



## Clinical Practice

## The role of meibography in ocular surface diagnostics: A review

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## A B S T R A C T

The meibomian glands are lipid-secreting glands located in the tarsal plates, whose secretory products cover the tear film, thereby reducing evaporation as well as ensuring lubrication of the ocular surface. The meibomian glands can be visualized at different levels of magnification by infrared meibography, laser confocal microscopy, and optical coherence tomography. These imaging modalities have been subject to much research and progress in clinical practice and have shaped our current understanding of meibomian glands in health and disease. In this review, we explore the evolution of meibography over the past decades, the major contributions of various meibographic modalities, and discuss their clinical significance.

## 1. Introduction

## 1.1. Meibomian glands

The meibomian glands (MGs) are modified sebaceous glands located superficially in the tarsal plates. In healthy subjects, the MG orifices are dispersed at regular intervals anterior to the mucocutaneous junction along the lid margins [1]. The number of glands in the upper eyelid usually range from 25 to 40, while the number of glands in the lower lid usually lie between 20 and 30 [2]. The MGs of the upper eyelid are longer and slimmer than those of the lower eyelid, measuring approximately 5.5 mm centrally in the upper eyelid, as compared to 2 mm in the lower eyelid [2].

The MGs are made up of meibocytes; these modified sebaceous cells synthesize and secrete a lipid compound referred to as meibum [2]. Meibum helps lubricate the ocular surface and prevent tear evaporation and thus dehydration of the corneal surface. It also functions as a hydrophobic barrier, shielding the eye from external noxious agents. The classic three-layer model of the tear film consists of an intermediate aqueous layer surrounded by an inner mucin layer and a superficial lipid layer [3]. In the latest Tear Film and Ocular Surface Society Dry Eye Workshop (TFOS DEWS) II report, the tear film subcommittee advocate a two-layer model comprising an inner mucoaqueous layer and a superficial lipid layer [3].

## 1.2. Meibomian gland dysfunction

Dry eye disease (DED) is a multifactorial disease whose core pathophysiological hallmark is the disruption of tear film homeostasis [4]. According to the most recent classification, aqueous-deficient and evaporative dry eye are not mutually exclusive entities; rather, they might coexist in unison along a spectrum. Evaporative DED is more common than aqueous-deficient DED, and MG dysfunction (MGD) is the most common cause of evaporative DED. The term “meibomian gland dysfunction” was established in 1980 by Korb and Henriquez [5]. The international workshop on MGD defines it as “a chronic, diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion. This may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease” [6]. The TFOS DEWS II epidemiology subcommittee conducted a meta-analysis, finding a DED prevalence of 5–50% [7]. MGD may be the cause of DED in as many as 65–86% of such cases [8–10].

## 1.3. Meibography

*Meibography* refers to the imaging of the MGs. Several modalities are currently available, each with inherent advantages and disadvantages.

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<https://doi.org/10.1016/j.jtos.2020.05.004>

Received 2 January 2020; Received in revised form 10 April 2020; Accepted 5 May 2020

Available online 19 May 2020

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Benefits of meibography include monitoring and staging of disease progression as well as evaluation of treatment potential and effects. Disadvantages include expensive equipment and, to varying degrees, time-consuming data analysis and procedures. Some modalities are also invasive and can be uncomfortable for the patient.

## 2. Methods

### 2.1. Methods

Articles assessed for inclusion in this review were identified by a PubMed Search until June 1, 2019, using individual and combinations of the following keywords: “dry eye disease,” “meibomian gland dysfunction,” and “meibography.” In addition, a review of the reference section of relevant publications was performed. Criteria for inclusion include relevance and full-text access. Criteria for exclusion were abstract only, lack of relevance, or a non-English language.

## 3. Meibographic modalities

### 3.1. Contact meibography

Contact meibography is considered the origin of meibography, and was introduced by Tapie et al., in 1977 [11]. It is an invasive procedure of infrared (IR) transillumination by a light probe applied directly to the skin of the everted eyelid. The procedure was further developed by Jester et al., in 1982 through their experiments on rabbits using white-light transillumination and a high-speed IR film on a slit lamp microscope [12], a method applied to humans in 1985 by Robin et al. [13]. The term meibography was first used by Mathers et al., in 1991 [14]. These early methods were cumbersome; IR film was expensive, and the invasiveness of the procedure made it uncomfortable for patients. These disadvantages spurred the development of a video meibography system with a redesigned transillumination probe in 1994 [15]. The next step in the evolutionary line of video meibography was presented in 1996 by Matsuoka and associates with the invention of the charge-coupled device (CCD) camera benefitting from penlight illumination [16]. This design was improved in 2007 with the introduction of a T-shaped probe that was more comfortable for the patient, providing a larger area of transillumination as well as aiding in the eversion of the eyelids [17]. However, the impact of this new design was soon overshadowed by the advent of several novel techniques in MG imaging, as discussed in the following sections.

### 3.2. Non-contact infrared meibography

Introduced in 2008 by Arita et al., non-contact IR meibography represents a non-invasive, more patient-friendly, and less time-consuming technique. The system is composed of a slit lamp equipped with an IR transmitting filter and an IR CCD video camera, negating the need for a transilluminating probe [18]. Due to the narrow observation field in contact meibography, the central area of the lower lid was occasionally extrapolated to represent the entire eyelid area [8,11,14,19,20]; a presumption no longer necessary when using non-contact meibography. A historical overview of meibographic modalities are summarized in Table 1.

Arita et al. presented yet another leap forward in 2013 with the introduction of the mobile pen-shaped meibography system [21]. This system bypasses the requirement for the patient to sit by the slit lamp, a quality of great value when examining infants or patients with severe systemic diseases such as Stevens-Johnson syndrome. The principle of non-contact IR meibography was utilized by all of the non-invasive IR meibography devices including Keratography and optical coherence tomography meibography. Therefore, the development of non-contact IR meibography became a break-through for MG research and contributed to clarify the effect on the structure of meibomian glands by various

**Table 1**

Historical overview of the introduction of new meibographic modalities.

