Special Issue

Meibography: A Japanese Perspective

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Meibography allows observation of meibomian glands in an objective and repeatable manner. Original meibography systems were invasive and not readily adopted by ophthalmology clinics. The development of noncontact infrared meibography allowed the rapid and noninvasive observation of meibomian glands, and such systems have now been widely adopted for standard examinations in dry eye clinics. Noncontact meibography has also spurred research into meibomian glands and has been applied to evaluation of their structure and status in various ocular surface diseases. Although the images obtained by meibography are objective and repeatable, the interpretation of these images is subjective, with the relationship between image features and actual gland structure and composition remaining unclear. Additional clinical and basic research with regard to the interpretation of meibography images is thus necessary. Future improvements to meibography will likely provide new insights into the pathophysiology of meibomian gland diseases as well as enhance its contribution to the diagnosis and evaluation of treatments for such diseases.

Keywords: medication, dry eyes, eyedrops

What Is Meibography?

Meibography is a method for visualization of meibomian glands in vivo. In 1977, Tapie[1] reported the visualization of meibomian gland morphology via transillumination with white light from the cutaneous aspect of the eyelid. Conventional meibography relies on such transillumination from the cutaneous aspect to capture images of meibomian glands on black-and-white film,[1,2] on infrared film,[3,4] with a near-infrared CCD (charge-coupled device) camera,[5] or with an infrared CCD camera.[6] However, given the difficulties in performing the examination and recording the transillumination image as well as the unpleasant sensation or pain induced by the direct contact of the patient's skin with the illuminating probe in such systems, conventional meibography was largely restricted to experimental investigations rather than clinical application. It was not until a decade ago that noncontact meibography based on an infrared filter and infrared CCD camera, with illumination from the conjunctival side of the eyelid, was developed.[7,8] This noninvasive approach has now been widely adopted for clinical use and has allowed the undertaking of many clinical studies of meibomian gland diseases, as described below.

Comparison Between Conventional Meibography and Noncontact Meibography

Conventional meibography reveals meibomian glands as transilluminated images from the conjunctival aspect on placement of an illuminating probe directly on the patient's skin. Meibomian glands thus appear as dark areas on a lighter background. In contrast, noncontact meibography reveals meibomian glands as reflected images, with the glands appearing as light areas against a darker background (Fig. 1).

Noncontact Meibography

Principle

The light regions visualized by noncontact meibography are assumed to be attributable to autofluorescence of healthy meibum. Corresponding dark regions are thus assumed to indicate loss of meibomian glands, lesions with accumulation of keratinized substances, or lesions lacking meibum or with an altered meibum condition. In other words, it is not always clear whether the dark areas reflect a complete loss of gland structure (dropout) or loss or degeneration of lipid content within a relatively intact gland structure.

Variants

Three types of noncontact meibography—slit lamp based, mobile, and topography equipped—are currently available commercially in Japan. All types allow the capture of meibomian gland morphology as photos or movies (Table 1). In addition, interferometry-equipped (LipiView2; TearScience, Johnson & Johnson, Jacksonville, FL, USA), fundus camera–equipped (Cobra; CSO, Firenze, Italy), combined conventional and noncontact (LipiScan; TearScience), and iPhone-connected mobile (Tearscope; SBM, Orbassano, Italy) meibography systems have been developed and distributed.

Scoring and Quantification

The meiboscore[7] (Fig. 2) and meibo-scale[9] are grading systems for quantifying the loss of meibomian gland area. Meiboscores for the upper and lower eyelids are summed to yield a total score of 0–6 for each eye.[7] In contrast, the meibo-scale assigns a value of 0–4 for each eyelid.[9] Meiboscores of 0–3 for each eyelid correspond to no loss of meibomian glands, a lost area of less than one-third of the total gland area, a lost area of between one- and two-thirds of the total gland area, and a lost area of

