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The Epidemiology of Meibomian Gland Dysfunction in an Elderly Population

Yousef A Alghamdi, MD¹, Carolina Mercado, MD², Allison L McClellan, OD¹, Hatim Batawi, MD¹, Carol L Karp, MD², and Anat Galor, MD, MSPH^{1,2}

¹Miami Veterans Administration Medical Center, 1201 NW 16th St, Miami, FL 33125

²Bascom Palmer Eye Institute, University of Miami, 900 NW 17th Street, Miami, FL, 33136

Abstract

Purpose—To study the epidemiology of meibomian gland dysfunction (MGD) in an elderly, predominantly male population.

Methods—Prospective study of 233 subjects seen in the Miami Veterans Affairs eye clinic. Patients underwent a complete ocular surface examination, including dry eye questionnaires and tear assessments (osmolarity, tear break up time (TBUT), corneal staining, Schirmer's). The main outcome measures were correlations between meibomian gland (MG) parameters and demographics, dry eye symptoms, and tear parameters. The studied MG parameters were eyelid vascularity and meibum quality; a score of 2 in either parameter was considered abnormal.

Results—Mean age of the 233 subjects was 63 (SD=11); 91% were male and 59% had at least one abnormal MG parameter (abnormal quality 55%; vascularity 17%). Demographically, patients with abnormal MG parameters were significantly older than their counterparts without these findings. Whites were more likely to have abnormal eyelid vascularity compared to blacks (n=36 (31%) versus n=1 (1%), $p < 0.0005$) but no differences were noted between races with respect to meibum quality. Abnormal meibum quality, but not abnormal vascularity, was significantly associated with more severe dry eye symptoms. Similarly, abnormal meibum quality, but not eyelid vascularity, significantly associated with worse dry eye signs, including decreased TBUT, and increased corneal staining ($p < 0.05$ for all).

Conclusion—MGD is a frequent finding in an elderly, predominantly male population with racial differences noted in the frequency of abnormal eyelid vascularity but not in MG quality. Abnormal meibum quality was significantly associated with more severe dry eye symptoms and signs.

Keywords

Meibomian gland dysfunction; eyelid vascularity; abnormal meibum quality; epidemiology

Corresponding Author: Anat Galor, MD, 1201 NW 16th Street., Miami, FL, 33125; Phone 305-326-6000; Fax 305-575-3312; agalor@med.miami.edu.

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Introduction

Meibomian glands (MG) are specialized sebaceous glands that secrete meibum, an essential component of the tear film.¹ Among its functions, meibum helps slow tear evaporation, protects the eye from microbes and organic particles, and preserves the clarity of the optical surface.² Meibomian gland dysfunction (MGD) is defined as a “chronic, diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion.”³ Clinically, MG changes can manifest as gland atrophy, orifice obstruction, change in meibum quality, and eyelid vascularity.³ Accompanying symptoms of MGD can range from none to severe, and MG changes can be accompanied by a variety of ocular surface findings such as decreased tear break up time and corneal staining. In fact, MGD is considered to be the leading cause of evaporative dry eye.^{3, 4}

Several studies have reported on the epidemiology of MGD in the US and worldwide (Table 1).⁵⁻⁷ The Salisbury Eye Evaluation Study evaluated individuals over the age of 65 and found that 3.5% had grade 2 or higher MG plugging or collarettes.⁸ In comparison, the Singapore Malay Eye Study reported a 56% MGD prevalence (defined as either meibomian gland orifice plugging or lid margin telangiectasia in at least one eye).⁹ Other studies in Asian countries have similarly reported high prevalence estimates ranging from 39% to 68%, each using a different definition of MGD.¹⁰⁻¹⁵ In clinic based studies and likewise using different definitions, MGD prevalence estimates range from 32% to 78% (Table 2).¹⁶⁻²⁴

Risk factors for MG have also been described in the above studies and include older age, male gender, high diastolic blood pressure, and certain medications (angiotensin II receptor blockers, isotretinoin).⁵ Despite this, there are still many gaps in the literature regarding the epidemiology of MGD. Most clinic based studies had a large female population^{17, 23, 25} and less has been published on MGD in men. Furthermore, associations between specific MGD parameters (meibum quality versus vascularity, for example) are missing. Our clinic at the Miami Veterans Administration Medical Center (VAMC) sees a unique patient population consisting of mostly older males, with a wide racial and ethnic distribution, and a high frequency of depression and post traumatic stress disorder (PTSD) diagnoses. As such, in this study we aimed to evaluate the epidemiology of MGD in this population, including frequencies and risk factors for specific MGD parameters.