Year	Modality	Author
1977	Introduction of CM	Tapie et al. [11]
1982	CM with high-speed IR film on a slit lamp	Jester et al. [12]
1994	CM with video, redesigned probe	Mathers et al. [15]
1996	CM with CCD camera and penlight illumination	Matsuoka et al. [16]
2005	IVCM first used to identify MGs	Kobayashi et al. [23]
2007	CM with redesigned, T-shaped probe	Yokoi et al. [17]
2008	Non-contact meibography with IR CCD camera on slit lamp	Arita et al. [18]
2010	OCT production of 2D and 3D images of MGs	Bizheva et al. [27]
2012	Non-contact meibography with OCULUS Keratograph 4	Srinivasan et al. [22]
2013	Non-contact meibography with mobile pen device	Arita et al. [21]
2013	OCT to capture IR images of MGs	Hwang et al. [28]
2013	FD-OCT reconstructing 3D images of MGs	Hwang et al. [29]

CM: contact meibography, IVCM: in vivo confocal microscopy, IR: infrared, CCD: charge-coupled device, MG: meibomian gland, FD: Fourier domain, OCT: optical coherence tomography.

ocular surface diseases.

### 3.3. Keratography

Originally designed for corneal topography, Srinivasan et al. used the OCULUS Keratograph 4 to evaluate the MGs and their morphological changes in 2012 [22]. With this, new objective measures such as MG tortuosity and acinar changes were proposed. In 2012, OCULUS (Wetzlar, Germany) introduced Keratograph 5 M, a device optimized for meibography. Other commercially available non-contact devices now include the Sirius Scheimpflug camera (CSO Italia, Florence, Italy), COBRA: Fundus Camera (CSO Italia), Eye Top topographer (CSO Italia), LipiView II (TearScience, Morrisville, NC, USA), BG-4M/DC-4 (Topcon, Tokyo, Japan), Meibom Pen (Japan Focus Corporation, Tokyo, Japan), and the Meiboviewer 2.0 (Visual Optics, Chuncheon, Korea).

### 3.4. In vivo confocal microscopy

In vivo confocal microscopy (IVCM) enables in vivo imaging at the cellular level that is comparable to histological analysis. The examination requires the instillation of a topical anesthetic and direct contact between the microscope and the everted eyelid for approximately 3–5 min. IVCM was first used to depict meibomian glands by Kobayashi et al., in 2005 [23]. In the following years, several new, objective parameters were introduced, such as the acinar unit diameter, acinar unit density (AUD), and periglandular inflammatory cell infiltrates [24,25]. These parameters have since been revised and supplemented to include MG acinar longest diameter (MGALD), MG acinar shortest diameter (MGASD), inflammatory cell density (ICD), and MG acinar unit density (MGAUD) [26].

### 3.5. Optical coherence tomography meibography

To our knowledge, Bizheva et al. were the first to describe the MGs using ultrahigh-resolution optical coherence tomography (OCT) [27]. They used a 1060-nm system, producing in vivo 2D and 3D tomograms. In 2013, Hwang et al. used a commercially available anterior segment OCT (AS-OCT) to capture IR meibographic images and tomograms [28]. Referring to the IR AS-OCT as “Hosik” meibography (named after the author, Ho Sik Hwang), the authors advocated the need for only one device to acquire both IR meibograms and tomograms. The AS-OCT system had a wavelength of 1310 nm and could not produce 3D images. This limitation led to the development of a Fourier-domain OCT capable of reconstructing 3D MG images, producing highly detailed

images through various stages of glandular dysfunction [29]. The advantages and disadvantages of the different meibographic modalities are summarized in Table 2.

#### 4. Interpretation of meibography

##### 4.1. Grading schemes of meibomian gland dropout

Several schemes for grading and quantifying MG dropout have been proposed, as presented in Table 3. Initially, grading the amount of MG dropout was subjective. Nichols et al. examined the inter-observer and intra-observer reliability of a gestalt scale and a scale based on the counting of whole glands [20]. They found fair to moderate reliability and a strong relationship between the scales. Another study, using a 4-grade scale, found moderate inter-observer reliability [30]. Since then, computerized grading of glandular dropout using software such as ImageJ (National Institutes of Health, Bethesda, MD, USA) have become available, as illustrated in Fig. 1. Inter-observer and intra-observer agreement is superior when using computerized grading when compared to a subjective 5- and 4-grade scale [31]. The 5-grade scale showed higher reliability than the 4-grade scale. Computerized grading necessitates manual outlining of the tarsal plate and gland-containing area within. Not only is it time-consuming, different operators may define these areas differently, affecting inter-rater reliability. Attempts at developing fully automated computational algorithms for recognizing the lid area and for isolating MGs have shown promising results [32–34].

#### 5. Major meibographic findings in health and disease

##### 5.1. Meibomian gland dysfunction

Using contact meibography, the MGs are visualized as hypolucent stripes perpendicular to the eyelid margin. In contrast, in non-contact meibography, the MGs are hyperlucent. IR meibography can visualize various MG abnormalities, such as MG dropout, gland shortening, and tortuosity. Compared to the MGs in healthy controls, DED is associated with a higher degree of MG dropout [92,104–109]. There are

correlations between MG dropout and lipid layer thickness [106,110], non-invasive tear film break-up time (NIBUT) [110], tear film break-up time (TBUT) [106,111], meibum expressibility [111,112], and tear film osmolarity [113]. Pult et al. showed that the MGs of the lower lid are significantly wider than that of the upper lid, while there is greater curvature in the MGs of the upper lid. There is a greater degree of MG dropout in the lower lid [110], a finding corroborated by other studies [106,112]. Whether there is an area of the lids more prone to dropout remains unresolved [111,114]. Comparing obstructive MGD to aqueous-deficient dry eye, the former has a higher meiboscore and Schirmer test result [115,116]. It has been hypothesized that the latter results from compensatory mechanisms to stabilize and maintain tear film homeostasis. Arita et al. demonstrated that the ocular symptom score, lid margin abnormality score, meiboscore, and TBUT are suited for differentiating between MGD and health [105]. They reported sensitivity of 84.9% and specificity of 96.7% for diagnosing MGD based on the combination of any two: reported symptoms, lid margin abnormalities, and meiboscore. The cut-off value for the meiboscore (by Arita et al.) was set to three or more [105]. A recent study using the OCULUS Keratograph 5 M reported sensitivity of 96.7% and specificity of 85% in diagnosing MGD based on meibography, with an average meibograde for all four eyelids of 0.5 or more [92].

