tvst

https://doi.org/10.1167/tvst.8.6.6

Article

The Role of Meibography in the Diagnosis of Meibomian Gland Dysfunction in Ocular Surface Diseases

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Received: 12 June 2019
Accepted: 28 August 2019
Published: 12 November 2019

Keywords: meibography; dry eye disease; meibomian gland dysfunction

Citation: Robin M, Liang H, Rabut G, Augstburger E, Baudouin C, Labbé A. The role of meibography in the diagnosis of meibomian gland dysfunction in ocular surface diseases. Trans Vis Sci Tech. 2019;8(6):6, https://doi.org/10.1167/tvst.8.6.6

Purpose: To evaluate dysfunction in various ocular surface diseases (OSDs) including primary meibomian gland disease (MGD), perennial allergic conjunctivitis, and primary and secondary Sjögren syndromes.

Methods: A retrospective analysis of 146 patients (111 women and 35 men) with symptomatic OSDs was performed. Patients were divided into two groups: the non-MGD group (55 patients) and the MGD group (91 patients). All patients had an evaluation of ocular surface symptoms and clinical tests, including tear film breakup time (BUT), the first and the mean noninvasive breakup time (NIKBUTf and NIKBUTavg, respectively). The meibomian gland loss of the lower eyelid was quantified using meibography and the meiboscale.

Results: There was no significant difference regarding age or sex ratio between the two groups. The meiboscale in the MGD group was significantly higher than that in the non-MGD group ($P = 0.003$). The non-MGD patients were more symptomatic than those in the MGD group ($P = 0.043$). There were no significant differences between MGD and non-MGD groups regarding a Schirmer test ($P = 0.195$), BUT ($P = 0.719$), NIKBUTf ($P = 0.96$), or NIKBUTavg ($P = 0.70$). In the whole population, there was a negative correlation between meiboscale and NIKBUT ($r = -0.21$, $P = 0.02$), but no other correlations were found.

Conclusions: Meibomian gland dysfunction was observed among different OSDs. Meibomian gland loss evaluated by meibography might help identify MGD in patients suffering from OSD.

Translation Relevance: Meibography provides a better understanding of MGD in several OSD. It may be useful to integrate this objective analysis to improve treatments of OSD associated to MGD.

Introduction

Meibomian gland disease (MGD) is defined as a chronic, diffuse abnormality of the meibomian glands (MGs), commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in glandular secretion. It may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease (OSD).[1–3] Prevalence of MGD in published studies varies from 20% to 70% according to the diagnostic criteria or geographic differences.[4–7] MGD is considered to be the main cause of evaporative dry eye disease (DED).[8,9]

The exact physiopathology of MGD is complex and involves several mechanisms, including primary obstructive keratinization of MG orifices, inflammation of the eyelids, abnormal MG secretion, changes in ocular surface microbial flora, or *Demodex* infestation.[10–12] The actual classification of MGD distin-

guishes primary obstructive MGD from MGD related to skin diseases, such as rosacea and seborrheic dermatitis, or induced by inflammatory disease.[2,13] Nevertheless, the association between MGD and OSDs remains incompletely understood. Although MGD may lead to DED with an increased evaporation of the tear film, the ocular surface inflammation in DED might affect MGs, leading to MG atrophy and loss or impairment of secretory function.[4,14,15]

Similarly, other OSDs, such as primary or secondary Sjögren syndrome (PSS or SSS) or perennial allergic conjunctivitis, might induce MG changes.[13,16,17]

For the evaluation of MGD, several clinical tests have been proposed, including a slit-lamp examination for lid morphology and gland expressibility, tear film lipid layer thickness, tear osmolarity, interferometry, evaporimetry, or meibography.[4,18] The clinical assessment of lid margin changes, gland expressibility, and meibum quality, as proposed by the 2017 MGD Diagnostic Workshop Committee, remains the most commonly used clinical test; meibography is a technique dedicated to the direct observation of MG morphology in vivo.[18–21] To quantify meibography images, several scoring systems have been developed, and many studies confirmed the sensitivity and specificity of meibography for the diagnosis of symptomatic MGD.[22–25] To our knowledge, however, to date no studies have explored and compared the MG changes in different OSDs.

