.5±34.7			
Macri and Pflugfelder[18]	1.9±2.3*				1.8±1.7	33.7±33.3			
Rolando and Refojo[11]							8.7±2.65		
Rolando et al[30]							7.87±2.80		
Shimazaki et al[12]		4.4±0.49‡			6.51±0.64		12.5±5¶		
Shimazaki et al[28]					3.24±1.41				
Tsubota and Yamada[22]							9.5±5.6		
Our Study	**5.14±2.80**	**12.8±8.1**	**1.89±1.95**	**0.25±0.32**	**12.9±11.9**	**45.8±29.2**	**7.58±4.38**	**11.67±6.13**	**13.50±11.77**

*NEI/Industry Workshop scale.
†Tear function index.
‡Tear clearance test.
§Schirmer with anesthetic.
¶Tear evaporation rates were reported as 10-7 g/sec; 40 % ambient humidity.

TABLE VIIB. TEAR PARAMETERS OF KCS WITH MGD PATIENTS

SOURCE	VITAL STAINING	TURNOVER (%/MIN)	VOLUME (µL)	FLOW (µL/MIN)	SCHIRMER 1 (MM)	DROPOUT (%)	EVAP PA ($G/CM^2/S) \times 10^{-7}$	EVAP TA ($G/CM^2/S) \times 10^{-7}$	TEAR THICKNESS (µM)
Goto et al[6]						5.8±2.71			
Mathers[5]		0.3±0.1†		16±7	2.4±2.3‡	49.9±21			
Mathers et al[4]		2.3±1.51	0.12±0.1	6±6	0.27±0.82‡	23.9±7.47			
Macri et al[17]	2.5±3.0*			16.6±8.1	62.6±27.8				
Macri and Pflugfelder[18]	2.6±3.0*			17.0±7.5	57.3±31.1				
Shimazaki et at[12]		5.03±0.71		8.26±0.95					
Our Study	4.26±1.09	13.8±10.0	2.89±3.01	0.41±0.54	14.6±10.9	48.4±32.3	7.74±4.64	10.55±7.08	18.85±17.64

*NEI/Industry Workshop scale.
†Volume in mm diameter.
‡Dropout of glands per lower lid.

RESULTS

Eighteen patients (35 eyes) and 11 normal controls (22 eyes) were evaluated. A statistically significant decrease in Schirmer value and an increase in meibomian gland dropout were found in both KCS patient groups compared to normals. Tear volume and flow were markedly decreased in both KCS patient groups but did not reach statistical significance. Tear turnover was somewhat lower and more likely to be low in patients with more severe surface drying (ie, in staining group 3 and all KCS patients with corneal staining). There was no increase in tear evaporation compared with normals (Table I).

When patients were stratified on the basis of the degree of staining, the Schirmer value for group 3 was statistically significantly decreased. Meibomian gland dropout tended to be less the more severe the staining pattern. Dropout was statistically greater in groups 1 and 2, but not group 3, compared with normals (Table II). When patients were stratified on the basis of presence or absence of corneal staining, a statistically significant difference in staining and degree of dropout relative to normals was found in both groups. The presence of corneal staining was associated with a statistically significant decrease in Schirmer's value compared to normals and KCS patients without cornea staining. Thus corneal staining correlates with a more severe dry eye (Table II).

Patients were also stratified according to the degree of meibomian gland dropout (ie, less or more than 50% and less or more than 20% dropout). There was a statistically significant correlation with degree of dropout and decreased Schirmer's value relative to normals (Table III) in the groups with greater dropout. There also was a statistically significant difference in decreased Schirmer's value in the greater than 50% dropout group compared to patients with less than 50% dropout. There was no correlation between degree of dropout and increased evaporation (Table III).

When patients with "classic" KCS were stratified according to degree of staining, degree of dropout was negatively correlated with severity of disease, and decreased Schirmer's values positively correlated. The degree of staining was statistically significantly worse in group 3 compared to group 1. There was a trend for tear volume and flow to be less with increased staining, but these values did not reach statistical significance. The Schirmer's value was significantly decreased in patients with corneal staining compared to those without corneal staining (Table IV).

The Schirmer's value was significantly lower than normal in patients with KCS and MGD who had more severe surface drying (eg, more surface staining) and in the presence of corneal staining. Patients with corneal staining had a statistically significant lower Schirmer's value compared to patients without corneal staining (Table V).