IVCM can image the glandular acinar units of MGs as convoluted structures surrounded by cuboidal basal cells with grey cytoplasm [117]. In patients with MGD, the acinar units can appear both dilated and atrophied due to the inspissation of meibum and the surrounding periglandular fibrosis, respectively [24]. Quantifiable parameters on the size and density of acini and the presence of inflammatory cell infiltrates are all significantly different in patients with MGD when compared to that of healthy controls [24,26,118]. These parameters correlate with tear functions, ocular surface staining, meibum expressibility, and degree of MG dropout [24,26,118,119]. MGAUD tends to be lower, while the remaining parameters tend to be higher, indicating dilation and dropout. An interesting finding is that as MGD progresses, the acinar size and density decrease, while the ICD increases [119]. The ability to visualize inflammatory cell infiltrates has proven valuable for explaining why some patients remain symptomatic following treatment despite improvement of the clinical parameters [120].

The use of OCT for meibography is still in its infancy. Different projections may be obtained using various techniques, such as 2D cross-sections [27], 3D imaging [27,29,121,122], IR 2D imaging resembling non-contact meibography [28,123], and cross-sections perpendicular to gland length [28,123]. Liang and co-workers examined 22 patients with obstructive MGD and found a significantly decreased mean MG length and width as well as increased conjunctival thickness in the patients when compared to controls [123]. The OCT meibography parameters correlated with ocular surface symptoms and clinical signs. Napoli et al. published a study comparing traditional contact meibography to IR meibography performed by a commercially available spectral-domain OCT [124]. The experiment involved 61 patients with obstructive MGD and 75 controls. The authors found complete agreement between the techniques for detecting and grading MG dropout, although significant asymmetry was detected for segmentation, perhaps due to the higher sensitivity of the OCT. Using a customized swept-source OCT, researchers have been able to visualize MG acini and ducts through 3D reconstruction in areas labelled as total MG dropout with IR meibography [122]. This is a reminder of our lack of knowledge of what MG dropout truly represents [125], be it due to qualitative or quantitative changes of the meibum, loss of glandular structure, agglomeration of substances, or an as of yet undiscovered mechanism.

##### 5.2. Children and adolescents

As the availability of meibographic techniques increases and the invasiveness of the procedure decreases, the possibility of studying the pediatric population has emerged. A study comparing healthy subjects

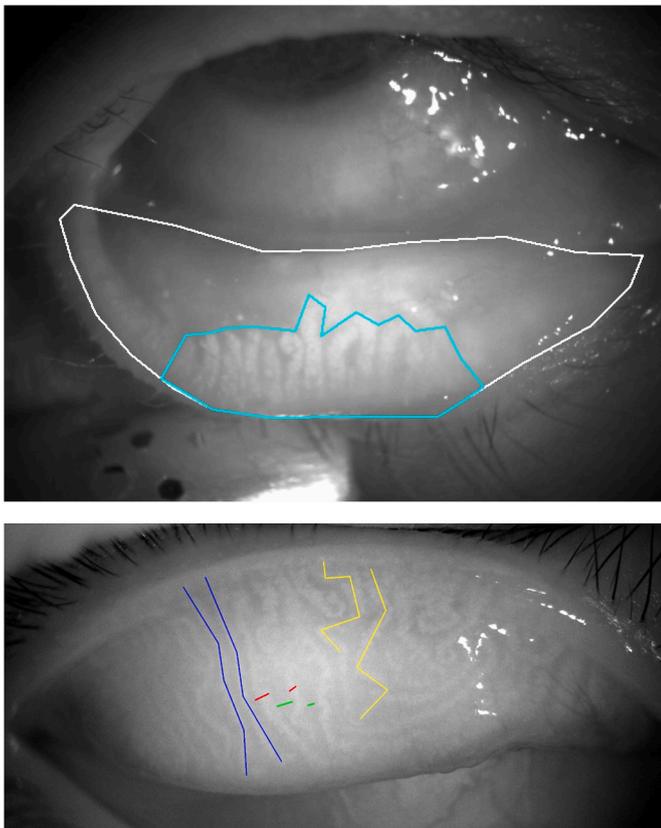
**Table 2**  
Advantages and disadvantages of various meibographic modalities.

	Advantages	Disadvantages
Contact meibography	–	Requires direct contact Uncomfortable/painful Time-consuming Does not depict the entire eyelid
Non-contact meibography	No direct contact Time-saving	–
Keratography	No direct contact Quick examination Allows for digital quantification Depicts entire eyelid Allows for supplemental measurements (NIBUT, TMH)	Time-consuming data analysis Expensive equipment
IVCM	Enables imaging comparable to histological analysis, allowing quantification of microscopic entities and inflammatory processes.	Expensive equipment Requires expertise Depicts only minute areas Requires direct contact Uncomfortable/painful Time-consuming procedure that requires extensive stitching of images and data-analysis
OCT	Allows 3D reconstruction and produce 2D IR meibograms	Expensive equipment Requires expertise

NIBUT: non-invasive break-up time, TMH: tear meniscus height, IVCM: in vivo confocal microscopy, OCT: optical coherence tomography, IR: infrared.