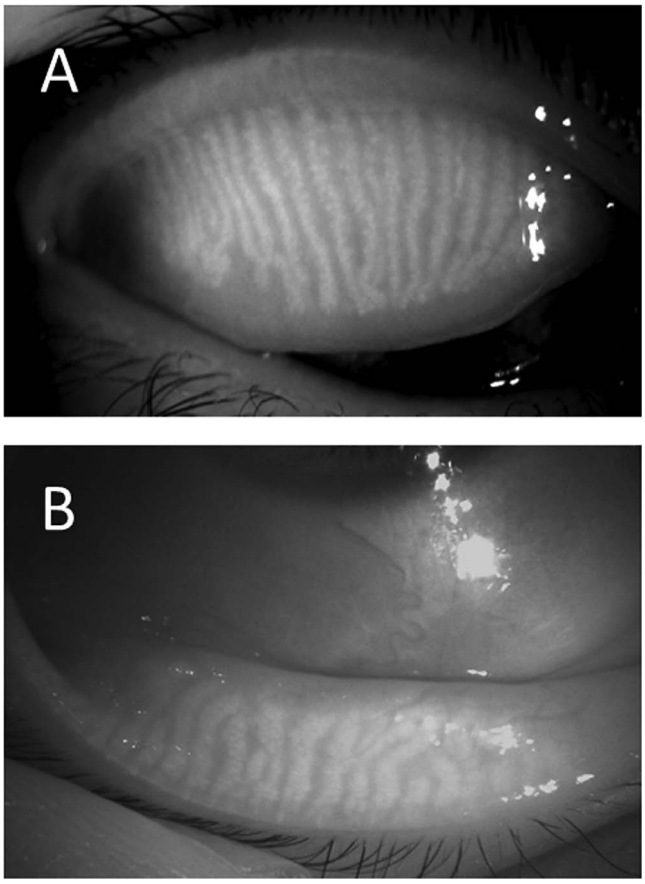

FIGURE 1. Representative images of meibomian glands in the upper and lower eyelids of a healthy subject obtained by noncontact meibography. Meibomian glands are detected as areas of high reflectivity, with those in the upper eyelid (**A**) being more slender and elongated than those in the lower eyelid (**B**).

more than two-thirds of the total gland area, respectively.[7] Nichols et al.[5] also proposed a four-point scale for quantification of meibomian gland loss, with scores of 0–3 corresponding to the absence of partial glands, <25% partial glands, 25%–75% partial glands, and >75% partial glands, respectively.[5] Although this scale and the meiboscore are both four-point scales, the cutoff values for evaluation of meibomian gland loss are different. The five-point meibo-scale assigns values of 0–4 for 0%; <25%; 26%–50%; 51%–75%; or >75% meibomian gland loss, respectively.[9,10] Pult and Riede-Pult[9,10] compared their five-point scale with the four-point scale of Nichols et al.[5] and found that intraobserver agreement was better for the former. The fact that meibomian glands can be readily assigned to three portions of the eyelid (nasal, central, and temporal) renders the meiboscore easy to apply. However, the five-point meibo-scale appears to be more sensitive for comparisons of treatment efficacy or evaluation of the severity of meibomian gland dysfunction (MGD).[9]

The development of software for automated measurement of meibomian gland area[11] has facilitated evaluation of the efficacy of eyedrop application,[12] eyelid warming,[13] and intraductal probing[14] for the treatment of individuals with MGD. Other versions of such software have also been developed[15] and applied to digital analysis of images for evaluation of the lost area of meibomian glands.[10] Although meibography itself is objective and repeatable, interpretation of the resulting images remains subjective. Implementation of user-friendly digital analysis software is likely to further promote the application of meibography in clinical practice.

Sensitivity and Specificity

The sensitivity and specificity for diagnosis of MGD by noncontact meibography (cutoff value for meiboscore of ≥3) as a single test were found to be 49.3% and 64.5%, respectively.[16] Diagnosis of obstructive MGD based on any one of three scores—ocular symptom score, lid margin abnormality score, and meiboscore—being abnormal yielded a sensitivity of 100% and specificity of 68.3%; diagnosis based on any two of the three scores being abnormal yielded a sensitivity of 84.9% and specificity of 96.7%; and diagnosis based on all three scores being abnormal yielded a sensitivity of 66.0% and specificity of 100%.[17]

Relation to the Lipid Layer of the Tear Film

Meibography reveals the morphology of meibomian glands and therefore does not allow direct evaluation of the lipid layer of the tear film. Whereas some studies have found that loss of meibomian gland area correlated with a decrease in lipid layer thickness,[18–20] which is an indicator of meibomian gland function, other researchers have found that meibomian gland loss detected by noncontact meibography, in particular in the nasal portion of the eyelid, was not associated with impairment of meibum expression, another indicator of meibomian gland function.[21,22]

Changes to Meibomian Glands in Various Conditions Revealed by Noncontact Meibography

Changes to meibomian glands associated with various ocular surface diseases and other conditions have been revealed by noncontact meibography (Table 2).