Evaporation was determined in three ways, but no correlation was found with any other tear or meibomian parameter. This included evaporation PA (palpebral aperture method), evaporation TA (true area method), and also percent evaporation of available volume (volume evaporated per second divided by tear volume). In general, all three absolute evaporation rate values were lower than in normals (Tables I through V). However, the percentage evaporation of available tears (ie, tear volume) was greater in the presence of more severe surface drying. The mean percentage of tear turnover in both KCS groups attributable to evaporation was 0.06%. The thickness of the preocular tear film was found to be thinner in patients with more severe dry eye (ie, the greater the interpalpebral surface vital staining, the thinner the tear film).

DISCUSSION

All patients with KCS, with or without slit-lamp manifestations of MGD, as evidenced by surface drying, had statistically significant decreases in Schirmer's values and increases in meibomian gland dropout and trends toward decreases in tear volume and flow with minimal correlation with turnover and none with evaporation. When both patient groups (ie, KCS with and without associated slit-lamp evidence of MGD were stratified by degree of overall staining, both groups had a statistically significant lower Schirmer's value and trends toward decreased volume and flow with increasing severity of disease. The presence of corneal staining also correlated with a more severe dry eye. Significant increased meibomian gland dropout was present in both types of KCS, but degree of dropout was negatively correlated with severity of disease, a finding that we cannot explain. However, when we segregated patients with higher dropout from those with lower dropout, we did find an association with a dryer eye, which is an apparent contradiction, also a finding that we cannot explain at this time.

We assessed tear evaporation by using two principal approaches: evaporation as a function of surface area and as a function of tear volume. We found a trend for a greater percentage evaporation as tear volume decreased. However, the percentage of available tear volume lost to evaporation raises the question of the potential clinically relevant contribution of evaporation to the development of an aqueous-deficient dry eye. Evaporation as a function of surface might have greater potential clinical relevance. Using true surface area determined from a digital image yielded the true surface area, which should be

more accurate than calculating the area mathematically with only one true measure (ie, the vertical interpalpebral distance). Neither method yielded an evaporation rate greater than that seen in normals, nor did it correlate with presence or absence of slit-lamp or meibographic MGD nor degree of dropout. These findings are in apparent disagreement with published reports of MGD.[5,12] However, our criterionfor study entry was evidence of ocular surface drying, whereas the published reports did not take this into account and principally entered patients into studies on the basis of their definition of MGD (ie, difficult-to-express turbid meibomian secretions or meibographic meibomian gland dropout).

The apparent discrepancy may be explained by the different patient populations being studied. A third group of patients is currently being evaluated (ie, those with various forms for clinical blepharitis). This study may give results that will allow resolution of this apparent discrepancy.

Our study agrees with published reports that have found that clinical KCS is characterized by ocular surface vital staining, decreased Schirmer 1 values, decreased tear volume and flow, as well as increased meibomian gland dropout (Tables VI and VII).[4-6,8,10-30] The role of increased dropout is not clear; however, aqueous tear deficiency has been thought to result in ocular surface drying.

We found no change from normals or within disease groups in degree of evaporation from the ocular surface. Furthermore, considering not only the small absolute amount of tear evaporation of available tear volume but also the relatively small contribution of evaporation to turnover, except in unusual circumstances, how clinically significant can evaporation be in aqueous deficiency? On the other hand, biochemical changes in the meibomian secretions could destabilize the tear film and lead to surface drying, an association we have previously reported. Whether slit-lamp or meibographic MGD represents meibomian gland disease or whether it will correlate with clinical KCS or any other disease process, and by what mechanism it might contribute to surface drying or other disease, remains unclear, but is under investigation.