**Table 3**  
Grading schemes for meibomian gland dropout.

Modality	Year introduced	Grading schemes	Advantages	Disadvantages	Grading schemes by reference
Contact meibography Shimazaki et al. [8]	1995	0 = no dropout 1 = less than half of the visualized inferior tarsus 2 = more than half of the visualized inferior tarsus		Limited to center part of lower eyelid	[35–37]
Meiboscopy (no images acquired) Pflugfelder et al. [38]	1998	0 = no dropout 1 = <33% 2 = 34%–66% 3 = ≥67%		Only center part of lower eyelid	[39]
Contact meibography Nichols et al. [20]	2005	Gestalt scale: 1 = no partial glands 2 = <25% partial glands 3 = 25%–75% partial glands 4 = >75% partial glands	Light source was shifted from white light to infrared	Solely the lower eyelid	[40]
Non-contact meibography Arita et al. [18]	2008	Meiboscore: 0 = lost area of MGs 1 = <33% lost area of MGs 2 = 33%–67% lost area of MGs 3 = >67% lost area of MGs Upper and lower lid scores are summed; score ranges 0–6	All parts in the upper and lower eyelids could be observed non-invasively without using ImageJ analyses		[41–78]
Contact meibography Call et al. [79]	2012	Meibograde: Gland distortion Gland shortening Gland dropout Each parameter is scored 0–3. 0 = no significant involvement 1 = <33% involvement 2 = 33%–66% involvement 3 = >66% involvement A given eyelid yields a maximum score of 9	Morphological characteristics, such as distortion, shortening, and dropout were scored		[79–81]
Non-contact meibography Pult et al. [31]	2013	5-grade pictorial and verbal meiboscale: 0 = ≈0% 1 = <25% 2 = 25%–50% 3 = 51%–75% 4 = >75%	Sensitive grading (five-point scale)	ImageJ analysis necessary for grading	[82–87]
Keratography Ngo et al. [88]	2014	7-point scale: 0 = 0% dropout 0.5 = 1%–16% dropout 1.0 = 17%–33% dropout 1.5 = 34%–50% dropout 2.0 = 51%–67% dropout 2.5 = 68%–84% dropout 3.0 = 85%–100% dropout	Particular sensitive grading (seven-point scale)	ImageJ analysis necessary for grading	
Noncontact meibography Arita et al. [89]	2016	Partial glands: 0 = No partial glands 1 = Fewer than 3 partial glands 2 = Three or more partial glands and fewer than 3 partial glands with loss of half or more of the full length 3 = Three or more partial glands with loss of half or more of the full length Gland Dropout: 0 = No gland dropout 1 = Fewer than 3 gland dropouts 2 = Three or more gland dropouts	Partial glands MG shortening and gland dropout were independently graded. MG dropout was the best parameter to diagnose MGD, circumventing the need for ImageJ analysis	Subjective scale	[90]
Keratography Zhao et al. [91]	2018	Distortion of glands: 0 = no distortion 1 = distortion >90°, area <1/3 2 = distortion >90°, area 1/3–2/3; distortion 45–90°, area <1/3 3 = distortion >90°, area >2/3; distortion 45–90°, area 1/3–2/3 4 = distortion 45–90°, area >2/3; distortion 45°, area <50% 5 = distortion < 45°, area >50%		ImageJ analysis necessary for grading. Time-consuming	[90]
Keratography Adil et al. [92]	2019	Modified 4-point scale: 0 = 0%–25% dropout 1 = 26%–50% dropout 2 = 51%–75% dropout 3 = 76%–100% dropout	Allows for physiological variations by setting grade 0 as < 25% dropout	ImageJ analysis necessary for grading	[93,94]
Digital percentile/ratio			Very precise	Time-consuming	[69,82,83, 95–103]



**Fig. 1.** Computerized grading of MG dropout in the lower eyelid (top) using ImageJ software. (Bottom) Computerized measurements of MG length (blue), thickness (red), interglandular space (green), and tortuosity (yellow) in the upper eyelid.

aged 1 month to 12 years with an adult population aged 24–39 years found increased density of upper MGs in the pediatric population and increased meiboscore, eyelid width, and number of lower MGs in the adult population [41]. The authors reported fully developed MGs in both the upper and lower eyelids in subjects as young as 1 month. Another study comparing children aged 3–11 years to adolescents aged 12–18 years found no significant difference in meiboscore [43]. There was, however, an increased number of MGs, MG duct width, and percent area of MG acini in the upper lids of the adolescent population. A study examining the MGs of 15-year-olds reported an average meiboscore of 2.4 in girls and 3.3 in boys, with a mean score of 2.8 [42]. The cause of the sex difference is unknown but could be caused by hormonal differences. However, a comparative study involving adolescents aged 12–18 years did not confirm sex differences and reported a mean meiboscore of 0.41 [43]. In both studies, the meiboscore did not correlate with lid margin abnormalities, which is usually seen in MGD in the elderly, suggesting a different underlying cause. A recently published study found significantly higher MG distortion and deficiency in children with physiological conjunctival follicles [91]. These studies were all conducted on children and adolescents in China and Japan, populations in which the adults have a higher incidence of DED [7].

A study involving 99 US-based, predominantly white subjects aged 4–17 year reported a mean meiboscore of 0.58 and a mean tortuosity score of 0.45 [84]. There were no significant differences in age, sex, or race regarding MG dropout. However, the boys had significantly higher tortuosity.

When comparing the Japanese (meiboscore = 2.8), Chinese (meiboscore = 0.41), and American (meiboscore = 0.58) studies, a striking difference in MG dropout becomes apparent. The cause of this difference remains unknown but could be due to a number of factors. Both the

Chinese and Japanese studies reported using Topcon non-contact meibography systems and the meiboscore as defined by Arita et al. [18]. The American study, however, used the LipiView II system for meibography and a 5-point scale as previously reported [31]. The use of the different grading systems may have affected the results and it has been noted that different meibographic systems might not be interchangeable [88,126]. Another possible factor is genetics. The Asian population has a higher prevalence of DED, and differences between Asian countries have been noted [7]. Whether these genetic variations correlate to MG dropout remain to be discerned.

Another recent study reported an increased degree of MG dropout in a pediatric cohort with Hashimoto's thyroiditis without thyroid-related ophthalmopathy when compared to that of age-matched, healthy controls [98].