Aging

Aging in healthy individuals has been found to be accompanied by a loss of meibomian glands.[7,16,23–26] Shirakawa et al.[24] compared the structure of meibomian glands between adults (age range of 24 to 39 years) and children, including infants (age range of 1 month to 12 years). They found that gland

TABLE 1. Characteristics of Noncontact Meibography Systems Commercially Available in Japan

Characteristics	Slit Lamp Attached	Mobile	Topography Equipped
Light wavelength	890 nm	940 nm	840 nm
Movie or photo	Both	Both	Photo only
Product name	SL-D701 BG-4M/DC4 BG-5	Meibom Pen	Keratograph 5M
Company	TOPCON (Tokyo, Japan)	Japan Focus Corp. (Tokyo, Japan)	OCULUS Optikgeräte GmbH (Wetzlar, Germany)

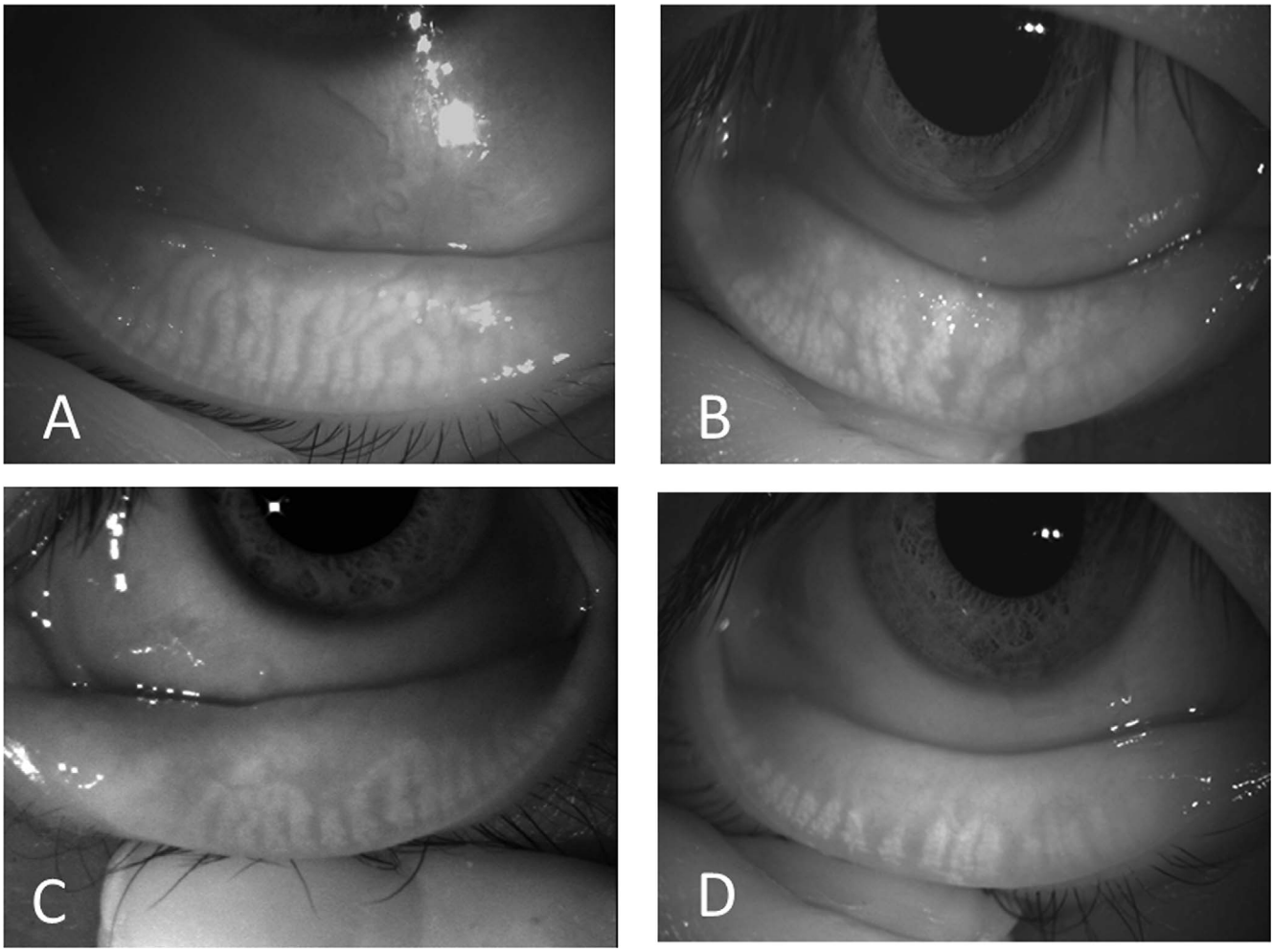

FIGURE 2. Meiboscore. Partial or complete loss of meibomian glands is graded from 0 to 3 for each eyelid. Representative noncontact meibography images of lower eyelids with meiboscores of 0, 1, 2, and 3 are shown in (**A–D**), respectively.

structure was as well developed even in infants at 1 month of age as in adults, with glands being distributed across the entire tarsal plates in both the upper and lower eyelids.[24] Byun et al.[27] investigated the embryonic development of human meibomian glands. Meibomian glands were apparent and had grown into the tarsal plate at 18 weeks of gestation. Branching of the glands was detected at 20 weeks, and they occupied almost the entire length of the tarsal plates at 36 weeks. Taken together, these observations thus indicate that the structure of meibomian glands is complete at the time of birth.

The impact of aging on the morphology of meibomian glands was examined by noncontact meibography in 236 healthy volunteers (age range of 4–98 years).