The Ocular Surface xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

The Ocular Surface

journal homepage: www.elsevier.com/locate/jtos

Clinical Practice

The role of meibography in ocular surface diagnostics: A review

Fredrik Fineide[a,b,*], Reiko Arita[c,g], Tor P. Utheim[a,b,d,e,f]

[a] Department of Medical Biochemistry, Oslo University Hospital, Norway
[b] The Norwegian Dry Eye Clinic, Ole Vigs Gate 32 E, 0366, Oslo, Norway
[c] Itoh Clinic, 626-11 Minaminakano, Minuma-ku, Saitama, Saitama, 337-0042, Japan
[d] Department of Plastic and Reconstructive Surgery, Oslo University Hospital, Norway
[e] Department of Ophthalmology, Sørlandet Hospital Arendal, Norway
[f] Department of Ophthalmology, Stavanger University Hospital, Norway
[g] Lid and Meibomian Gland Working Group, Japan

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 pathophysiologic 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. Benefits of meibography include monitoring and staging of disease progression as well as evaluation of treatment potential and effects.

* Corresponding author. the Norwegian Dry Eye Clinic, Oslo, Norway.
E-mail address: fre_fin@hotmail.com (F. Fineide).

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

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 ocular surface diseases.

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.

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.

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.

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 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

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 or 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]

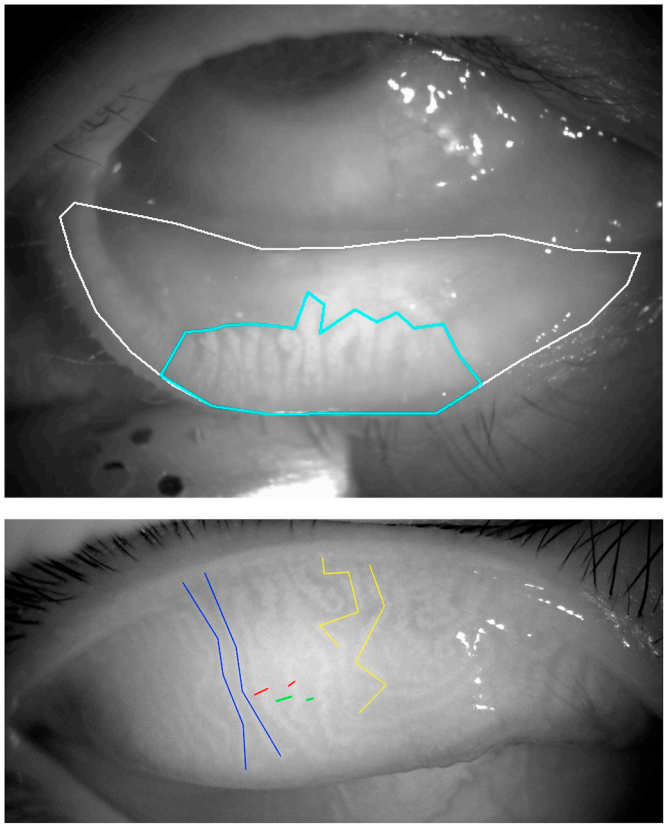

Fig. 1. Computerized grading of MG dropout in the lower eyelid (top) using ImageJ software. (Bottom) Computerized measurements of MG length (blue), thickness (red), interglandular space (green), and tortuosity (yellow) in the upper eyelid.

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 IVCM 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 IVCM 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 IVCM 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 IVCM 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 subtarsal fibrosis in 40% of the eyes in the GvHD group. Although there were no significant differences in IVCM 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]. IVCM 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]. IVCM 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], long-standing 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]. IVCM 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

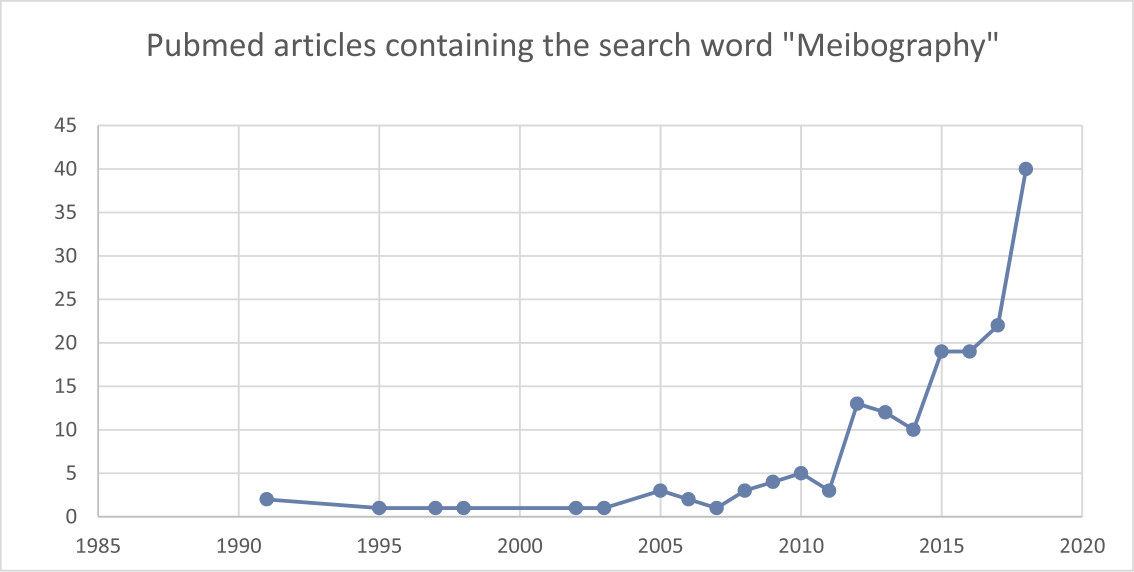

Fig. 2. Overview of the rapidly increasing interest in meibography.