The purpose of the present study was to investigate the relationship between infrared meibography and other OSD clinical tests in patients with MGD, allergy, PSS, and SSS.

Methods

Patients

This retrospective single-center study was conducted at the Center for Clinical Investigation (CIC INSERM 1423) of the Quinze-Vingts National Ophthalmology Hospital, Paris, France. The study was conducted in accordance with the tenets of the Declaration of Helsinki and approved by the Ethics Committee CPP-Ile de France (number 10793). In this study, 226 randomly selected eyes of 226 patients (age, 54 ± 17 years; 172 women and 54 men) followed at the CIC INSERM 1423 for an OSD were evaluated for MGD-related criteria. Inclusion criteria were as follows: >21 years of age with a diagnosis of DED according to the Dry Eye Workshop II (DEWS II) report[20]: (1) an OSD Index (OSDI) score ≥13 and (2) at least one among the following: noninvasive tear breakup time <10 seconds, or osmolarity ≥308 mOsm/L in either eye, or an interocular difference >8 mOsm/L, or a conjunctival lissamine green staining score of 1 or more (range, 0–6, with higher scores indicating greater abnormality), a corneal fluorescein staining score of 4 or more (range, 0–15, with higher scores indicating greater abnormality). Exclusion criteria were as follows: previous ocular surgery or trauma within 3 months before inclusion, recent ocular infections, contact lens wear, or diabetes.

Patients were divided into two groups: the MGD and the non-MGD groups. Among these 226 patients, 80 patients were excluded from the study because they met the inclusion criteria for either both MGD and non-MGD groups or neither of them. The primary MGD group included 91 patients (65 women and 26 men) diagnosed according to the MGD international workshop criteria[14,18]: (1) alteration of the meibum expressibility on the eight central glands, (2) anomaly in meibum quality in eight central glands, including meibum described as a cloudy particulate fluid, inspissated or like toothpaste, or more than one lid margin abnormality (irregular lid margin, vascular engorgement, plugged MG orifices, displacement of the mucocutaneous junction), and (3) absence of inflammatory skin disorders such as atopic dermatitis and rosacea.

The non-MGD group included 55 patients (46 women and nine men) with allergic conjunctivitis or PSS or SSS. The allergic conjunctivitis group included 23 patients (16 women and seven men, 23 cases of perennial allergic conjunctivitis) diagnosed by the association of (1) comorbidity with other allergic diseases (including allergic rhinitis, atopic dermatitis, or asthma) and (2) at least one slit-lamp abnormality: either conjunctival papillary hypertrophy or follicles, and (3) exclusion of either atopic keratoconjunctivitis or vernal keratoconjunctivitis.[16,20] The PSS group included 23 patients (21 women and two men) diagnosed according to the American College of Rheumatology whose definition requires at least two out of the following criteria[26]: (1) positive serum anti-SSA and/or anti-SSB or positive rheumatoid factor and anti-nuclear antibody ≥1:320; (2) ocular staining score (OSS) ≥3 (the OSS is the sum of a 0–6 score for fluorescein staining of the cornea and a 0–3 score for lissamine green staining of both nasal and temporal bulbar conjunctivae, yielding a total score ranging from 0 to 12); and (3) presence of focal lymphocytic sialadenitis with a focus score ≥1 focus/4 mm^2 in

labial salivary gland biopsies. The SSS group included nine patients (all women) with four cases of rheumatoid polyarthritis, three systemic lupus erythematosus, and two systemic sclerosis. SSS was defined as the association of (1) a Sjögren syndrome as defined in the SSS group and (2) a systemic autoimmune disease diagnosed according to the EULAR recommendations (for rheumatoid polyarthritis, systemic lupus erythematosus, and systemic sclerosis).[27–29]

Ocular Surface Tests

Before all clinical tests, patients were asked to complete a symptom questionnaire, the OSDI. The OSDI includes six questions related to visual disturbance (blurred vision or poor vision) or visual function (problems reading, driving at night, working on a computer, or watching TV).