[7] A significant positive correlation between age and morphologic changes to the glands (meiboscore) was detected regardless of sex. In the 20- to 29-year-old age group, the average meiboscore in men was greater than that in women ($P = 0.0195$), but Bonferroni's correction for multiple measurements rendered this difference insignificant. Another study found that meibomian gland dropout was also significantly correlated with age (age range of 19–75 years).[23] In addition, another group detected a significant decline in meibomian gland area with age in 370 subjects (age range of 25–66 years).[25] Mizoguchi et al.[26] examined the morphology of meibomian glands in adolescents (15 years of age) and detected shortening or distortion of the glands, with these changes being more prominent in boys than in girls. Taken together, the results of these various studies indicate that aging is an important risk factor for the development of MGD. It should be noted that hormonal and environmental influences on the structure of meibomian glands may be confounding factors in such studies, however.[28,29]

Contact Lens Wear

Many studies have shown that contact lens wear negatively affects the condition of meibomian glands,[30–38] although some have found no relation between lens wear and gland condition.[39–41] In wearers of rigid gas-permeable lenses, gland changes were detected at the temporal side in the upper eyelid, whereas wearers of soft contact lenses manifested linear shortening at the distal side in the lower eyelid (Fig. 3).[32] The mechanism of such linear shortening is unclear, but it may involve mechanical friction due to blinking, eyelid pressure, or a chemical effect of multipurpose solution. Given that sample sizes have been modest at best in studies of the effects of contact lens wear on meibomian glands, further prospective and longitudinal studies with larger subject populations are warranted.

Table 2. Studies That Have Applied Noncontact Meibography to Reveal Morphologic Changes to Meibomian Glands Associated With Various Conditions