REFERENCES

1. Gudmundsen KJ, O'Donnell BF, Powell FC. Schirmer testing for dry eyes in patients with rosacea. *J Am Acad Dermatol* 1992;26:211-214.
2. Foulks GN. Challenges and pitfalls in clinical trials of treatments for dry eye. *The Ocular Surface* 2003;1:20-30.
3. Shine WE, McCulley JP. Keratoconjunctivitis sicca associated with meibomian secretion polar lipid abnormality. *Arch Ophthalmol* 1998;116:849-852.
4. Mathers WD, Lane JA, Sutphin JE, et al. Model for ocular tear film function. *Cornea* 1996;15:110-119.
5. Mathers WD. Ocular evaporation in meibomian gland dysfunction and dry eye. *Ophthalmology* 1993;100:347-351.
6. Goto E, Endo K, Suzuki A, et al. Tear evaporation dynamics in normal subjects and subjects with obstructive meibomian gland dysfunction. *Invest Ophthalmol Vis Sci* 2003;44:533-539.
7. Best JA van, Benitez del Castillo JM, Coulangeon L-M. Measurement of basal tear turnover using a standardized protocol European concerted action on ocular fluorometry. *Graefes Arch Clin Exp Ophthalmol* 1995;233:1-7.
8. Mathers WD, Daley TE. Tear flow and evaporation in patients with and without dry eye. *Ophthalmology* 1996;103:664-669.
9. Eter N, Gobbels M. A new technique for tear film fluorophotometry. *Br J Ophthalmol* 2002;86:616-619.
10. Mathers WD, Binarao G, Petroll M. Ocular water evaporation and the dry eye. A new measuring device. *Cornea* 1993;12:335-340.
11. Rolando M, Refojo MF. Tear evaporimeter for measuring water evaporation rate from tear film under controlled conditions in humans. *Exp Eye Res* 1983;36:25-33.
12. Shimazaki J, Sakata M, Tsubota K. Ocular surface changes and discomfort in patients with meibomian gland dysfunction. *Arch Ophthalmol* 1995;113:1266-1270.
13. Alfonso AA, Monroy D, Stern ME, et al. Correlation of tear fluorescein clearance and Schirmer test scores with ocular irritation symptoms. *Ophthalmology* 1999;106:803-810.
14. Battat L, Macri A, Dursun D, et al. Effects of laser in situ keratomileusis on tear production, clearance, and the ocular surface. *Ophthalmology* 2001;108:1230-1235.
15. Goebbels M. Tear secretion and tear film function in insulin dependent diabetics. *Br J Ophthalmol* 2000;84:19-21.
16. Jordan A, Baum J. Basic tear flow. Does it exist? *Ophthalmology* 1980;87:920-930.
17. Macri A, Rolando M, Pflugfelder S. A standardized visual scale for evaluation of tear fluorescein clearance. *Ophthalmology* 2000;107:1338-1343.
18. Macri A, Pflugfelder S. Correlation of the Schirmer 1 and fluorescein clearance tests with the severity of corneal epithelial and eyelid disease. *Arch Ophthalmol* 2000;118:1632-1638.
19. Mathers WD, Lane JA, Zimmerman MB. Tear film changes associated with normal aging. *Cornea* 1996;15:229-234.
20. Mishima S, Gasset A, Klyce SD, et al. Determination of tear volume and tear flow. *Invest Ophthalmol Vis Sci* 1966;5:264-275.
21. Stolwijk TR, Best JA van, Lemkes HHPJ, et al. Determination of basal tear turnover in insulin-dependent diabetes mellitus patients by fluorophotometry. *Int Ophthalmol* 1991;15:377-382.
22. Tsubota K, Yamada M. Tear evaporation from the ocular surface. *Invest Ophthalmol Vis Sci* 1992;33:2942-2950.
23. Webber WRS, Jones DP, Wright P. Fluorophotometric measurements of tear turnover rate in normal healthy persons: evidence for a circadian rhythm. *Eye* 1987;1:615-620.

24. Creech JL, Do LT, Fatt I, et al. In vivo tear-film thickness determination and implications for tear-film stability. *Curr Eye Res* 1998;17:1058-1066.
25. Prydal J, Artal P, Woon H, et al. Study of human precorneal tear film thickness and structure using laser interferometry. *Invest Ophthalmol Vis Sci* 1992;33:2006-2011.
26. Mishima S. Some physiological aspects of the precorneal tear film. *Arch Ophthalmol* 1965;73:233-241.
27. King-Smith PE, Fink BA, Fogt N, et al. The thickness of the human precorneal tear film: evidence from reflection spectra. *Invest Ophthalmol Vis Sci* 2000;41:3348-3359.
28. Shimazaki J, Goto E, Ono M, et al. Meibomian gland dysfunction in patients with Sjogren syndrome. *Ophthalmology* 1998;105:1485-1488.
29. Xu K-P, Yagi Y, Toda I, et al. Tear function index: a new measure of dry eye. *Arch Ophthalmol* 1995;113:84-88.
30. Rolando M, Refojo MF, Kenyon KR. Increased tear evaporation in eyes with keratoconjunctivitis sicca. *Arch Ophthalmol* 1983;101:557-558.

DISCUSSION

DR MITCHELL H. FRIEDLAENDER. Dry eye can, theoretically, be caused by decreased tear production or increased tear evaporation. Decreased tear production occurs with aging, and most significantly, with autoimmune disease, such as Sjogren's syndrome. Increased tear evaporation could be caused by an abnormality of the precorneal tear film, believed to be a multilayered structure with a mucin inner layer, an aqueous middle layer, and an oily outer layer. The oily outer layer is produced by the meibomian glands of the lids, and is believed to reduce evaporation of tears from the ocular surface. In meibomitis, a form of blepharitis, the oily layer is altered, possibly leading to increased evaporation.