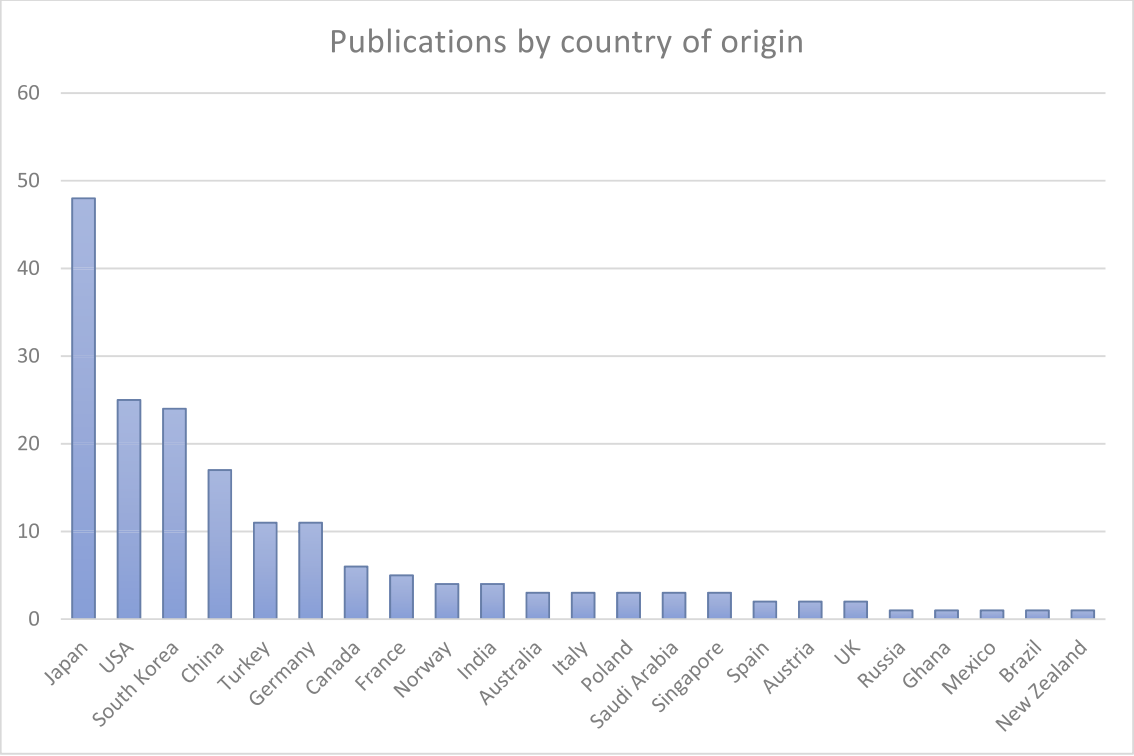

Fig. 3. Publications by country of origin.

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]

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 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 IVCM, has furthered knowledge of meibomian pathophysiology. IVCM 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 IVCM in clinical practice remains cumbersome as compared to the non-invasive and more easily 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.

References

[1] Tomlinson A, Bron AJ, Korb DR, Amano S, Paugh JR, Pearce EI, et al. The international workshop on meibomian gland dysfunction: report of the diagnosis subcommittee. Invest Ophthalmol Vis Sci 2011;52:2006–49.

[2] Knop E, Knop N, Millar T, Obata H, Sullivan DA. The international workshop on meibomian gland dysfunction: report of the subcommittee on anatomy, physiology, and pathophysiology of the meibomian gland. Invest Ophthalmol Vis Sci 2011;52:1938–78.

[3] Willcox MDP, Argueso P, Georgiev GA, Holopainen JM, Laurie GW, Millar TJ, et al. TFOS DEWS II tear film report. Ocul Surf 2017;15:366–403.

[4] Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo CK, et al. TFOS DEWS II definition and classification report. Ocul Surf 2017;15:276–83.

[5] Korb DR, Henriquez AS. Meibomian gland dysfunction and contact lens intolerance. J Am Optom Assoc 1980;51:243–51.

[6] Nelson JD, Shimazaki J, Benitez-del-Castillo JM, Craig JP, McCulley JP, Den S, et al. The international workshop on meibomian gland dysfunction: report of the definition and classification subcommittee. Invest Ophthalmol Vis Sci 2011;52:1930–7.

[7] Stapleton F, Alves M, Bunya VY, Jalbert I, Lekhanont K, Malet F, et al. TFOS DEWS II epidemiology report. Ocul Surf 2017;15:334–65.

[8] Shimazaki J, Sakata M, Tsubota K. Ocular surface changes and discomfort in patients with meibomian gland dysfunction. Arch Ophthalmol 1995;113:1266–70.

[9] Rabensteiner DF, Aminfar H, Boldin I, Schwantzer G, Horwath-Winter J. The prevalence of meibomian gland dysfunction, tear film and ocular surface parameters in an Austrian dry eye clinic population. Acta Ophthalmol 2018;96:e707–11.

[10] Lemp MA, Crews LA, Bron AJ, Foulks GN, Sullivan BD. Distribution of aqueous-deficient and evaporative dry eye in a clinic-based patient cohort: a retrospective study. Cornea 2012;31:472–8.

[11] Tapie R. Biomicroscopial study of Meibomian glands. ETUDE BIOMICROSCOPIQUE DES GLANDES DE MEIBOMIUS; 1977.

[12] Jester JV, Rife L, Nii D, Luttrull JK, Wilson L, Smith RE. In vivo biomicroscopy and photography of meibomian glands in a rabbit model of meibomian gland dysfunction. Invest Ophthalmol Vis Sci 1982;22:660–7.