### 5.3. Senescence

Whether the number of available MGs decreases with age has long been discussed and researched. Contact meibography was used to examine 177 subjects with no known ocular symptoms or disorders [127]. Significant associations between disruptions of MG anatomy, abnormal lid margin anatomy, meibum expressibility, MG dropout, and aging were uncovered. In 2008, Arita et al. presented their novel non-contact meibography system in a study examining the age-related changes of MGs in the ophthalmologically healthy population [18]. This research revealed a significant correlation between their newly proposed meiboscore and age. They also documented significant negative correlations between TBUT, Schirmer test score, and age. Since then, others have confirmed the association between MG dropout, MG expressibility, meibum quality, and age [107,110,111,128–130]. Surprisingly, Yeotikar et al. found increased tear meniscus height and invasive TBUT as well as decreased tear osmolarity in association with aging [130]. It is worth noting that the Schirmer test score tends to decrease in senescence while remaining unchanged in MGD. The prevalence of aqueous-deficient dry eye, which causes a decreased Schirmer test value, increases with age [7]. This might be due to an age-related decrease in lacrimal gland function [131]. Another possible contributing factor to decreased Schirmer test values is the use of prescription medications [132]. A number of pharmaceuticals typically used by the elderly population inhibits lacrimal secretion [132].

Studies applying IVCM to aging MGs have reported negative correlations between age and goblet cell density, as well as MG acinar diameter and density [133,134]. These studies observed no signs of inflammatory cell infiltration or MG obstruction. They did, however, report increased secretion reflectivity and wall inhomogeneity, hypothesized to represent qualitative changes in the meibum itself [133]. These findings substantiate the hypothesis of non-obstructive, non-inflamed age-related MG atrophy.

### 5.4. Diabetes

The impact of diabetes on ocular health has been thoroughly researched. However, there are only a few studies on its impact on MG morphology. One study examining the ocular surface in a pediatric population with diabetes reported significantly higher tear film osmolarity in the diabetic group, although no differences in MG dropout were observed [99]. Examining an adult cohort with type 2 diabetes, Lin et al. reported significantly higher MG dropout, higher lipid layer thickness, and lower MG expressibility in the diabetic group as compared to controls [46]. Two recent studies found increased MG dropout in patients with type 2 diabetes when compared to healthy controls [45,48]. Whether glandular dropout correlates with disease progression remains to be explored. A study that used both the OCULUS Keratograph 5 M and IVCM reported a significantly higher meiboscore and Ocular Surface Disease Index (OSDI) score as well as significantly lower NIBUT in the diabetic group [47]. Confocal microscopy revealed significantly

increased MG acinar diameters and decreased MGAUD. The authors also commented on observing increased ICD surrounding the acini, indicating a combined obstructive and inflammatory pathomechanism.

### 5.5. Allergic keratoconjunctivitis

One study using non-contact meibography reported increased frequency of MG distortion as well as higher meibum expression score and superficial punctate keratopathy scores in patients with allergic conjunctivitis [44]. No significant increase in meiboscore was documented. A consequent study used meibography and IVCN to compare patients with atopic keratoconjunctivitis (AKC) to patients with obstructive MGD and to healthy controls [135]. The AKC groups had significant worse MG dropout, meibum expressibility, and confocal microscopy values compared to both of the other groups.

### 5.6. Contact lens wear

Applying contact meibography to the lower lids of 360 participants, Nichols and Sinnott found no significant differences in MG dropout in the dry eye group compared to the non-dry eye group [40]. However, all participants in that study wore contact lenses and were grouped according to symptomatology. One study compared patients with contact lens-related allergic conjunctivitis to contact lens wearers without allergic conjunctivitis and to patients with perennial allergic conjunctivitis and healthy controls [51]. The authors reported a significantly higher degree of MG distortion in both groups with allergic conjunctivitis when compared to the healthy controls and the contact lens-wearing patients without allergic conjunctivitis. They also found a statistically non-significant ( $p = 0.051$ ) tendency for higher meiboscores in both contact lens-wearing groups, indicating that allergic conjunctivitis causes distortion and that contact lens wear may cause MG dropout. Some studies have found associations between MG dropout and contact lens wear [136–140], while others have not [69,141]. Even though Pucker et al. did not demonstrate a significant univariate association between MG dropout and the use of contact lenses, a best-fitting multivariate regression model revealed a statistically significant association between increased meiboscores and contact lens wear with an odds ratio of 2.45 [69]. Also, both Pucker et al. and Machalinska et al. found significant correlations between contact lens wear and clinical parameters associated with MGD [69,141]. Overnight orthokeratology has revealed MG distortion and papillary hypertrophy in children and adolescents [142]. Two separate studies have shown that morphologic alterations in the MGs become apparent after 2 and 3 years of contact lens use [136,138]. The underlying pathomechanism of MG dropout in contact lens wearers remains in need of further elucidation. Hypotheses such as mechanical trauma and the accumulation of epithelial cells blocking the glandular orifices have been proposed [5,143,144]. Arita et al. recognized a uniform pattern of MG shortening from the distal side of the glands in contact lens wearers [137]. This led to the proposition of chronic friction between the contact lens and conjunctiva as a possible mechanism of MG dropout. Their findings corroborated a hypothesis that MG dropout appears to be dependent on the duration of contact lens wear, but not on the material composition of the contact lens itself.

Villani et al. used IVCN to compare asymptomatic contact lens wearers to healthy controls [139]. They found significant alterations in several parameters of the MGs and periglandular interstice in the lower lids of the contact lens-wearing cohort, indicating obstruction, inflammation, and glandular atrophy.

### 5.7. Aniridia

Two recent studies revealed a greater degree of MG dropout in patients with aniridia; the glands were thinner and had lower density [93, 94]. Furthermore, a number of proinflammatory cytokines were elevated in the aniridia group and correlated with MG dropout.