An advanced corneal topographer (Keratograph 5M [K5M]; Oculus, Wetzlar, Germany) was used to analyze the first and the mean noninvasive breakup time (NIKBUTf and NIKBUTavg) and the lower tear meniscus height (TMH). Patients were requested to keep their eyes open as long as possible during measurement of the NIKBUT. When the first breakup appeared in the placido ring, it was automatically detected by the device software. The corresponding time indicated the NIKBUTf, and the average time of all breakup incidents on the cornea was documented as the NIKBUTavg. Inferior TMH images were captured with the K5M and measured with an electronic ruler perpendicular to the lid margin at the central point relative to the pupil center.

The Schirmer I test was performed using Schirmer strips placed in the inferior conjunctival fornix and measured after 5 minutes (Haag-Streit UK, Essex, UK). The score corresponded to the measured length of wetting after a 5-minute period.

Fluorescein staining of the conjunctiva and cornea was evaluated according to the Oxford grading, 2 minutes after instillation of a single drop of fluorescein (Fluoreszein SE Thilo; Alcon Pharma GmbH, Freiburg im Breisgau, Germany).[30]

MG expressibility was graded as recommended by the MGD workshop according to how many of the five central glands in the lower eyelid could express secretion through the Meibomian Gland Evaluator (TearScience Inc., Morrisville, NC) maintained for 10 seconds.[4,18,20] The quality of expressed secretion was also graded according to the MGD workshop recommendations.[18] Meibography was performed using the K5M. The evaluation was based on the criteria proposed by Pult and Riede-Pult,[22] and the MGs of the lower eyelid were visualized and graded.[22] The area of MG loss was defined as the percentage of area without visible glands in relation to the total visible tarsal area and given a score from 0 to 4. A score of 0 represented no atrophy; a score of 1, 0% to 25% MG loss; a score of 2, 25% to 50%; a score of 3, 50% to 75%; and a score of 4, >75%.

Statistical Analysis

Statistical analysis was performed using a spreadsheet program (Excel 2010; Microsoft Corp., Redmond, WA) and statistical analysis software (GraphPad Prism, ver. 6; GraphPad Inc., San Diego, CA). Dry eye parameters were compared between the MGD and non-MGD groups using the χ^2 method and the Mann-Whitney test for subgroup analysis. The normal distribution was evaluated using the Kolmogorov-Smirnov test. For normally distributed values, a linear Pearson's correlation coefficient was used, and for nonnormally distributed values the linear Spearman correlation coefficient was used. A *P*-value of 0.05 was considered statistically significant.

Results

Comparisons of MGD and Non-MGD Groups

Among the 226 patients initially recruited, 146 were analyzed, 91 patients belonging to the MGD group and 55 to the non-MGD group. OSDI levels were severe in both the MGD (mean OSDI, 55.37 ± 22.05) and non-MGD groups (mean OSDI, 62.88 ± 20.49), with the non-MGD group being more symptomatic ($P = 0.043$). The MGD group had a significantly higher THM than did the non-MGD group ($P = 0.008$). Similarly, the MGD group had a significantly higher meiboscale than did the non-MGD group ($P = 0.003$) (Fig. 1). There was no significant difference regarding age ($P = 0.067$) or sex ratio ($P = 0.086$) between the two groups. Similarly, there were no significant differences between the MGD and non-MGD groups regarding the Schirmer test ($P = 0.195$), breakup time (BUT) ($P = 0.719$), NIKBUTf ($P = 0.96$), or NIKBUTavg ($P = 0.70$). The mean and median values of the parameters investigated are shown in Table 1.

Correlations Between Meiboscale and Ocular Surface Clinical Tests in All Subjects

For all patients included, the meiboscale was significantly correlated with NIKBUTf ($P = 0.05$)

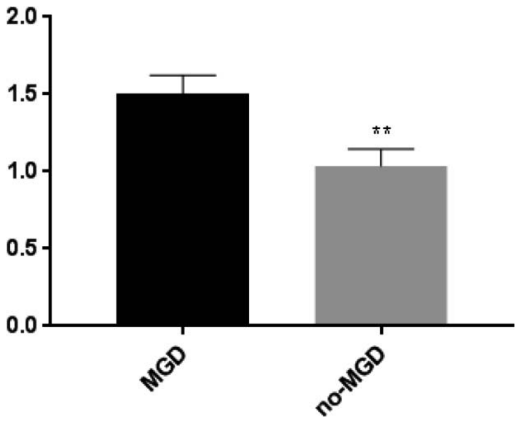

Figure 1. The MGD group had a significantly higher meiboscale than the non-MGD group ($P = 0.003$).

and NIKBUTavg ($P = 0.02$). There was no significant correlation between meiboscale and age ($P = 0.09$), OSDI ($P = 0.87$), BUT ($P = 0.92$), THM ($P = 0.62$), or Schirmer test ($P = 0.53$). The results of the correlations are presented in Table 2.