[13] Robin JB, Jester JV, Nobe J, Nicolaides N, Smith RE. In vivo transillumination biomicroscopy and photography of meibomian gland dysfunction. A clinical study. Ophthalmology 1985;92:1423–6.

[14] Mathers WD, Shields WJ, Sachdev MS, Petroll WM, Jester JV. Meibomian gland dysfunction in chronic blepharitis. Cornea 1991;10:277–85.

[15] Mathers WD, Daley T, Verdick R. Video imaging of the meibomian gland. Arch Ophthalmol 1994;112:448–9.

[16] Matsuoka T, Tsumura T, Ueda H, Hasegawa E. Video-meibographic observations of the meibomian gland 1996.

[17] Yokoi N, Komuro A, Yamada H, Maruyama K, Kinoshita S. A newly developed video-meibography system featuring a newly designed probe. Jpn J Ophthalmol 2007;51:53–6.

[18] Arita R, Itoh K, Inoue K, Amano S. Noncontact infrared meibography to document age-related changes of the meibomian glands in a normal population. Ophthalmology 2008;115:911–5.

[19] Mathers WD, Lane JA, Zimmerman MB. Tear film changes associated with normal aging. Cornea 1996;15:229–34.

[20] Nichols JJ, Berntsen DA, Mitchell GL, Nichols KK. An assessment of grading scales for meibography images. Cornea 2005;24:382–8.

[21] Arita R, Itoh K, Maeda S, Maeda K, Amano S. A newly developed noninvasive and mobile pen-shaped meibography system. Cornea 2013;32:242–7.

[22] Srinivasan S, Menzies K, Sorbara L, Jones L. Infrared imaging of meibomian gland structure using a novel keratograph. Optom Vis Sci 2012;89:788–94.

[23] Kobayashi A, Yoshita T, Sugiyama K. In vivo findings of the bulbar/palpebral conjunctiva and presumed meibomian glands by laser scanning confocal microscopy. Cornea 2005;24:985–8.

[24] Matsumoto Y, Sato EA, Ibrahim OM, Dogru M, Tsubota K. The application of in vivo laser confocal microscopy to the diagnosis and evaluation of meibomian gland dysfunction. Mol Vis 2008;14:1263–71.

[25] Matsumoto Y, Shigeno Y, Sato EA, Ibrahim OM, Saiki M, Negishi K, et al. The evaluation of the treatment response in obstructive meibomian gland disease by in vivo laser confocal microscopy. Graefes Arch Clin Exp Ophthalmol 2009;247:821–9.

[26] Ibrahim OM, Matsumoto Y, Dogru M, Adan ES, Wakamatsu TH, Goto T, et al. The efficacy, sensitivity, and specificity of in vivo laser confocal microscopy in the diagnosis of meibomian gland dysfunction. Ophthalmology 2010;117:665–72.

[27] Bizheva K, Lee P, Sorbara L, Hutchings N, Simpson T. In vivo volumetric imaging of the human upper eyelid with ultrahigh-resolution optical coherence tomography. J Biomed Optic 2010;15:040508.

[28] Hwang HS, Park CW, Joo CK. Novel noncontact meibography with anterior segment optical coherence tomography: hosik meibography. Cornea 2013;32:40–3.

[29] Hwang HS, Shin JG, Lee BH, Eom TJ, Joo CK. Vivo 3D meibography of the human eyelid using real time imaging fourier-domain OCT. PloS One 2013;8:e67143.

[30] Powell DR, Nichols JJ, Nichols KK. Inter-examiner reliability in meibomian gland dysfunction assessment. Invest Ophthalmol Vis Sci 2012;53:3120–5.

[31] Pult H, Riede-Pult B. Comparison of subjective grading and objective assessment in meibography. Contact Lens Anterior Eye 2013;36:22–7.

[32] Koh YW, Celik T, Lee HK, Petznick A, Tong L. Detection of meibomian glands and classification of meibography images. J Biomed Optic 2012;17:086008.

[33] Arita R, Suehiro J, Haraguchi T, Shirakawa R, Tokoro H, Amano S. Objective image analysis of the meibomian gland area. Br J Ophthalmol 2014;98:746–55.

[34] Koprowski R, Wilczynski S, Olczyk P, Nowinska A, Weglarz B, Wylegala E. A quantitative method for assessing the quality of meibomian glands. Comput Biol Med 2016;75:130–8.

[35] Agnifili L, Fasanella V, Costagliola C, Ciabattoni C, Mastropasqua R, Frezzotti P, et al. In vivo confocal microscopy of meibomian glands in glaucoma. Br J Ophthalmol 2013;97:343–9.

[36] Ban Y, Ogawa Y, Ibrahim OM, Tatematsu Y, Kamoi M, Uchino M, et al. Morphologic evaluation of meibomian glands in chronic graft-versus-host disease using in vivo laser confocal microscopy. Mol Vis 2011;17:2533–43.

[37] Hong J, Yu Z, Cui X, Qian T, Le Q, Wei A, et al. Meibomian gland alteration in patients with primary chronic dacryocystitis: an in vivo confocal microscopy study. Curr Eye Res 2015;40:772–9.

[38] Pflugfelder SC, Tseng SC, Sanabria O, Kell H, Garcia CG, Felix C, et al. Evaluation of subjective assessments and objective diagnostic tests for diagnosing tear-film disorders known to cause ocular irritation. Cornea 1998;17:38–56.

[39] Jung JW, Kim JY, Chin HS, Suh YJ, Kim TI, Seo KY. Assessment of meibomian glands and tear film in post-refractive surgery patients. Clin Exp Ophthalmol 2017;45:857–66.

[40] Nichols JJ, Sinnott LT. Tear film, contact lens, and patient-related factors associated with contact lens-related dry eye. Invest Ophthalmol Vis Sci 2006;47:1319–28.