Dr McCulley and his associates have evaluated the role of meibomian gland dysfunction in dry eye patients. All patients had keratoconjunctivitis sicca, symptoms of dry eye, and interpalpebral staining. They were divided into two groups, those with meibomian gland dysfunction (MGD), and those without MGD. All patients, whether or not they had MGD, had decreased Schirmer tests compared to normals, and a tendency toward decreased tear volume and tear flow. There was no statistically significant increase in tear evaporation among any of the dry eye patients, whether or not they had MGD. But, all dry eye patients had significant meibomian gland dropout compared to normals.

Additionally, there was a correlation between the amount of dryness and interpalpebral staining. Unexpectedly, the group of patients with the most meibomian gland dropout had less interpalpebral staining than the group with the least meibomian gland dropout. It is not clear why this occurred, but it suggests that meibomian secretions in these patients had an adverse effect on the ocular surface. An analysis of the biochemical and microbiologic properties of these secretions may shed further light on this observation.

There seems to be a very tenuous connection between dry eye and meibomian gland dysfunction. Dr McCulley's study does not support the concept that meibomian gland dysfunction leads to dry eye, nor that evaporation of tears from the ocular surface is an etiology for dry eye. This should not be surprising since meibomitis and dry eye are separate entities with separate etiologies. Dry eye is most often caused by aging, autoimmune disease, or systemic drugs. Meibomitis is genetically determined, and most often, a manifestation of rosacea.

Dr McCulley has done pioneering work in the biochemical characterization of meibomian secretions and in the classification of blepharitis and meibomitis. Further biochemical studies are planned for dry eye patients. It would not be surprising if these studies provide further evidence that dry eye and meibomitis are two distinct entities.

DR GEORGE L. SPAETH. For year oculoplastic surgeons have been advising their patient with dry eyes to use flaxseed oil I started advising some patients with dry eyes to try flaxseed oil and it seemed to help some patients. It seemed to make them feel less symptomatic. In the last month I've had four patients volunteer that ever since they started taking Omega-3 fish oil their dry eyes are better. How do you explain the apparent beneficial effect of these oils (flaxseed and Omega III) or other alternative medications or complimentary approaches to health?

DR RICHARD W. GREEN. You used the term meibomian dropout. Could you define what you mean by that and can that be translated to a morphologic feature other than the dye that you use to show the ducts of the meibomian glands?

DR BARTLEY R. FRUEH. There's another aspect of how much fluid is in the eye and that is the lacrimal drainage system. We use punctual plug and punctual occlusion for treating the dry eye. That should be a much bigger factor than evaporation in the normal patient. Is it possible that some people hyper drain their tear draining system? How do you look at this? Does this fit into the equation of what you're looking at?

DR J. DANIEL NELSON. Dogma as it relates to dry eye has always stated that either you have either too few tear secretions or you have evaporation. Dr McCulley has shown that the issue of evaporation is called into question. It leaves us asking the next dogmatic question: Is tear secretion important either? It's curious that, if you go back

over the last 20 years and the studies that have been done, no correlation between symptoms and signs as it relates to dry eye has been firmly established. Establishing correlation between signs, except for corneal staining, has never really been firmly established. So now we find that meibomian gland dropout does not seem to be correlated and evaporation doesn't seem to be correlated. And evaporation seems to be minimal. So when we get back to the basic issues such as how do we classify? How we diagnose? How do we determine exactly what is a dry eye? And the answer may be that a dry eye is not really dry.

Dr Brian R. Younge. I see a lot of patients from the neurologists that have peripheral neuropathy and many of these patients have either dry mouth and dry eye symptoms. When you are considering future studies you might look into the patients with peripheral neuropathy to see whether they in fact have meibomian gland dropout or whether it's a neurogenic stimulus or lack thereof that contributed to this.

Dr Dan B. Jones. Dry eye symptoms get worse during the day and we have always said that it is due to evaporation. It gets worse in people depending upon the position of the eye and the frequency of blinking. People using computers have their eye in down gaze, are concentrating, and blink less frequently and have more symptoms. Is that a myth? Does this say evaporation doesn't occur during the day and tear function doesn't vary during the day? If you did your study at different times of day and would that make a difference?

Before we get meibomian gland dysfunction too far separated, you define this group as non-inflammatory. And you define "dys" as decreased meibomian gland function. Are you getting ready to say that meibomian gland dysfunction in terms of its inflammatory form does not have a role in dry eye or has this study not been done yet?