Comparisons Between Ocular Surface Tests Between the MGD and Non-MGD Subgroups

Patients in the allergic group were younger ($P = 0.0001$), and the meiboscale was significantly lower ($P = 0.019$) as compared to the MGD group. There was no significant difference in OSDI ($P = 0.843$), BUT ($P = 0.051$), NIKBUTf/NIKBUTavg ($P = 0.39$ and $P = 0.632$), THM ($P = 0.608$), or Schirmer test ($P = 0.196$) between allergic patients and MGD patients.

The PSS group was highly symptomatic, with an OSDI value significantly higher than in the MGD group ($P = 0.018$), the Schirmer test was shorter ($P = 0.013$), and the BUT was also shorter in that group ($P = 0.017$). THM was also shorter in the PSS population ($P = 0.0001$), and the meiboscale was statistically lower in the PSS group ($P = 0.044$). There was no difference regarding age ($P = 0.649$), NIKBUTf ($P = 0.112$), and NIKBUTavg ($P = 0.107$) between this group and the MGD group.

In the SSS group, the parameters showed no significant differences when compared to the MGD group. These results are presented in Table 3.

Comparisons in Non-MGD Patients

Patients in the PSS group were significantly older than the allergy group ($P = 0.0001$), more symptomatic regarding the OSDI ($P = 0.028$), with a shorter BUT ($P = 0.003$), a shorter Schirmer test ($P = 0.005$), and a lower THM ($P = 0.007$). The patients in the allergy group were also significantly younger ($P = 0.001$), had a better Schirmer test ($P = 0.018$), and had lower OSDI scores as compared to the SSS group ($P = 0.048$). There were no significant differences between the PSS and SSS groups for all parameters. The results are presented in Table 4.

Discussion

The diagnostic value of meibography associated with the MG loss grading scale has been established to diagnose MGD.[21,31] Several studies have shown that there is significantly more MG loss in symptomatic MGD patients as compared to asymptomatic patients.[21,32] Diagnostic cut-off values for the MG loss scale in combination with symptoms and lid margin abnormalities demonstrated a sensitivity of 84.9% and specificity of 96.7% to differentiate obstructive MGD from normal eyes.[21] However, no studies have reported on the potential to diagnose MGD within patients with different OSDs. Therefore, in the present study, we

Table 1. MGD Group Versus Non-MGD Group Data

Parameters	MGD	Non-MGD Allergy, PSS, and SSS Groups	*P*-Value
Age	56.32 ± 15.85	50.96 ± 18.88	0.067
Sex, % of women	71.4	85	0.086
OSDI	55.37 ± 22.05	62.88 ± 20.49	**0.043**
Schirmer 1	13.593 ± 9.329	11.655 ± 9.717	0.195
BUT	5.46 ± 2.64	5.29 ± 2.96	0.719
NIKBUTf	7.29 ± 5.32	7.24 ± 5.55	0.96
NIKBUTavg	10.96 ± 5.83	10.54 ± 5.99	0.70
THM	0.31 ± 0.16	0.24 ± 0.16	**0.008**

Bold type signifies significant results.

Table 2. Correlations Between Meiboscale and Ocular Surface Parameters for All Patients

		Age		OSDI		BUT		NIKBUTf		NIKBUTavg		THM		Schirmer	
	n	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Overall population	145	0.14	0.09	−0.01	0.87	−0.01	0.92	−0.18	**0.05**	−0.21	**0.02**	0.04	0.62	−0.05	0.53

Bold type signifies significant results.

included patients with different etiologies of OSD and evaluated MG loss with meibography. Although patients with MGD showed significantly more alterations of MG, other causes of OSD also demonstrated MG meibographic changes.