[41] Shirakawa R, Arita R, Amano S. Meibomian gland morphology in Japanese infants, children, and adults observed using a mobile pen-shaped infrared meibography device. Am J Ophthalmol 2013;155:1099–10103 e1.

[42] Mizoguchi T, Arita R, Fukuoka S, Morishige N. Morphology and function of meibomian glands and other tear film parameters in junior high school students. Cornea 2017;36:922–6.

[43] Wu Y, Li H, Tang Y, Yan X. Morphological evaluation of meibomian glands in children and adolescents using noncontact infrared meibography. J Pediatr Ophthalmol Strabismus 2017;54:78–83.

[44] Arita R, Itoh K, Maeda S, Maeda K, Furuta A, Tomidokoro A, et al. Meibomian gland duct distortion in patients with perennial allergic conjunctivitis. Cornea 2010;29:858–60.

[45] He F, Zhao Z, Liu Y, Lu L, Fu Y. Assessment of ocular surface damage during the course of type 2 diabetes mellitus. J Ophthalmol 2018;2018:1206808.

[46] Lin X, Xu B, Zheng Y, Coursey TG, Zhao Y, Li J, et al. Meibomian gland dysfunction in type 2 diabetic patients. J Ophthalmol 2017;2017:3047867.

[47] Yu T, Shi WY, Song AP, Gao Y, Dang GF, Ding G. Changes of meibomian glands in patients with type 2 diabetes mellitus. Int J Ophthalmol 2016;9:1740–4.

[48] Zeng X, Lv Y, Gu Z, Jia Z, Zhang C, Lu X, et al. The effects of diabetic duration on lacrimal functional unit in patients with type II diabetes. J Ophthalmol 2019;2019:8127515.

[49] Arita R, Itoh K, Maeda S, Maeda K, Furuta A, Tomidokoro A, et al. Effects of long-term topical anti-glaucoma medications on meibomian glands. Graefes Arch Clin Exp Ophthalmol 2012;250:1181–5.

[50] Arita R, Itoh K, Maeda S, Maeda K, Furuta A, Tomidokoro A, et al. Comparison of the long-term effects of various topical antiglaucoma medications on meibomian glands. Cornea 2012;31:1229–34.

[51] Arita R, Itoh K, Maeda S, Maeda K, Tomidokoro A, Amano S. Association of contact lens-related allergic conjunctivitis with changes in the morphology of meibomian glands. Jpn J Ophthalmol 2012;56:14–9.

[52] Choi W, Ha JY, Li Y, Choi JH, Ji YS, Yoon KC. Comparison of the meibomian gland dysfunction in patients with chronic ocular graft-versus-host disease and Sjogren's syndrome. Int J Ophthalmol 2019;12:393–400.

[53] Fukuoka S, Arita R, Shirakawa R, Morishige N. Changes in meibomian gland morphology and ocular higher-order aberrations in eyes with chalazion. Clin Ophthalmol 2017;11:1031–8.

[54] Han KE, Yoon SC, Ahn JM, Nam SM, Stulting RD, Kim EK, et al. Evaluation of dry eye and meibomian gland dysfunction after cataract surgery. Am J Ophthalmol 2014;157:1144–11450 e1.

[55] Hwang HS, Ha M, Kim HS, Na KS. Longitudinal analysis of meibomian gland dropout in patients with ocular graft-versus-host disease. Ocul Surf 2019;17(3):464–9. https://doi.org/10.1016/j.jtos.2019.04.009.

[56] Ito Y, Hiraoka T, Minamikawa Y, Oshika T. [Morphological changes in meibomian glands following radiotherapy]. Nippon Ganka Gakkai Zasshi 2012;116:715–20.

[57] Jang SY, Lee SY, Yoon JS. Meibomian gland dysfunction in longstanding prosthetic eye wearers. Br J Ophthalmol 2013;97:398–402.

[58] Kang YS, Lee HS, Li Y, Choi W, Yoon KC. Manifestation of meibomian gland dysfunction in patients with Sjogren's syndrome, non-Sjogren's dry eye, and non-dry eye controls. Int Ophthalmol 2018;38:1161–7.

[59] Kim JA, Lee YJ, Jang SY. Meibomian gland dysfunction in patients who underwent transconjunctival approach surgery for inferior orbital wall fractures. J Craniofac Surg 2019;30(6):1891–3. https://doi.org/10.1097/SCS.0000000000005518.

[60] Kim YS, Kwak AY, Lee SY, Yoon JS, Jang SY. Meibomian gland dysfunction in Graves' orbitopathy. Can J Ophthalmol 2015;50:278–82.

[61] Klein-Theyer A, Horwath-Winter J, Dieter FR, Haller-Schober EM, Riedl R, Boldin I. Evaluation of ocular surface and tear film function following modified Hughes tarsoconjunctival flap procedure. Acta Ophthalmol 2014;92:286–90.

[62] Lee YB, Kim JJ, Hyon JY, Wee WR, Shin YJ. Eyelid tattooing induces meibomian gland loss and tear film instability. Cornea 2015;34:750–5.

[63] Machalinska A, Zakrzewska A, Markowska A, Safranow K, Wiszniewska B, Parafiniuk M, et al. Morphological and functional evaluation of meibomian gland dysfunction in rosacea patients. Curr Eye Res 2016;41:1029–34.