### 5.8. Sjögren's syndrome

Several studies have demonstrated an increased degree of MG dropout in patients with Sjögren's syndrome when compared to both healthy controls and patients with non-Sjögren's dry eye [58,64,95, 145]. Two separate studies used IVCN to compare Sjögren's syndrome to MGD and healthy controls [146,147]. They reported a greater degree of glandular and periglandular inflammation among patients with primary Sjögren's syndrome as compared to the other cohorts. Patients with MGD had wider acinar unit diameters and lower AUD compared to the other groups, indicating a greater degree of MG obstruction and dropout.

### 5.9. Stem cell transplant and ocular graft-versus-host disease

A study involving patients with various hematologic malignancies examined the effects of stem cell transplantation on MG dropout [82]. Patients who developed ocular graft-versus-host disease (GvHD) demonstrated a greater degree of MG dropout than pre-allogeneic stem cell transplantation patients. Pre-transplantation patients had a higher degree of MG dropout than healthy controls. Interestingly, there were no significant differences between patients following stem cell transplantation without ocular GvHD when compared to healthy controls or patients prior to stem cell transplantation. The finding that patients with hematologic malignancies present with increased MG dropout even prior to allogeneic stem cell transplantation was corroborated in a recent study [83]. The OCULUS Keratograph 5 M was recently used to compare patients with chronic ocular GvHD to patients with MGD or Sjögren's syndrome, and to healthy controls [52]. The chronic ocular GvHD group had the highest degree of MG dropout, followed by the MGD, Sjögren's syndrome, and control group in a decreasing order of magnitude. A very recent publication documented worsening meiboscore at 1-year follow-up after diagnosis of chronic ocular GvHD despite ongoing dry eye treatment [55]. Deteriorating meiboscore was noted in 18.9% of examined eyes; surprisingly, the authors also noted improved meiboscore in 5.4% of the included eyes.

One research team used both non-contact IR meibography as well as IVCN in a study examining hematological patients after they had received hematopoietic stem cell transplantation [36]. The dry eye group had a significantly increased degree of MG dropout, lower MGAUD, and MG size, as well as increased fibrosis grade. Interestingly, the authors discovered that the degree of fibrosis was highest in the patients with systemic GvHD, followed by the non-systemic chronic GvHD cohort. Patients with neither dry eyes nor chronic GvHD had the least fibrosis, indicating that the degree of fibrosis and inflammation lie along a spectrum and represent a major pathogenetic drive in the development of DED in these patients. A study comparing patients with GvHD to symptom severity-matched dry eye controls found no significant differences in the superior palpebral conjunctival epithelial immune cell density [148]. Another recent study involving patients with GvHD and symptom severity-matched dry eye controls found no significant differences in MG dropout, or conjunctival epithelial or stromal immune cell density [100]. The authors did, however, report sub tarsal fibrosis in 40% of the eyes in the GvHD group. Although there were no significant differences in IVCN parameters in the fibrotic group, the authors demonstrated an increased tendency of MG dropout. The results were contradicted by a study that reported no correlation between clinical conjunctival scarring or subepithelial fibrosis and MG atrophy [101]. A case study using AS-OCT to compare a patient with ocular GvHD following allogeneic stem cell transplantation to a healthy control found a less visible MG orifice surrounded by scarring, as well as inflammation of the MGs [149].

### 5.10. Chemotherapy

Two separate studies examining the effects of a chemotherapeutic

combination containing tegafur, gimeracil, and oteracil potassium reported MG dropout [65,102]. Eom et al. examined 20 patients after chemotherapy, and found that 10 had chemotherapy-induced lacrimal drainage obstruction [97]. MG dropout was significantly higher in the lacrimal obstruction group and was most pronounced in the lower lid. Interestingly, in a study of the MGs of patients with hematological malignancies prior to stem cell transplantation, researchers found that patients who had received chemotherapy had less MG dropout [83].

### 5.11. Radiotherapy

When comparing patients with ocular adnexal lymphoma who had undergone radiotherapy to healthy controls, investigators found an increased degree of MG dropout in the radiotherapy group [56]. In patients who had received unilateral radiation, the difference between the fellow eyes were not significant. A recent study reported higher meiboscores, meibum expressibility scores, and OSDI score in the radiotherapy group when compared to healthy controls [74]. The degree of MG dropout was significantly correlated with both age and total dose of received radiation. Patients who received unilateral radiotherapy had a significantly higher meiboscore in the irradiated eye than in the non-irradiated eye.

### 5.12. Rosacea

A study that used OCT to capture IR meibographic images reported that patients with ocular rosacea had a greater degree of MG dropout when compared to healthy controls [66]. These findings were later corroborated with non-contact meibography [63]. IVCN of patients with ocular rosacea revealed significant differences in meibum reflectivity, inflammatory cell infiltration, and fibrosis grade as compared to healthy controls [150].

### 5.13. Glaucoma

The deleterious effects of topical antiglaucoma eyedrops on MG dropout have been well-documented [35,49,50,86]. Only one of these studies compared preservative-free and preservative-containing medications, and reported no significant difference in MG dropout [35]. Preservatives such as benzalkonium chloride, which is used in antiglaucoma eyedrops, have a well-documented injurious effect on the tear film [151–156]. IVCN studies have revealed significantly worse confocal parameters in patients under glaucomatous treatment when compared to healthy controls [35,157]. Confocal parameters in patients under treatment with preservative-free antiglaucoma medications are significantly worse when compared to healthy controls but better than that in patients receiving preservative-containing medication, suggesting that preservatives may be a contributing factor of MG dropout in these patients. Significant MG dropout has been noted following trabeculectomy with mitomycin C [71]. The greatest degree of glandular loss was noted in the bleb-contacting regions. The possible causes include drug toxicity from mitomycin C and/or chronic irritation from the sutures or the bleb itself.

### 5.14. Following surgery

One study found no significant increase in MG dropout in patients following cataract surgery [54]. However, two other studies found contradictory evidence, documenting increased MG dropout following refractive surgery [39,96]. In patients undergoing the modified Hughes tarsoconjunctival flap procedure, significant MG dropout was observed in patients from whom tumors >15 mm had been removed [61]. Significantly increased MG dropout was also observed in patients following surgical excision of chalazion [53]. Recently, a group of researchers reported significant glandular diminution in patients following surgery for inferior orbital wall fractures by the

transconjunctival approach [59].