Sjögren syndrome (SS) is one of the leading causes of dry eye, and several recent studies report that MGD may play an essential role in SS.[33–35] SS patients were reported to have significantly more MG loss than both non-SS dry eyes and controls.[34] Similarly, SS patients showed higher prevalence of MGD, a higher tear evaporation rate, and more severe MG dropout than in non-SS dry eyes.[35] Previous studies that have imaged MG changes through in vivo confocal microscopy showed a greater disturbance of MG architecture in PSS than in both non-SS dry eye patients and healthy controls.[36]

These results are consistent with the present study in which significant alterations in MG were found in SS patients. The mechanisms underlying MG changes in SS patients remain unclear, but several hypotheses have been put forth, such as a lymphocyte infiltration of the MGs, hyperkeratinization of the ductal epithelium at the MG orifices, and, more recently, androgen insufficiency.[10,33–35] In the present study, MG alteration in the SSS group tended to be more severe than in the PSS group (mean meiboscale in SSS was 1.22 versus 1.0 in the PSS subgroup) and did not differ from the primary MGD group. It is interesting that the SSS group was composed only of women with a higher risk of androgen insufficiency.[37] This might explain the more severe glandular dysfunction observed with the meiboscale in that group, although the small number of patients (nine) might have made this result nonsignificant.

Arita et al.[38,39] had previously reported MG alterations with meibography among contact lens-related allergic conjunctivitis and perennial allergic patients. In this study, MG changes were also observed with meibography in patients with ocular allergy. The pathophysiology of atopic keratoconjunctivitis and perennial allergic conjunctivitis involves mostly a Th2 lymphocyte mechanism: In both of these conditions, the conjunctiva is inflamed, the corneal epithelium may be damaged, and the corneal nerves may be affected.[10] The tear film is rich in

Table 3. Ocular Surface Parameters in MGD, Allergy, PSS, and SSS Groups

		Age		OSDI		BUT		NIKBUTf	
	N	Mean	*P*	Mean	*P*	Mean	*P*	Mean	*P*
MGD	91	56.32 ± 15.85		55.37 ± 22.05		5.46 ± 2.64		7.29 ± 5.32	
Allergy	23	37.78 ± 16.23	**0.0001**	54.70 ± 18.78	0.843	6.61 ± 2.76	0.051	8.68 ± 6.25	0.39
PSS	23	58.09 ± 14.17	0.649	67.85 ± 20.34	**0.018**	4.04 ± 2.98	**0.017**	6.04 ± 5.0	0.112
SSS	9	66.44 ± 13.72	0.138	71.08 ± 19.65	0.059	5.22 ± 2.33	0.846	6.55 ± 4.53	0.74

Bold type signifies significant results.

Table 3. Extended

	NIKBUTavg		THM		Meiboscale		Schirmer	
	Mean	*P*	Mean	*P*	Mean	*P*	Mean	*P*
MGD	10.96 ± 5.83		0.31 ± 0.16		1.50 ± 1.13		13.593 ± 9.329	
Allergy	11.81 ± 6.38	0.632	0.31 ± 0.20	0.608	0.91 ± 0.73	**0.019**	16.348 ± 8.947	0.196
PSS	8.61 ± 5.14	0.107	0.17 ± 0.10	**0.0001**	1.0 ± 0.74	**0.044**	8.478 ± 9.610	**0.013**
SSS	12.39 ± 6.43	0.598	0.228 ± 0.08	0.095	1.22 ± 0.83	0.685	7.778 ± 7.345	0.066