Methodology

Study population

Patients were recruited prospectively from the VAMC eye clinic and underwent a complete ocular surface examination. Patients were excluded if they had any ocular or systemic diseases in themselves associated with dry eye including contact lenses wear, ocular medications with the exception of artificial tears, anatomic abnormality of the eyelid (e.g. ectropion), conjunctivae (e.g. pterygium), or cornea (e.g. edema), active external ocular process, history of refractive, glaucoma or retinal surgery, cataract surgery within the last 6 months, human immunodeficiency virus, sarcoidosis, graft-versus host disease, Sjogren

syndrome, or collagen vascular disease were excluded. The study was conducted in accordance to the principles of the Declaration of Helsinki. Miami VAMC Institution Review Board approval was obtained to allow the prospective evaluation of patients.

Data collected

From each participant demographic information, past ocular history, medical history, and medication information was collected. Patients filled out standardized questionnaires regarding dry eye symptoms including the dry eye questionnaire 5 (DEQ5)²⁶ (score 0–22) and ocular surface disease index (OSDI) (score 0–100). Subjects were also 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.” This type of 0–10 NRS is recommended as the primary outcome measure in pain clinical trials.²⁷ Furthermore, all patients underwent tear film assessment including (1) tear osmolarity (TearLAB, San Diego, CA) (once in each eye), (2) tear breakup time (TBUT) (5 µl fluorescein placed, 3 measurements taken in each eye and averaged), (3) corneal staining (NEI scale, 5 areas of cornea assessed (score 0–4 in each))²⁸, Schirmer’s strips with anesthesia, and eyelid and meibomian gland assessment.²¹ Eyelid vascularity was graded on a scale of 0 to 4 (0 = none; 1 = mild telangiectasias; 2 = moderate telangiectasias; 3 = severe telangiectasias) as was meibum quality (0 = clear; 1 = cloudy; 2 = granular; 3 = toothpaste; 4 = no meibum extracted). Data were entered into a standardized database.

Main outcome measure

Main outcome measures were the frequency of MGD in the population and evaluation of risk factors (demographics, co-morbidities) by specific MGD parameters. In this study, for both eyelid vascularity and meibum quality, we defined an abnormal parameter as a score of 2 or greater in the more severely affected eye.

Statistical analysis

Statistical analysis was done using SPSS Statistical package 21.0. Descriptive statistics were used to summarize patient demographic and clinical information. Pearson correlations were used to evaluate the strengths of association between the above parameters.

Results

Study population

In our population of 233 patients, mean age was 63 (SD=11, range 27–89); 91% were male due to the unique VAMC population. Further demographics of the study population are found in Table 3.

Overall, 59% had at least one abnormal MG parameter (grade ≥ 2), with 17% (n=39) having abnormal vascularity, 55% (n=129) abnormal quality. MG abnormalities were associated with one other, with 31 patients having both abnormal vascularity and quality and 86 patients having normal parameters on both measures. One hundred and five patients, on the other hand, had discordant findings, 7 abnormal vascularity only and 98 abnormal quality only (p=0.001).

MG parameters and demographics and systemic co-morbidities

Patients with abnormal eyelid vascularity and meibum quality were older than their counterparts without these findings (normal vascularity: mean 62 years (SD 11); abnormal vascularity: mean 68 (SD 9), $p < 0.0005$; normal quality: mean 61 years (SD 11); abnormal quality: mean 64 (SD 11), $p = 0.01$). Whites were more likely to have abnormal eyelid vascularity compared to blacks ($p < 0.0005$) but no differences were noted between races with respect to meibum quality ($p = 0.48$) (Table 3).