Study	Number of Subjects or Eyes	Sex Ratio, M/F	Mean Age (Range), y	Subjects or Condition
Arita et al.[7]	236 eyes	114/122	41.2 ± 23.1 (4–98)	Effect of age documented over wide age range, regardless of sex.
Ban et al.[23]	37 eyes	23/14	46.5 ± 15.4 (19–75)	Effect of age detected in a cohort spanning young adults to seniors.
Shirakawa et al.[24]	78 subjects	30/48	4.1 ± 3.4 (1–12)	Glands found to be well developed in children, including infants.
Yeotikar et al.[25]	370 eyes	261/109	43.9 ± 11.8 (25–66)	Effect of age on gland morphology was accompanied by reduced quality and quantity of meibum, regardless of sex, ocular symptoms, or meibum lipid class.
Mizoguchi et al.[26]	111 eyes	56/55	15 years	Gland morphologic changes detected in adolescents, with the changes being more prominent in males than in females.
Arita et al.[32]	121 subjects	47/74	31.8 ± 8.0	Shortening and dropout of glands detected in contact lens wearers, with the changes being proportional to the duration of lens wear.
Pucker et al.[41]	70 subjects	26/44	30.6 ± 12.4	No significant association of contact lens wear with meibomian gland atrophy.
Alghamdi et al.[37]	100 subjects	49/51	25.4 ± 4.1 (18–35)	Changes to gland morphology and function in contact lens wearers apparent within 2 y of the onset of lens wear.
Arita et al.[42]	55 eyes	11/44	32.3 ± 15.6	Gland duct distortion detected in patients with allergic conjunctivitis.
Na et al.[43]	58 subjects	18/40	(7–18)	Gland distortion and papillary hypertrophy apparent at 24 mo after overnight orthokeratology.
Arita et al.[17]	53 subjects	18/35	71.4 ± 10.0	Gland dropout, shortening, distortion, and dilation detected in MGD patients. Combination of ocular symptoms, lid margin abnormalities, and meiboscore found useful for MGD diagnosis.
Eom et al.[20]	26 subjects	6/20	58.9 ± 9.9 (37–74)	Gland loss and meibum grade greater in lower eyelids than in upper eyelids of MGD patients. Gland loss correlated with meibum grade, but not with tear film breakup time or corneal staining.
Finis et al.[16]	128 subjects	36/92	57 ± 17	Gland atrophy (meiboscore) greater in the nasal third than in the middle and temporal thirds of the eyelid in MGD patients. Meiboscore, meibum grade, and tear film breakup time were correlated.
AlDarrab et al.[44]	36 patients (vs. 43 healthy controls)	21/15	63.5 ± 9.0	Gland dropout, distortion, and shortening were significantly greater in patients with posterior blepharitis than in controls.
Srinivasan et al.[47]	Case report	1 female	29	Partial or complete gland loss in area affected by chalazion.
Nemoto et al.[49]	5 chalazion and 3 sebaceous carcinoma patients	3/5	57.5 ± 25.7 (29–89)	Chalazion detected as lesions of low overall reflectivity, whereas sebaceous carcinoma detected as poorly marginated lesions of high reflectivity.
Fukuoka et al.[48]	7 patients (and 7 controls)	7 males	44.3 ± 11.2 (29–56)	Gland dropout and shortening found to be associated with chalazion and related to tear film breakup time and stability of ocular higher-order aberrations.
Arita et al.[50]	31 eyes (vs. untreated contralateral eyes)	18/13	65.0 ± 13.0	Gland morphologic changes detected in eyes treated with antiglaucoma eyedrops.
Sagara et al.[52]	55 eyes	26/13	66.7 (40–93)	Gland loss for bleb-contacting areas of upper eyelid was greater than that for noncontacting areas in patients post trabeculectomy.
Suzuki et al.[55]	16 eyes	4/9	13.8 ± 8.6	Gland loss detected in patients with phlyctenular keratitis.
Koh et al.[54]	Case report	1 female	16	Marked changes to glands apparent in a patient with marginal staphylococcal keratitis.
Palamar et al.[56]	36 eyes		50.2 ± 9.5 (32–65)	Significant meibomian gland loss detected in ocular rosacea.
Machalinska et al.[57]	82 eyes	11/30	58.37 ± 7.3	Gland area and density found to be reduced in rosacea patients.
Chen et al.[58]	34 patients	34 females	52.9 ± 11.9 (32–72)	Gland loss detected in patients with primary Sjögren's syndrome.
Engel et al.[59]	86 eyes	48/38	51.3 ± 14.1 (13–75)	Gland loss detected in patients with ocular graft-versus-host disease.
Kusne et al.[60]	21 eyes	8/13	52.4 ± 12.1 (30–76)	Gland atrophy did not correlate with clinical conjunctival scarring or subepithelial fibrosis in ocular graft-versus-host disease.
Sakimoto[61]	11 patients	3/8	64.1 ± 12.5	Gland loss or shortening detected in patients with granular corneal dystrophy type 2.
Ito et al.[62]	13 eyes	2/6	65.1 ± 17.6	Gland dropout and meiboscore found to be greater in patients after radiotherapy.
Woo et al.[63]	28 patients	11/17	46.0 ± 16.9	Percentage gland dropout was significantly correlated with age and total radiation dose in eyes that received periocular radiotherapy.
Eom et al.[69]	20 patients	12/8	62.3 ± 15.4 (33–81)	Gland loss was greater and the lipid layer of the tear film thinner in patients receiving chemotherapy with lacrimal duct obstruction than in those without obstruction.