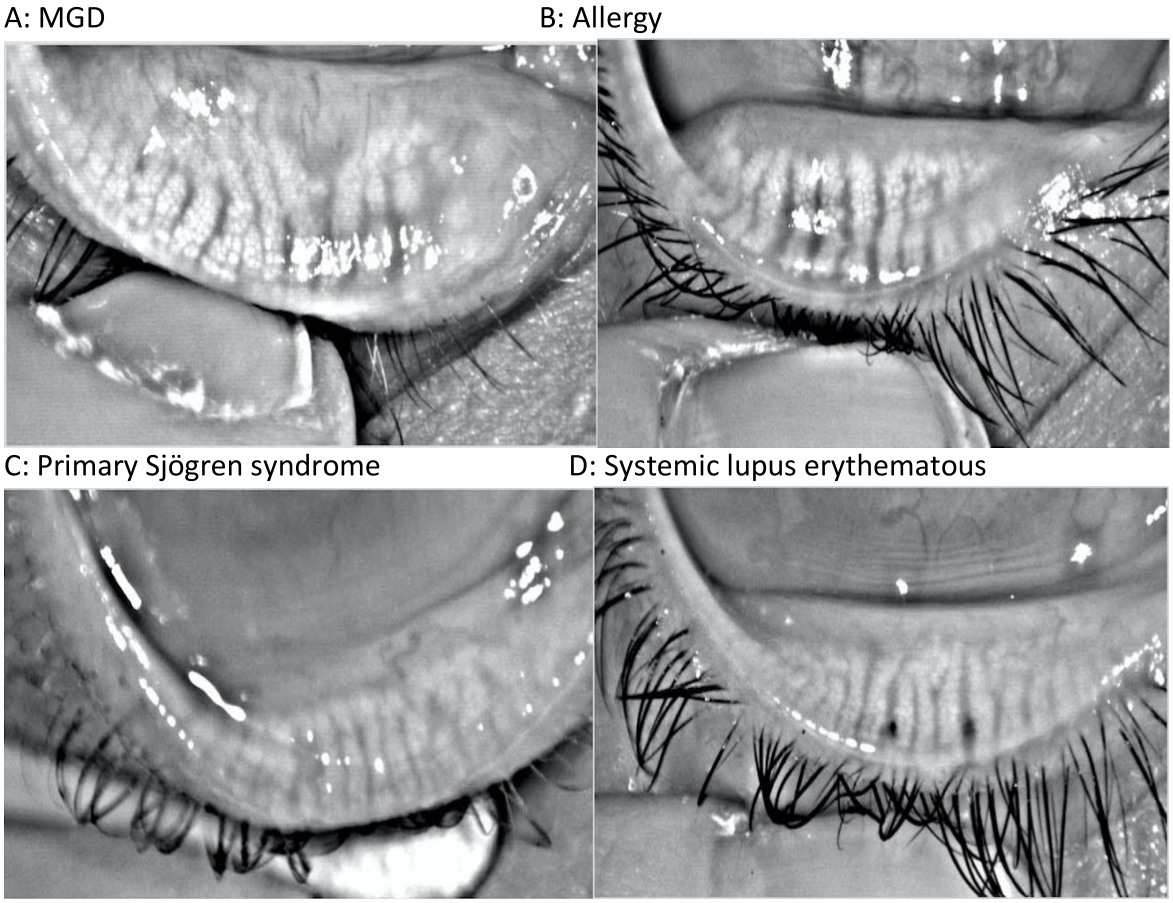

Figure 2. Examples of meibography in MGD and non-MGD groups. (A) 57-year-old woman suffering from MGD (MGD group); (B) 31-year-old woman suffering from allergy (non-MGD group); (C) 74-year-old man with PSS (non-MGD group); (D) 72-year-old woman with systemic lupus erythematous (non-MGD group).

inflammatory cytokines, mediators, and neuromediators, which can initiate and maintain chronic ocular surface inflammation.[40] The possible mechanism of MGD in ocular allergy could be direct inflammatory damage to MGs and surrounding eyelid tissues due to the increase of inflammatory cytokines, including tumor necrosis factor, interleukin-4, and interleukin-5.[41] Tumor necrosis factor and interleukin-4 are well-known inducers of fibrosis in soft tissues and may lead to alterations in MG structure and function.[42] As a consequence, the resulting disturbances in tear film quality due to MG changes may lead to an aggravation of the OSD in allergic patients.[43]

Table 4. Significant Differences (*P*) for Ocular Surface Parameters in Non-MGD Group: Allergy, PSS, and SSS Groups

	Allergy	PSS	SSS
Allergy	—		
Age		0.0001	0.001
OSDI		0.028	0.048
Schirmer		0.005	0.018
BUT		0.003	
THM		0.007	
PSS		—	No differences