### 5.15. Infection and inflammation

Significant MG dropout and altered MG morphology have been demonstrated in patients with blepharitis when compared to healthy controls [14,81,90,158]. In addition, deleterious effects on MGs have been noted in phlyctenular keratitis [73], trachoma [80], seborrheic dermatitis [75], and in a case report of unilateral marginal staphylococcal keratitis [159]. Taken together, these outcomes might indicate a pernicious effect on MGs caused by infection or chronic inflammation.

### 5.16. Primary chronic dacryocystitis

As compared to controls, patients with primary chronic dacryocystitis demonstrate an increased degree of MG dropout in both the affected and unaffected eye [37]. Interestingly, there were no significant differences between the two eyes. Patients with primary chronic dacryocystitis also present with decreased MGAUD as well as increased MG acinar diameters and periglandular ICD.

### 5.17. Assorted conditions

Significant changes in MG morphology or atrophy have been documented using IR meibography in facial nerve palsy [79], longstanding use of prosthetic eyes [57], thyroid eye disease [68], granular corneal dystrophy type 2 [72], eyelid tattooing [62], vitiligo [67], X-linked hypohidrotic ectodermal dysplasia [87,160], lamellar ichthyosis [76], pseudophakic bullous keratopathy [77], Graves' orbitopathy [60], and Rothmund-Thomson syndrome [161]. IVCN revealed significant changes in confocal parameters in patients with primary blepharospasm [162], as well as increased Langerhans cell density at the lid margins and in the stroma surrounding the MGs in vernal keratoconjunctivitis [163].

During the past decade, clinical and scientific interest in DED and meibography has increased considerably. This focus is exemplified by the growing number of publications on these topics, as illustrated in Fig. 2 and shown by geographical location in Fig. 3.

Table 5 summarizes the different study designs of the included clinical studies. The majority of clinical studies fall within Level 2 of evidence according to the modified American Academy of Ophthalmology Preferred Practices guidelines [164] (Table 4). Only two randomized control trials were found, which could be due to authors mostly focusing on the role of meibography in diagnostics, rather than therapy.

## 6. The relevance of meibography in making therapeutic decisions

Following thermal pulsation system (LipiFlow,® Johnson & Johnson, US) treatment, Finis et al. reported subjective and objective improvement [78]. The authors found higher symptomatic amelioration in patients included with less severe meibomian gland dropout compared with those with severe dropout. Thus, the authors suggested that performing meibography prior to LipiFlow treatment is necessary to predict the therapeutic effects. There was no change of MG dropout six months after treatment. In comparison, Maskin et al. demonstrated by noncontact meibography that intraductal meibomian gland probing was associated with the increased MG tissue-area growth of atrophied MGs [85]. Moreover, Intense Pulsed Light Therapy appears capable of improving the area of MGs visualized with noncontact meibography [70,103]. These studies demonstrate the vital role of meibography in monitoring treatment.

## 7. Limitations

Meibography alone remains insufficient for diagnosing MGD as it does not reveal the function and composition of remaining MGs. Hence, meibography should be coupled with additional clinical parameters and

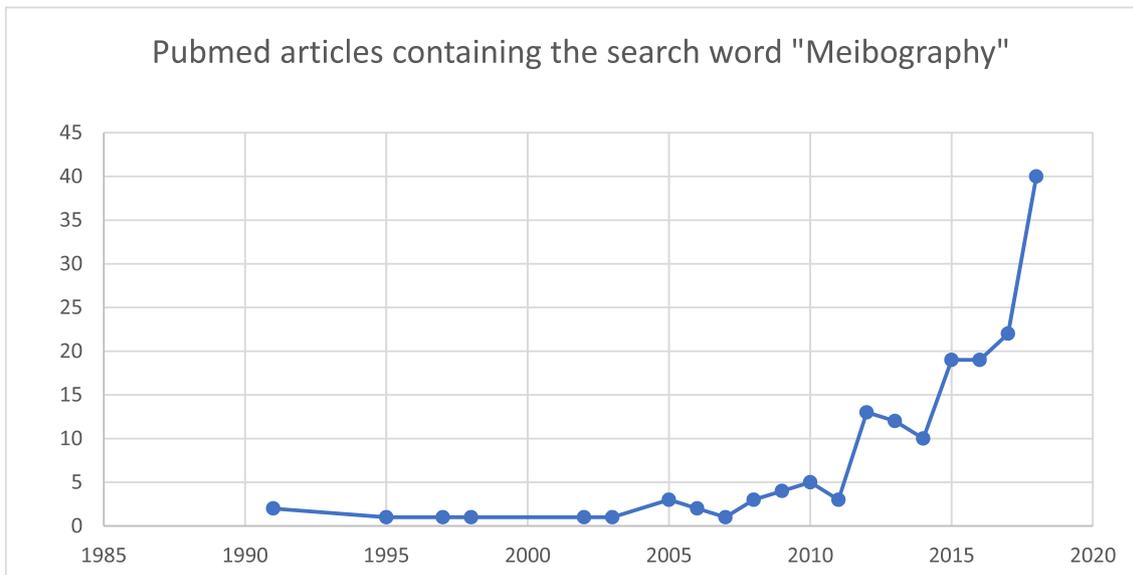


Fig. 2. Overview of the rapidly increasing interest in meibography.