Patients with depression were less likely to have abnormal vascularity as were patients on an anti-depressant. Patients with a diagnosis of sleep apnea, on the other hand, were more likely to have abnormal vascularity. The presence of benign prostatic hyperplasia (BPH) was associated with both abnormal vascularity and meibum quality. Those taking non-steroidal anti-inflammatory drugs (NSAIDs) were less likely to have abnormal eyelid vascularity. A multivariable model considering age and BPH found that BPH alone remained significantly associated with abnormal meibum quality (odds ratio (OR) 3, 95% confidence interval (CI) 1.2–7.2). A multivariable model considering all factors significantly associated with eyelid vascularity found that NSAID use and black race remained protective factors (OR=0.2, 95% CI 0.07–0.63 and OR=0.02, 95% CI 0.003–0.16, respectively) and that sleep apnea remained a risk factor (OR=3.3, 95% CI 1.3–8.3).

Looking at lipid levels (total cholesterol, high density lipoprotein, low density lipoprotein, triglycerides), no differences were seen with respect to the presence or absence of abnormal eyelid vascularity or meibum quality.

MG parameters and dry eye

Abnormal meibum quality, but not abnormal vascularity, was significantly associated with dry eye symptoms and ocular pain (Table 4). Patients with abnormal meibum quality were also more likely to report ocular itching. Abnormal meibum quality, but not eyelid vascularity, was also significantly associated with worse dry eye signs, including decreased TBUT, and increased corneal staining (Table 4).

Discussion

We found that MGD is a frequent finding in an elderly, predominantly male population. Our frequency of 59% is within the range reported in other clinic based studies^{15–19} (Table 2). Differences in MGD definition, however, make comparisons between studies difficult. Not surprisingly, we found that patients with abnormal MG parameters were older than their counterparts without these abnormalities, a finding well supported in the literature both in animal and clinical studies.^{13, 29, 30} In humans without dry eye symptoms, *in vivo* laser scanning confocal microscopy has demonstrated atrophic, nonobstructive meibomian gland changes with age including significantly decreased acinar unit density, increased secretion reflectivity, and increased wall inhomogeneity.³¹ Similarly, noncontact infrared meibography demonstrated decreased mean duct length and percent acini area and increased gland dropout in older, as compared to younger, asymptomatic individuals.^{32, 33} Meibum properties also differs with age as asymptomatic older individuals have been shown to have

less CH(3) and C=C groups and higher aldehyde-to-lipid hydroperoxide ratios compared to younger individuals, as detected by H nuclear magnetic resonance (NMR) spectra.³⁴ Histologically, meibomian gland acini of older mice have significantly reduced nuclear staining of the proliferation marker, Ki67, compared to younger mice.²⁹ Declining androgen levels in the aging male may underlie some of the noted changes, as similar to other sebaceous glands, the function of meibomian glands is affected by androgen levels.³⁵

In our study, we also found a differential effect of race on MG parameters, with telangiectasias more frequently found in white patients while abnormal meibum quality was distributed through the races. This is likely due to pigment on the eyelid margin masking our ability to detect telangiectasias and not due to a decreased frequency of MGD in blacks, given similar frequencies of abnormal meibum quality.

Prior studies have examined risk factors for MGD, with androgen deficiency, contact lens use³⁶, and systemic medications (retinoic acid) all implicated.⁵ This study has gone a step farther to look at systemic risk factors as they relate to specific MG abnormalities. We found that while some systemic co-morbidities (e.g. BPH) associated with both abnormal vascularity and meibum quality, others, such as sleep apnea differentially associated with abnormal vascularity. In a similar manner, several systemic medications (depression, anti-depressants, NSAIDS) were associated with more normal MG parameters. The significance of these associations is currently unknown. Despite a prior study which reported a positive relationship between systemic hypercholesterolemia and MGD (defined as a score of 2 or higher on either glandular obstruction or meibum quality)³⁷, we did not find such a relationship in our study. Interestingly, while another study also reported higher total cholesterol levels in patients with MGD (similarly defined), this difference was driven by higher HDL levels. In fact, MGD patients were also found to have lower triglyceride levels compared to the general population.³⁸ These contradictions highlight the complex relationship between systemic lipids and sebaceous gland function.