Dr Alan M. Laties. Further comment on the cohexanoic acid, if you take the fatty acid, can you actually alter the form of pro-inflammatory prostaglandins the body makes and change the degree of inflammation?

Dr James P. McCulley. It's meibomian gland dysfunction (MGD), it's meibomian gland dropout, and I do not know if either one of those are a component of meibomian gland disease. Is there meibomian gland disease? Yes. But how MGD, as it has been defined, by either drop out or the turbid lipids, plays a part in disease, I do not know at this time.

I don't know where MGD, as it has been defined, is going to fit. I don't know if it's causative or, contributory to disease. I don't know if it's an epiphenomenon, related to other disease. I don't know if it's just potentially an aging phenomenon or a normal variant. I just don't know yet how it contributes to disease. . We did have a negative correlation with the degree of meibomian gland drop out and the aqueous tear deficiency. That suggests to me that indeed, MGD may be contributing. Because when it's higher, there's ocular surface drying, with more aqueous tears. However, it does not appear to be contributing significantly.

I presented some work years ago about the association of chronic blepharitis and dry eyes and the biochemical abnormality we'd found associated with the dry eye. There was the question of whether the biochemical abnormality in the meibomian glands was leading to the dry eye. At that point I thought it might be evaporation. Dr Bill Bourne questioned at that time, "With the amount of evaporation that takes place, is it possible that it can indeed cause an aqueous tear deficiency?" I thought about it as we started analyzing our data and thinking indeed we're going to prove what others have been saying, i.e. MGD leads to an evaporative dry eye. However, we did not. When we did our calculations to determine how much evaporation can do when we've got a blinking, non-inflamed eye that covers with the blink, we found very little and certainly not enough evaporation to cause an aqueous deficient dry eye. However, evaporation can certainly exacerbate an already aqueous deficient dry eye.

Two people brought up essential fatty acids and the two that are prominent in the press at this time are Omega-3 and Omega-6. We need them both and we need them in the right balance. What we have found to date is that there's only linoleic in the meibomian secretions. Linoleic is an Omege-6. We need the 6s we need but we don't need too many of them. If we have too many of them, and the balance relative to 3 and 6 is too much in favor of 6, it induces inflammation. We want an increase in Omega-3 that's in fish oils and in other compounds for general health. I don't know their role yet in tear function. We are in the process of going through the IRB to get approval to evaluate the tears pre and post dosing with essential fatty acids. I think as long as patients are not overdosing and that they're being certain that they take both Omega 3 and 6 there is apt to be no harm. Keep in mind that overdoses with Omega 3 and 6 can lead to a vitamin E deficiency. So they may need to be supplemented with a vitamin E. Dr Green, your question about the dropouts was on meibography. It's infrared photography and there are no secretions within the lumen of the gland. I do not have any anatomic correlation to that, so I don't know what anatomically, pathologically, or histologically is going on in those glands. The question about the drainage system. Most of the tears are not being lost

through evaporation since only 2.0 to 4.0 percent of tear loss is through evaporation. The rest is going somewhere and it's most likely going down the nasal-lacrimal duct. We did not try to determine the nasal-lacrimal duct function in these patients although we did look at aqueous tear volume and turnover. So I think we normalized for those issues.

The key to a dry eye is surface staining. If you don't have surface staining, you don't have drying of the ocular surface. There are other things that can cause staining of the surface; we don't have time or want to go into that but I think staining is the key. We don't know enough to come up with a classification system. Rose-Bengal and lissamine green are both vital stains and they are interchangeable. Just make sure you have enough stain to put on the surface to get the cells.

I am not sure why symptoms increase during the day. Dry spots tend to be self-perpetuating, and the tear film has a great deal of difficulty staying intact over them. As we do close work we tend to blink less frequently, so there are other factors that may contribute. Plus, we're exposed to challenging environments that are going to vary with our location. Evaporation can contribute to tear loss and potentially exacerbate an already aqueous deficient dry eye. But, once again, there does not appear to be enough evaporation-taking place to cause a dry eye.

I don't want to distance us from meibomian gland dysfunction. I just don't know what function is "dys'ed." If we have an inflammatory condition involving the meibomian glands, then we have meibomianitis that has other pathways contributing to disease. It's in these clinically uninflamed eyes that I'm not sure how MGD contributes to disease. When you introduce inflammation, you introduce so many variables, that it's difficult to sort out which pathways we're dealing with.. Meibomian gland disease including inflammatory disease processes is very real. We can imagine pathways by which disease is created. However in the uninflamed state with meibomian gland dysfunction, as defined, I'm not sure what mechanisms are at play.