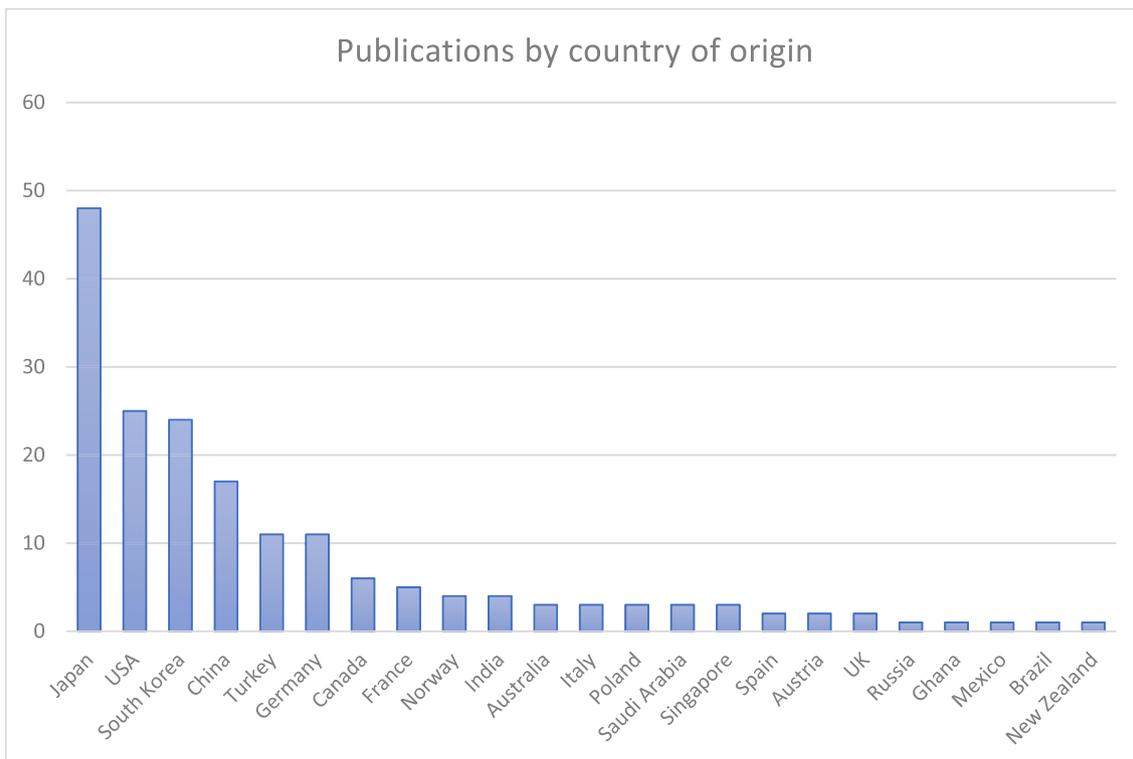


Fig. 3. Publications by country of origin.

ocular symptom scores [105,111,165]. Inflammation and surrounding edema might obscure the structure of meibomian glands. This issue might partly explain variations in the MG area before and after treatment. The ability to discern inflammation and edema, for example, by introducing highly sensitive and high-resolution techniques, would represent a substantial improvement.

**8. Conclusion**

With the advent of non-contact approaches, meibography can be an integrated part of general ophthalmological practice, especially if more

clinician-friendly and affordable devices are developed.

The introduction of various meibography modalities over the past two decades, including in vivo histological evaluation of the MGs and the surrounding tissues through IVCN, has furthered knowledge of meibomian pathophysiology. IVCN enables the clinician to observe disease progression at cellular level, which was previously not possible. This enables evaluation of treatment response and potentially could tailor individual treatment. However, knowledge on how the in vivo data can be translated into clinical practice remains limited. Besides being very expensive, the application of IVCN in clinical practice remains cumbersome as compared to the non-invasive and more easily

**Table 4**  
Study design grading scheme [164].

Clinical studies	
Level 1	Evidence obtained from at least one properly conducted, well-designed, randomized, controlled trial, or evidence from well-designed studies applying rigorous statistical approaches
Level 2	Evidence obtained from one of the following: a well-designed controlled trial without randomization, a well-designed cohort or case-control analytic study, preferably from one or more centers, or a well-designed study accessible to more rigorous statistical analysis
Level 3	Evidence obtained from one of the following categories: descriptive studies, case reports, reports of expert committees, and expert opinion

**Table 5**  
Study designs of included clinical studies.

Prospective studies	
Prospective, randomized control trials	[46,151]
Other prospective studies	[8,24,26,42,48,54,61,68,75,78,80,81,83,88,96,99,102,108,113,127,128,135,142,145,147,162]
Retrospective studies	
Case-control	[14,35–37,44,47,50–53,56,58,60,62–64,67,69,70,72–74,76,82,87,90,93–95,98,104,106,107,109,120,123,124,138–141,143,144,146,148,157,158,160,163]
Cross-sectional	[18,20,30,31,39–41,43,45,49,55,57,66,71,79,84–86,91,92,97,100,101,103,110–112,114–116,119,126,129,130,133,134,136,137,150]
Case report/series	[59,65,77,105,149,153,156,159,161]

operated meibography.

The 3D rendering of MGs through OCT has provided more thorough understanding of MG morphology and function. The possibility of acquiring IR meibographic images comparable to non-contact meibography using OCT has been demonstrated. This versatility opens OCT to a wide variety of applications in clinical practice. However, OCT is expensive equipment, which may result in limited accessibility if meibography were to be performed routinely. Moreover, the IR meibographic images acquired by OCT thus far are of lower resolution as compared to non-contact meibography and require manual adjustment, which is time-consuming. These drawbacks render OCT inferior to non-contact meibography for evaluating MGs in everyday clinical practice. Meibography is currently the most clinically useful procedure available for evaluation of MG morphology and determining the prognosis of MGD patients. Moreover, it can differentiate aqueous deficiency from evaporative dry eye. With quantitative analysis of the meibomian glands, meibography has the potential for monitoring treatment efficacy.

Even though the last decade has yielded great advances in knowledge of MGD, further research is warranted in several fields. There is a need for longitudinal studies in different age groups to illuminate the risk factors and predispositions for MGD. Larger population-based studies should be undertaken to reveal geographical and occupational differences in the prevalence of MG dropout, as such information may provide clues to the predisposing factors. Longitudinal studies investigating the effect of various treatment modalities on MG morphology and dropout would be of particular interest, considering the high prevalence MGD and its consequences on quality of life, productivity, and cost to society.

#### Declaration of competing interest

The authors report no conflicts of interest.

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