While it is well known that some patients with MG abnormalities are asymptomatic¹³, we found a differential relationship between our measured metrics, with abnormal meibum quality associating with dry eye symptoms and ocular pain while abnormal vascularity did not. In a similar manner, abnormal quality was also associated with tear film abnormalities. The lack of relationship between eyelid vascularity and dry eye symptoms and signs may be due to the fact that our current physiologic testing is not sufficiently accurate to detect abnormal vessels in patients with skin pigmentation. In pigmented patients, lid margin findings may be misleadingly benign and mask underlying MG dysfunction. An alternative hypothesis is that poor meibum quality is more directly related to tear dysfunction than abnormal lid vascularity.

As with all studies, our findings must be considered in light of the study limitations which include a unique patient population, and specific measures of both MGD and dry eye. Despite this, our study is important as it highlights the clinical findings and relationships of MGD in an elderly male population. Also, relying on telangiectasia in the diagnosis of MGD could lead to an overestimation in white patients and under estimation in other racial groups.

In summary, MGD is a common eyelid disorder. Occurring in almost 60% of our male population, abnormal meibum quality was significantly associated with more severe dry eye symptoms, ocular pain, and worse dry eye signs, including decreased TBUT, and increased corneal staining. Future identification of risk factors and co-morbidities can potentially help to modulate manifestations of this disease.

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Table 1
Population based studies of meibomian gland dysfunction (MGD) definitions and frequencies.

Author, Year	Location	n	Definition*	Population	Frequency
<i>United States (US), Europe, Australia</i>					
McCarty ⁶ , 1998	Australia	926	Poor meibum quality	40 years 47% Male	29%
Schein ⁸ , 1997	US	2,482	MG plugging, collarettes	65 years 43% male	4%
Viso ⁷ , 2011	Spain	654	MG plugging, telangiectasias, poor meibum quality	40–96 years 37% males	31%
<i>Asia</i>					
Den ¹³ , 2006	Japan	354	MG dropout, poor meibum quality, telangiectasias	21–93 years 43% male All asymptomatic	39%
Jie ¹¹ , 2009	China	1,957	Telangiectasias	40 years 43% Male	68%
Lekhanont ¹⁴ , 2006	Thailand	550	MG plugging, collarettes, telangiectasias	40 years 27% Male	63%
Lin ¹⁰ , 2003	Taiwan	1,361	MG plugging, telangiectasia	65 years 60% male	61%
Ong ¹⁵ , 1996	Kuala Lumpur	231	Poor expressability	15–40 Years	43%
Siak ⁹ , 2012	Singapore	3,271	MG plugging, telangiectasia	40–80 years 48% male	56%
Uchino ¹² , 2006	Japan	113	MG dropout, poor expressability, poor meibum quality	60 years 44% male	62%

MG=meibomian gland

* in at least one eye

Table 2
Clinical based studies of meibomian gland dysfunction (MGD) definitions and frequencies.

References	Location	n	Definition*	Population	Frequency
<i>United States, Europe, and Australia</i>					
Akpek ²⁰ , 1997	US	131	MG plugging, poor expressability	23–85 57% male Rosacea	78%
Galor ²¹ , 2013	US	263	MG plugging, poor meibum quality, telangiectasias	50–95 100% male	65%
Ghanem ²² , 2003	US	176	MG plugging, collarettes, telangiectasia	28–79 39% male Rosacea	46%
Hom ¹⁹ , 2005	US	398	Poor meibum quality	>10 years 50% male Hispanics	39%
Horwath-Winter ²³ , 2003	Austria	97	MG plugging, poor expressability	30–90 20% male	33%
<i>Asia</i>					
Basak ²⁴ , 2012	India	3,023	Poor meibum quality	>30 years	32%
Shinazaki ¹⁷ , 1998	Japan	94	MG dropout	45–75 25% male Sjogrens	75%
Zhang ¹⁸ , 2003	China	115	MG plugging or dropout, poor meibum quality	11% Sjogren	35%

* in at least one eye

Table 3

Frequency of MGD in population by demographics, comorbidities and medication use.