The actual physiopathology of MGD is understood to be a self-perpetuating vicious circle.[10,15,17] The MG changes such as meibum stagnation, microbiological changes, liberation of lipases and esterases, increased meibum melting temperature, or hyperosmolarity induce an inflammatory cascade at the level of the ocular surface. This chronic inflammation leads directly to hyperkeratinization of MGs, inducing meibomian obstruction and even atrophy stages at the advanced stage of MGD.[17,44] In the present study, primary MGD had more severe MG loss than the secondary MGD associated with SS or allergy. The initial inflammatory mechanism, located

directly at the level of MG in primary MGD, might explain the more severe MG alterations in that group as compared to secondary MGD in which gland alterations result from other ocular surface tissue damage through inflammatory cascades.

In this study, TMH was significantly lower in the non-MGD group, whereas the Schirmer test was normal in both the MGD and the non-MGD group. Previous observations found that the Schirmer test and the TMH are a reflectance of tear secretion.[13,45] Tear fluid secretion, Schirmer, and TMH are supposed to be increased in patients with MGD as a compensatory mechanism to lipid layer deficiency in order to stabilize the tear film, whereas tear secretion, Schirmer, and TMH are decreased in PSS and SSS.[46,47] Despite its limitations, Schirmer test is a common method for evaluation of lacrimal gland secretion function.[48,49] In this study, the Schirmer test was normal in both the MGD and the non-MGD group. Although we found a lower Schirmer test in the PSS and SSS groups (8.478 $\pm$ 9.610 and 7.778 $\pm$ 7.345 mm, respectively), it was within normal range in the allergic group as previously reported (16.348 $\pm$ 8.947 mm).[38,39] These results associated with the lack of repeatability and sensibility of the Schirmer test might have contributed to the absence of difference between the MGD and non-MGD group and the discordant result with TMH.[49,50] Similarly, no significant difference was observed between MGD and non-MGD groups regarding BUT, NIKBUTf, or NIKBUTavg. This result is in accordance with several studies that could not find BUT difference between patients with aqueous tear deficiency (PSS and SSS), tear film instability (MGD group), or mixed dry eye.[13,51,52]

The diagnosis of MGD is frequently made in clinical practice by the association of symptoms of dryness and clinical assessment of lid margin changes, gland expressibility, and meibum quality.[18] In the present study, except for meibography, the results of classical clinical tests (Schirmer, BUT, NIKBUT) were not different between the MGD and non-MGD groups. In nonobvious cases of MGD, the evaluation of MG function requires specific examination of MG loss.[53] Meibography might be useful in identifying alterations of MG in different OSDs and consequently improve their management. Lid hygiene, topical macrolide, and systemic tetracyclines are widely considered to be effective therapies for MGD and blepharitis and could be a successful therapy in patients with secondary MGD related to either SS or allergy.[54] Diagnosing MG loss through meibography in patients with SS or allergy could improve the global efficiency of treatments by adding specific MGD therapy such as lid hygiene and topical or systemic antibiotics.

Several limitations should be considered when interpreting our results. In the present study, we did not find a significant correlation between age and MG loss, probably because in contrast to previous studies, our population comprised only patients with symptomatic OSD. Other studies found a significant correlation between OSDI and the meiboscale, which we did not observe in the present study.[25,55] This might be due to the large proportion of patients with SS or allergic conjunctivitis in which symptoms are not only related to MG alterations but also to their own ocular surface damage. Eventually, the regional origin of our population was not evaluated. This could have made comparison with other studies difficult. Moreover, SS and allergic patients are known to have the highest level of discordance between signs and symptoms.[56]

In conclusion, noninvasive meibography is an efficient tool to evaluate MG loss not only in primary MGD but also in MGD secondary to other OSDs. MG alterations seemed greater in primary MGD than in the other OSDs. Meibography combined with other clinical parameters could be valuable to discriminate and refine the treatment of OSD associated with MGD.

Acknowledgments

The authors thank Linda Northrup for manuscript editing.

Disclosure: **M. Robin**, None; **H. Liang**, None; **G. Rabut**, None; **E. Augstburger**, None; **C. Baudouin**, None; **A. Labbé**, None

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