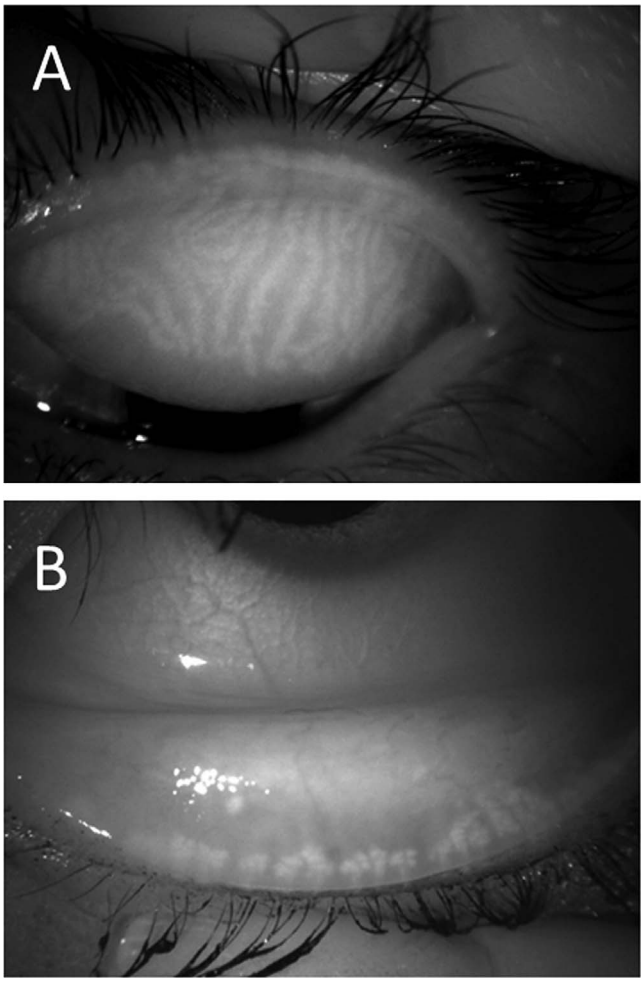

FIGURE 3. Representative images of meibomian glands in the upper and lower eyelids obtained from a wearer of disposable soft contact lenses by noncontact meibography. Distortion and shortening of gland ducts are apparent in the upper (**A**) and lower (**B**) eyelids, respectively.