[64] Menzies KL, Srinivasan S, Prokopich CL, Jones L. Infrared imaging of meibomian glands and evaluation of the lipid layer in Sjogren's syndrome patients and nondry

eye controls. Invest Ophthalmol Vis Sci 2015;56:836–41.
[65] Mizoguchi S, Okada Y, Kokado M, Saika S. Abnormalities in the meibomian glands in patients with oral administration of anticancer combination drug-capsule TS-1((R)): a case report. BMC Canc 2015;15:796.
[66] Palamar M, Degirmenci C, Ertam I, Yagci A. Evaluation of dry eye and meibomian gland dysfunction with meibography in patients with rosacea. Cornea 2015;34:497–9.
[67] Palamar M, Kiyat P, Ertam I, Yagci A. Evaluation of dry eye and meibomian gland dysfunction with meibography in vitiligo. Eye 2017;31:1074–7.
[68] Park J, Baek S. Dry eye syndrome in thyroid eye disease patients: the role of increased incomplete blinking and Meibomian gland loss. Acta Ophthalmol 2018;97(5). https://doi.org/10.1111/aos.14000.
[69] Pucker AD, Jones-Jordan LA, Li W, Kwan JT, Lin MC, Sickenberger W, et al. Associations with meibomian gland atrophy in daily contact lens wearers. Optom Vis Sci 2015;92:e206–13.
[70] Ruan F, Zang Y, Sella R, Lu H, Li S, Yang K, et al. Intense pulsed light therapy with optimal pulse technology as an adjunct therapy for moderate to severe blepharitis-associated keratoconjunctivitis. J Ophthalmol 2019;2019:3143469.
[71] Sagara H, Sekiryu T, Noji H, Ogasawara M, Sugano Y, Horikiri H. Meibomian gland loss due to trabeculectomy. Jpn J Ophthalmol 2014;58:334–41.
[72] Sakimoto T. Granular corneal dystrophy type 2 is associated with morphological abnormalities of meibomian glands. Br J Ophthalmol 2015;99:26–8.
[73] Suzuki T, Morishige N, Arita R, Koh S, Sakimoto T, Shirakawa R, et al. Morphological changes in the meibomian glands of patients with phlyctenular keratitis: a multicenter cross-sectional study. BMC Ophthalmol 2016;16:178.
[74] Woo YJ, Ko J, Ji YW, Kim TI, Yoon JS. Meibomian gland dysfunction associated with periocular radiotherapy. Cornea 2017;36:1486–91.
[75] Yasar E, Kemeriz F, Gurlevik U. Evaluation of dry eye disaster and meibomian gland dysfunction with meibography in seborrheic dermatitis. Contact Lens Anterior Eye 2019;42(6):675–8. https://doi.org/10.1016/j.clae.2019.03.005.
[76] Palamar M, Karaca I, Onay H, Ertam I, Yagci A. Dry eye and Meibomian gland dysfunction with meibography in patients with lamellar ichthyosis. Contact Lens Anterior Eye 2018;41:154–6.
[77] Palamar M, Kiyat P, Yagci A. Dry eye and meibomian gland dysfunction in pseudophakic bullous keratopathy. Int Ophthalmol 2018;39(2):393–6. https://doi.org/10.1007/s10792-018-0824-3.
[78] Finis D, Konig C, Hayajneh J, Borrelli M, Schrader S, Geerling G. Six-month effects of a thermodynamic treatment for MGD and implications of meibomian gland atrophy. Cornea 2014;33:1265–70.
[79] Call CB, Wise RJ, Hansen MR, Carter KD, Allen RC. In vivo examination of meibomian gland morphology in patients with facial nerve palsy using infrared meibography. Ophthalmic Plast Reconstr Surg 2012;28:396–400.
[80] AlDarrab A, Al-Faky YH, Mousa A, Alsuhaibani AH. Meibography of eyes with sequelae of trachoma. Cornea 2018;37:416–20.
[81] AlDarrab A, Alrajeh M, Alsuhaibani AH. Meibography for eyes with posterior blepharitis. Saudi J Ophthalmol 2017;31:131–4.
[82] Engel LA, Wittig S, Bock F, Sauerbier L, Scheid C, Holtick U, et al. Meibography and meibomian gland measurements in ocular graft-versus-host disease. Bone Marrow Transplant 2015;50:961–7.
[83] Giannaccare G, Bonifazi F, Sebastiani S, Sessa M, Pellegrini M, Arpinati M, et al. Meibomian gland dropout in hematological patients before hematopoietic stem cell transplantation. Cornea 2018;37:1264–9.
[84] Gupta PK, Stevens MN, Kashyap N, Priestley Y. Prevalence of meibomian gland atrophy in a pediatric population. Cornea 2018;37:426–30.
[85] Maskin SL, Testa WR. Growth of meibomian gland tissue after intraductal meibomian gland probing in patients with obstructive meibomian gland dysfunction. Br J Ophthalmol 2018;102:59–68.
[86] Portela RC, Fares NT, Machado LF, Sao Leao AF, de Freitas D, Paranhos Jr. A, et al. Evaluation of ocular surface disease in patients with glaucoma: clinical parameters, self-report assessment, and keratograph analysis. J Glaucoma 2018;27:794–801.
[87] Romero-Caballero MD, Lozano-Garcia I, Caravaca-Alegria A, Gomez-Rivera S. Morphology of the Meibomian gland evaluated using meibography in patients with hypohidrotic ectodermal dysplasia. Arch Soc Esp Oftalmol 2019;94:165–70.
[88] Ngo W, Srinivasan S, Schulze M, Jones L. Repeatability of grading meibomian gland dropout using two infrared systems. Optom Vis Sci 2014;91:658–67.
[89] Arita R, Minoura I, Morishige N, Shirakawa R, Fukuoka S, Asai K, et al. Development of definitive and reliable grading scales for meibomian gland dysfunction. Am J Ophthalmol 2016;169:125–37.
[90] Al-Hayouti H, Daniel M, Hingorani M, Calder V, Dahlmann-Noor A. Meibography and corneal volume optical coherence tomography to quantify damage to ocular structures in children with blepharokeratoconjunctivitis. Acta Ophthalmol 2019;97(7). https://doi.org/10.1111/aos.14124.
[91] Zhao Y, Chen S, Wang S, Chen Y, Li J, Fu Y, et al. The significance of meibomian gland changes in asymptomatic children. Ocul Surf 2018;16:301–5.
[92] Adil MY, Xiao J, Olafsson J, Chen X, Lagali NS, Raeder S, et al. Meibomian gland morphology is a sensitive early indicator of meibomian gland dysfunction. Am J Ophthalmol 2019;200:16–25.
[93] Landsend ECS, Pedersen HR, Utheim OA, Xiao J, Adil MY, Tashbayev B, et al. Meibomian gland dysfunction and keratopathy are associated with dry eye disease in aniridia. Br J Ophthalmol 2018;103(1):119–24. https://doi.org/10.1136/bjophthalmol-2017-310927.
[94] Landsend ECS, Utheim OA, Pedersen HR, Aass HCD, Lagali N, Dartt DA, et al. The level of inflammatory tear cytokines is elevated in congenital aniridia and associated with meibomian gland dysfunction. Invest Ophthalmol Vis Sci 2018;59:2197–204.