	Abnormal eyelid vascularity [†]	Abnormal meibum quality [†]
Gender		
male, n (%)	38 (18%)	119 (59%)
female, n (%)	1 (5%)	10 (53%)
Race		
white, n (%)	36 (31%)	71 (62%)
black, n (%)	1 (1%)**	53 (54%)
Ethnicity		
Hispanic, n (%)	11 (17%)	37 (58%)
Non-Hispanic, n (%)	28 (17%)	92 (58%)
Co-morbidities		
Current Smoking		
Yes, n (%)	6 (8%)	46 (61%)
No, n (%)	33 (21%)*	83 (57%)
Hypertension		
Yes, n (%)	31 (18%)	93 (57%)
No, n (%)	8 (13%)	36 (60%)
Hypercholesterolemia		
Yes, n (%)	28 (20%)	84 (63%)
No, n (%)	11 (12%)	45 (51%)
Diabetes		
Yes, n (%)	10 (15)	38 (59%)
No, n (%)	29 (18%)	90 (57%)
Post traumatic stress disorder		
Yes, n (%)	6 (11%)	32 (60%)
No, n(%)	33 (19%)	97 (57%)
Depression		
Yes, n (%)	13 (10%)	69 (54%)
No, n (%)	26 (26%)*	60 (64%)
Arthritis		
Yes, n (%)	13 (13%)	61 (64%)
No, n (%)	26 (20%)	67 (54%)
Sleep apnea		
Yes, n (%)	14 (30%)	27 (60%)

	Abnormal eyelid vascularity [†]	Abnormal meibum quality [†]
No, n(%)	25 (13%)*	102 (58%)
Benign prostatic hyperplasia		
Yes, n (%)	10 (29%)	25 (78%)
No, n (%)	29 (15%)*	104 (55%)*
Medications		
Anti-depressants		
Yes, n (%)	10 (10%)	52 (57%)
No, n (%)	29 (21%)*	77 (59%)
Anti-anxiolytics,		
Yes, n (%)	10 (11%)	49 (56%)
No, n (%)	29 (21%)	80 (60%)
Anti-histamine		
Yes, n (%)	10 (24%)	19 (50%)
No, n (%)	29 (15%)	110 (60%)
Nonsteroidal anti-inflammatory agents		
Yes, n (%)	4 (5%)	44 (54%)
No, n (%)	35 (23%)**	85 (60%)

n=number in group;

* p value<0.05;

** p value<0.00005

[†] Eyelid vascularity graded on scale of 0 to 3; meibum quality on scale of 0 to 4. For both measures, an abnormal value was defined as a score of 2 or greater in the more severely affected eye.

Table 4

Relationship between specific MGD parameters and dry eye symptoms and signs

	Normal eyelid Vascularity	Abnormal eyelid vascularity [†]	Normal meibum quality [†]	Abnormal meibum quality
DEQ5	11.8 (5.2)	11.3 (5.2)	10.5 (5.6)	12.1 (4.7) *
OSDI	34 (22)	35 (26)	32 (25)	36 (26)
Average ocular pain intensity over 1 week recall period (range 0–10)	3.3 (2.7)	3.4 (2.7)	2.8 (2.7)	3.7 (2.6) *
Itchiness	1.2 (0.9)	1.6 (0.9)	1.2 (1.0)	1.4 (0.9) *
Osmolarity [§]	307 (18)	300 (17) *	306 (20)	305 (16)
TBUT [§]	9.8 (4.1)	8.0 (3.1)	10.9 (3.9)	8.6 (3.8) **
Corneal staining [§]	1.9 (2.4)	2.6 (2.7)	1.5 (2.1)	2.3 (2.3) *
Schirmer's [§]	14.2 (7.6)	13.2 (5.9)	15.1 (7.7)	13.2 (6.7)

DEQ5= dry eye questionnaire; OSDI= Ocular surface disease index; TBUT=tear break up time;

* p value<0.05;

** p value<0.00005

[†]Eyelid vascularity graded on scale of 0 to 3; meibum quality on scale of 0 to 4. For both measures, an abnormal value was defined as a score of 2 or greater in the more severely affected eye.[§]value from more severely affected eye