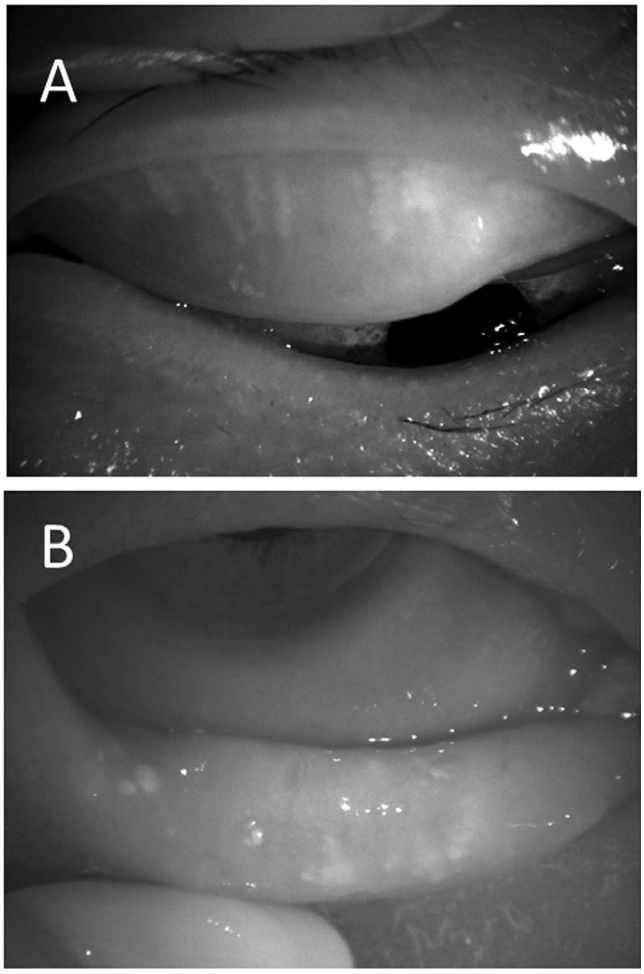

FIGURE 4. Representative images obtained by noncontact meibography from a patient with MGD. Various morphologic changes of meibomian glands including dropout, shortening, and distortion are apparent in both upper (**A**) and lower (**B**) eyelids.

Allergic Conjunctivitis

Distortion of meibomian gland ducts has been observed in the upper eyelid of individuals with allergic conjunctivitis.[42,43] This distortion has been proposed to result from mechanical stimuli associated with the relief of itching, but the mechanism is unknown.[42]

Meibomian Gland Dysfunction

Changes to meibomian gland morphology associated with MGD include dropout, shortening, truncation, distortion, and dilation[16,17,20,44] (Fig. 4). Given that meibography is an objective and repeatable examination method, taken together with subjective symptoms and lid margin findings, it allows highly reliable diagnostic evaluation of MGD.[17] The loss of meibomian gland area was also found to show a significant positive correlation with meibum grade.[18–20] Moreover, the combination of noncontact meibography and Schirmer's test value for tear fluid production was effective for differential diagnosis of MGD and aqueous-deficient dry eye (ADDE): meiboscore of 4.17 ± 1.60 (mean ± SD) versus 2.07 ± 1.28 ($P = 0.0004$) and Schirmer's test value of 14.5 ± 6.80 vs. 1.00 ± 1.78 mm ($P < 0.0001$) for MGD versus ADDE.[45] An epidemiologic study based on these diagnostic criteria revealed that 86% of dry eye patients have MGD.[46] Taken together, the results of these various studies indicate that noncontact meibography is useful for the diagnosis of MGD as well as for observation of the eyelid margins.

Chalazion and Sebaceous Carcinoma

A case report of a 29-year-old woman with recurrent chalazion described meibomian gland dropout and shortening in the eyelid with active chalazion.[47] Chalazion lesions were revealed by noncontact meibography as dark areas corresponding to the destruction of gland structure,[47,48] whereas lesions of sebaceous carcinoma were detected as light areas with an unclear margin.[49] Noncontact meibography thus also has the potential to identify malignancy of eyelid tumors.[49]

Treatment With Antiglaucoma Eyedrops

Topical application of antiglaucoma drugs can damage components of the ocular surface. Although such treatment has been found to adversely affect the structure of meibomian glands, it remains unclear to what extent these effects are attributable to the preservative or the active ingredient of the eyedrops.[50–53] A study of meibomian glands in glaucoma patients after trabeculectomy with mitomycin C revealed that the glands adjacent to the bleb were damaged compared with

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those distant from the bleb,[52] suggesting that drug-induced meibomian gland injury occurred through the palpebral conjunctiva.

Phlyctenular Keratitis

Morphologic changes to meibomian glands have been observed in association with phlyctenular keratitis,[54,55] suggesting that chronic inflammation or infection might promote meibomian gland loss.

Rosacea

The meiboscore of individuals with ocular rosacea was found to be significantly higher than that of control subjects,[56–58] suggesting that rosacea, a condition with which MGD is often associated, affects the morphology of meibomian glands.

Ocular Graft-Versus-Host Disease

Patients with ocular graft-versus-host disease were found to show a significant loss of meibomian glands compared with control individuals, suggesting that gland abnormalities may be a cause of dry eye in such patients.[59,60] Further research is required to help elucidate the role of acute versus chronic inflammation in driving the meibomian gland changes observed in graft-versus-host-disease.