[95] Chen X, Utheim OA, Xiao J, Adil MY, Stojanovic A, Tashbayev B, et al. Meibomian gland features in a Norwegian cohort of patients with primary Sjogren s syndrome. PloS One 2017;12:e0184284.
[96] El Ameen A, Majzoub S, Vandermeer G, Pisella PJ. [Influence of cataract surgery on Meibomian gland dysfunction (French translation of the article)]. J Fr Ophtalmol 2018;41:526–35.
[97] Eom Y, Baek S, Kim HM, Song JS. Meibomian gland dysfunction in patients with chemotherapy-induced lacrimal drainage obstruction. Cornea 2017;36:572–7.
[98] Gunay M, Celik G, Yildiz E, Bardak H, Kirmizibekmez H, Koc N, et al. Ocular surface evaluation in pediatric Hashimoto's thyroiditis without thyroid-associated ophthalmopathy. Arq Bras Oftalmol 2019;82(4):283–8. https://doi.org/10.5935/0004-2749.20190056.
[99] Gunay M, Celik G, Yildiz E, Bardak H, Koc N, Kirmizibekmez H, et al. Ocular surface characteristics in diabetic children. Curr Eye Res 2016;41:1526–31.
[100] Kheirkhah A, Coco G, Satitpitakul V, Dana R. Subtarsal fibrosis is associated with ocular surface epitheliopathy in graft-versus-host disease. Am J Ophthalmol 2018;189:102–10.
[101] Kusne Y, Temkit M, Khera N, Patel DR, Shen JF. Conjunctival subepithelial fibrosis and meibomian gland atrophy in ocular graft-versus-host disease. Ocul Surf 2017;15:784–8.
[102] Ohtomo K, Arita R, Shirakawa R, Usui T, Yamashita H, Seto Y, et al. Quantitative analysis of changes to meibomian gland morphology due to S-1 chemotherapy. Transl Vis Sci Technol 2018;7:37.
[103] Cheng SN, Jiang FG, Chen H, Gao H, Huang YK. Intense pulsed light therapy for patients with meibomian gland dysfunction and ocular demodex infestation. Curr Med Sci 2019;39:800–9.
[104] Abdelfattah NS, Dastiridou A, Sadda SR, Lee OL. Noninvasive imaging of tear film dynamics in eyes with ocular surface disease. Cornea 2015;34(Suppl 10):S48–52.
[105] Arita R, Itoh K, Maeda S, Maeda K, Furuta A, Fukuoka S, et al. Proposed diagnostic criteria for obstructive meibomian gland dysfunction. Ophthalmology 2009;116:2058–20563 e1.
[106] Eom Y, Lee JS, Kang SY, Kim HM, Song JS. Correlation between quantitative measurements of tear film lipid layer thickness and meibomian gland loss in patients with obstructive meibomian gland dysfunction and normal controls. Am J Ophthalmol 2013;155:1104–11010 e2.
[107] Pult H. Relationships between meibomian gland loss and age, sex, and dry eye. Eye Contact Lens 2018;44(2):318–24. https://doi.org/10.1097/ICL.0000000000000467.
[108] Qi Y, Zhang C, Zhao S, Huang Y, Yang R. A novel noninvasive ocular surface analyzer for the assessment of dry eye with Meibomian gland dysfunction. Exp Ther Med 2017;13:2983–8.
[109] Zhu K, Xie W, Ying J, Yao Y. [Evaluation of tear film and meibomian gland function in dry eye patients using Keratograph 5M]. 45. Zhejiang Da Xue Xue Bao Yi Xue Ban; 2016. p. 422–8.
[110] Pult H, Riede-Pult BH, Nichols JJ. Relation between upper and lower lids' meibomian gland morphology, tear film, and dry eye. Optom Vis Sci 2012;89:E310–5.
[111] Finis D, Ackermann P, Pischel N, Konig C, Hayajneh J, Borrelli M, et al. Evaluation of meibomian gland dysfunction and local distribution of meibomian gland atrophy by non-contact infrared meibography. Curr Eye Res 2015;40:982–9.
[112] Eom Y, Choi KE, Kang SY, Lee HK, Kim HM, Song JS. Comparison of meibomian gland loss and expressed meibum grade between the upper and lower eyelids in patients with obstructive meibomian gland dysfunction. Cornea 2014;33:448–52.
[113] Rico-Del-Viejo L, Benitez-Del-Castillo JM, Gomez-Sanz FJ, Garcia-Montero M, Llorens-Quintana C, Madrid-Costa D. The influence of meibomian gland loss on ocular surface clinical parameters. Contact Lens Anterior Eye 2019;42(5):562–8. https://doi.org/10.1016/j.clae.2019.04.004.
[114] Korb DR, Blackie CA. Meibomian gland diagnostic expressibility: correlation with dry eye symptoms and gland location. Cornea 2008;27:1142–7.
[115] Arita R, Itoh K, Maeda S, Maeda K, Tomidokoro A, Amano S. Efficacy of diagnostic criteria for the differential diagnosis between obstructive meibomian gland dysfunction and aqueous deficiency dry eye. Jpn J Ophthalmol 2010;54:387–91.
[116] Arita R, Morishige N, Koh S, Shirakawa R, Kawashima M, Sakimoto T, et al. Increased tear fluid production as a compensatory response to meibomian gland loss: a multicenter cross-sectional study. Ophthalmology 2015;122:925–33.
[117] Efron N, Al-Dossari M, Pritchard N. In vivo confocal microscopy of the palpebral conjunctiva and tarsal plate. Optom Vis Sci 2009;86:E1303–8.
[118] Liang QF, Gao C, Liang H, Du XH, Wang NL, Labbe A. [In vivo confocal microscopy evaluation of meibomian glands in meibomian gland dysfunction patients]. Zhonghua Yan Ke Za Zhi 2016;52:649–56.
[119] Zhao H, Chen JY, Wang YQ, Lin ZR, Wang S. In vivo confocal microscopy evaluation of meibomian gland dysfunction in dry eye patients with different symptoms. Chin Med J 2016;129:2617–22.
[120] Qazi Y, Kheirkhah A, Blackie C, Cruzat A, Trinidad M, Williams C, et al. In vivo detection of clinically non-apparent ocular surface inflammation in patients with meibomian gland dysfunction-associated refractory dry eye symptoms: a pilot study. Eye 2015;29:1099–110.
[121] Ju MJ, Shin JG, Hoshi S, Yasuno Y, Lee BH, Tang S, et al. Three-dimensional volumetric human meibomian gland investigation using polarization-sensitive optical coherence tomography. J Biomed Optic 2014;19:30503.
[122] Yoo YS, Na KS, Byun YS, Shin JG, Lee BH, Yoon G, et al. Examination of gland dropout detected on infrared meibography by using optical coherence tomography meibography. Ocul Surf 2017;15:130–138 e1.
[123] Liang Q, Pan Z, Zhou M, Zhang Y, Wang N, Li B, et al. Evaluation of optical coherence tomography meibography in patients with obstructive meibomian gland dysfunction. Cornea 2015;34:1193–9.
[124] Napoli PE, Coronella F, Satta GM, Iovino C, Sanna R, Fossarello M. A simple novel

technique of infrared meibography by means of spectral-domain optical coherence tomography: a cross-sectional clinical study. PloS One 2016;11:e0165558.
[125] Arita R. Meibography: a Japanese perspective. Invest Ophthalmol Vis Sci 2018;59:DES48–55.
[126] Wong S, Srinivasan S, Murphy PJ, Jones L. Comparison of meibomian gland dropout using two infrared imaging devices. Contact Lens Anterior Eye 2018;42(3):311–7. https://doi.org/10.1016/j.clae.2018.10.014.
[127] Den S, Shimizu K, Ikeda T, Tsubota K, Shimmura S, Shimazaki J. Association between meibomian gland changes and aging, sex, or tear function. Cornea 2006;25:651–5.
[128] Ban Y, Shimazaki-Den S, Tsubota K, Shimazaki J. Morphological evaluation of meibomian glands using noncontact infrared meibography. Ocul Surf 2013;11:47–53.
[129] Feng Y, Gao Z, Feng K, Qu H, Hong J. Meibomian gland dropout in patients with dry eye disease in China. Curr Eye Res 2014;39:965–72.
[130] Yeotikar NS, Zhu H, Markoulli M, Nichols KK, Naduvilath T, Papas EB. Functional and morphologic changes of meibomian glands in an asymptomatic adult population. Invest Ophthalmol Vis Sci 2016;57:3996–4007.
[131] Rocha EM, Alves M, Rios JD, Dartt DA. The aging lacrimal gland: changes in structure and function. Ocul Surf 2008;6:162–74.
[132] Bron AJ, de Paiva CS, Chauhan SK, Bonini S, Gabison EE, Jain S, et al. TFOS DEWS II pathophysiology report. Ocul Surf 2017;15:438–510.
[133] Villani E, Canton V, Magnani F, Viola F, Nucci P, Ratiglia R. The aging Meibomian gland: an in vivo confocal study. Invest Ophthalmol Vis Sci 2013;54:4735–40.
[134] Wei A, Hong J, Sun X, Xu J. Evaluation of age-related changes in human palpebral conjunctiva and meibomian glands by in vivo confocal microscopy. Cornea 2011;30:1007–12.
[135] Ibrahim OM, Matsumoto Y, Dogru M, Adan ES, Wakamatsu TH, Shimazaki J, et al. In vivo confocal microscopy evaluation of meibomian gland dysfunction in atopic-keratoconjunctivitis patients. Ophthalmology 2012;119:1961–8.
[136] Alghamdi WM, Markoulli M, Holden BA, Papas EB. Impact of duration of contact lens wear on the structure and function of the meibomian glands. Ophthalmic Physiol Optic 2016;36:120–31.
[137] Arita R, Itoh K, Inoue K, Kuchiba A, Yamaguchi T, Amano S. Contact lens wear is associated with decrease of meibomian glands. Ophthalmology 2009;116:379–84.
[138] Tang Y, Wu Y, Rong B, Li HL, Yang SL, Yan XM. [The effect of long-term contact lens wear on the morphology of meibomian glands]. Zhonghua Yan Ke Za Zhi 2016;52:604–9.
[139] Villani E, Ceresara G, Beretta S, Magnani F, Viola F, Ratiglia R. In vivo confocal microscopy of meibomian glands in contact lens wearers. Invest Ophthalmol Vis Sci 2011;52:5215–9.
[140] Ucakhan O, Arslanturk-Eren M. The role of soft contact lens wear on meibomian gland morphology and function. Eye Contact Lens 2019;45(5):292–300. https://doi.org/10.1097/ICL.0000000000000572.
[141] Machalinska A, Zakrzewska A, Adamek B, Safranow K, Wiszniewska B, Parafiniuk M, et al. Comparison of morphological and functional meibomian gland characteristics between daily contact lens wearers and nonwearers. Cornea 2015;34:1098–104.
[142] Na KS, Yoo YS, Hwang HS, Mok JW, Kim HS, Joo CK. The influence of overnight orthokeratology on ocular surface and meibomian glands in children and adolescents. Eye Contact Lens 2016;42:68–73.
[143] Ong BL, Larke JR. Meibomian gland dysfunction: some clinical, biochemical and physical observations. Ophthalmic Physiol Optic 1990;10:144–8.
[144] Henriquez AS, Korb DR. Meibomian glands and contact lens wear. Br J Ophthalmol 1981;65:108–11.
[145] Shimazaki J, Goto E, Ono M, Shimmura S, Tsubota K. Meibomian gland dysfunction in patients with Sjogren syndrome. Ophthalmology 1998;105:1485–8.