Granular Corneal Dystrophy Type 2

Meibomian gland morphology was compared in one study between patients with granular corneal dystrophy type 2 positive for the R124T point mutation of the *TGFBI* gene and age- and sex-matched control subjects.[61] Dropout and shortening of meibomian glands were significantly greater in the patient group than in the control group. It was deemed possible that abnormal phospholipids found to accumulate in the cornea of such patients were derived from meibomian gland secretions.

Radiotherapy

Examination of the effect of radiotherapy on meibomian glands has revealed that such treatment can induce morphologic changes such as gland dropout or atrophy.[62,63]

Chemotherapy

Treatment with several chemotherapeutic agents such as docetaxel, 5-fluorouracil, and S-1 (tegafur) has been shown to result in lacrimal dysfunction and epiphora.[64–67] These agents induce keratinization of epithelial cells and ductal structural fibrosis that lead to obstruction of the nasolacrimal duct system.[64] Oral administration of S-1 was also found to result in meibomian gland loss,[68] and patients with chemotherapy-induced lacrimal obstruction were found to manifest more severe meibomian gland loss and a thinner lipid layer of the tear film than patients without lacrimal obstruction.[69] These findings indicate that the structure and function of meibomian glands are affected by chemotherapeutic agents, as are those of lacrimal ducts.

Meibography for Studies of MGD Pathophysiology

Noncontact meibography has been applied to the study of homeostasis of tear film components. The positive relation apparent between the area of meibomian gland loss and Schirmer's test value suggests that decreased production of the components of the lipid layer of the tear film is compensated for by increased production of tear fluid (compensation theory).[25,70–72]

Limitations of Meibography

Identification of defects in meibomian gland morphology by noncontact meibography has increased awareness of meibomian gland–related diseases and prompted the development of new treatments. Despite the repeatability and objectivity of noncontact meibography, however, further clinical and basic research is required to improve interpretation of the resulting images. The current subjective nature of such an interpretation is in part due to the lack of definitive evidence linking meibography findings to the true structure and composition of meibomian glands. This issue might be resolved by the introduction of highly sensitive and high-resolution techniques, such as three-dimensional meibography based on optical coherence tomography, that are able to reveal the acinar structure of the glands in more detail.[73]

Meibography is also not sufficiently sensitive or specific to indicate symptomatology. There are several possible explanations for this deficiency. First, the quality of the lipid layer of the tear film (which reflects gland function) may not correlate with meibomian gland dropout.[21] Second, not all meibomian glands are active at any one time.[74,75] And third, meibomian glands may appear relatively normal on meibography but experience nonobvious obstruction that results in marked symptoms.[76] As of now, therefore, a combination of a morphology test (such as meibography) and function test (such as meibomian gland expression) is recommended to guide therapy.

Future Directions

Despite the high prevalence of MGD, the pathophysiology of this condition remains unclear. The development of noncontact meibography has greatly facilitated observation of the morphologic changes of meibomian glands associated with various ocular surface diseases as well as investigations into MGD pathophysiology. Given the presumed importance of early detection and treatment of MGD, it is recommended that meibography be applied to observe the morphology of meibomian glands and that the condition of the tear film be evaluated and corneal-conjunctival staining performed when a patient with dry eye symptoms is first seen by an ophthalmologist. Meibography is the most clinically useful procedure available at the current time for evaluation of meibomian gland morphology and the prognosis of MGD patients. It can also assist in the identification of possible causes of dry eye symptoms, helping to differentiate aqueous deficiency from evaporative dry eye. In addition, information from the quantitative analysis of the meibomian gland area may have the potential to be applied to monitoring of treatment efficacy. In the future, further development of hardware, such as detection devices and light sources, will provide additional information regarding the state of meibomian glands such as the condition of meibum and atrophy of gland ducts. Meibography has the potential to become routinely adopted as a contributing feature to the diagnosis of MGD. Moreover, the combination of tear interferometry and meibography will allow morphologic and functional evaluation of meibomian glands and thereby provide a detailed picture of the lipid layer of the tear film, with such an approach likely to become the gold standard in dry eye clinics.

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