[146] Villani E, Beretta S, De Capitani M, Galimberti D, Viola F, Ratiglia R. In vivo confocal microscopy of meibomian glands in Sjogren's syndrome. Invest Ophthalmol Vis Sci 2011;52:933–9.
[147] Villani E, Magnani F, Viola F, Santaniello A, Scorza R, Nucci P, et al. In vivo confocal evaluation of the ocular surface morpho-functional unit in dry eye. Optom Vis Sci 2013;90:576–86.
[148] Kheirkhah A, Qazi Y, Arnoldner MA, Suri K, Dana R. Vivo confocal microscopy in dry eye disease associated with chronic graft-versus-host disease. Invest Ophthalmol Vis Sci 2016;57:4686–91.
[149] Li P, Sun Y, Hariri S, Zhou Z, Inamoto Y, Lee SJ, et al. Anterior segment optical coherence tomography evaluation of ocular graft-versus-host disease: a case study. Quant Imag Med Surg 2015;5:163–70.
[150] Liang H, Randon M, Michee S, Tahiri R, Labbe A, Baudouin C. In vivo confocal microscopy evaluation of ocular and cutaneous alterations in patients with rosacea. Br J Ophthalmol 2017;101:268–74.
[151] Baudouin C, de Lunardo C. Short-term comparative study of topical 2% carteolol with and without benzalkonium chloride in healthy volunteers. Br J Ophthalmol 1998;82:39–42.
[152] Burstein NL. The effects of topical drugs and preservatives on the tears and corneal epithelium in dry eye. Trans Ophthalmol Soc U K 1985;104(Pt 4):402–9.
[153] Kuppens EV, de Jong CA, Stolwijk TR, de Keizer RJ, van Best JA. Effect of timolol with and without preservative on the basal tear turnover in glaucoma. Br J Ophthalmol 1995;79:339–42.
[154] Norn MS, Opauszki A. Effects of ophthalmic vehicles on the stability of the precorneal film. Acta Ophthalmol 1977;55:23–34.
[155] Pauly A, Meloni M, Brignole-Baudouin F, Warnet JM, Baudouin C. Multiple endpoint analysis of the 3D-reconstituted corneal epithelium after treatment with benzalkonium chloride: early detection of toxic damage. Invest Ophthalmol Vis Sci 2009;50:1644–52.
[156] Wilson WS, Duncan AJ, Jay JL. Effect of benzalkonium chloride on the stability of the precorneal tear film in rabbit and man. Br J Ophthalmol 1975;59:667–9.
[157] Agnifili L, Mastropasqua R, Fasanella V, Brescia L, Scatena B, Oddone F, et al. Meibomian gland features and conjunctival goblet cell density in glaucomatous patients controlled with prostaglandin/timolol fixed combinations: a case control, cross-sectional study. J Glaucoma 2018;27:364–70.
[158] McCann LC, Tomlinson A, Pearce EI, Diaper C. Tear and meibomian gland function in blepharitis and normals. Eye Contact Lens 2009;35:203–8.
[159] Koh S, Maeda N, Nishida K. Visualization of the meibomian glands by means of noncontact mobile-type meibography (Meibopen) in a 16-year-old girl with unilateral marginal staphylococcal keratitis. J AAPOS 2014;18:99–101.
[160] Kaercher T, Dietz J, Jacobi C, Berz R, Schneider H. Diagnosis of X-linked hypohidrotic ectodermal dysplasia by meibography and infrared thermography of the eye. Curr Eye Res 2015;40:884–90.
[161] Chinmayee JT, Meghana GR, Prathiba RK, Ramesh TK. Ophthalmic manifestations in Rothmund-Thomson syndrome: case report and review of literature. Indian J Ophthalmol 2017;65:1025–7.
[162] Lin T, Gong L. In vivo confocal microscopy of meibomian glands in primary blepharospasm: a prospective case-control study in a Chinese population. Medicine (Baltim) 2016;95:e3833.
[163] Wei Q, Le Q, Hong J, Xiang J, Wei A, Xu J. In vivo confocal microscopy of meibomian glands and palpebral conjunctiva in vernal keratoconjunctivitis. Indian J Ophthalmol 2015;63:327–30.
[164] Jones L, Downie LE, Korb D, Benitez-Del-Castillo JM, Dana R, Deng SX, et al. TFOS DEWS II management and therapy report. Ocul Surf 2017;15:575–628.
[165] Pult H, Riede-Pult BH. Non-contact meibography: keep it simple but effective. Contact Lens Anterior Eye 2012;35:77–80.