Japanese Journal of Ophthalmology (2023) 67:448–539
https://doi.org/10.1007/s10384-023-00995-8

THE OFFICIAL INTERNATIONAL JOURNAL OF THE JAPANESE OPHTHALMOLOGICAL SOCIETY

GUIDELINE

Meibomian Gland Dysfunction Clinical Practice Guidelines

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Received: 30 November 2022 / Accepted: 21 December 2022 / Published online: 23 June 2023

Abbreviations

ADDE	Aqueous-deficient dry eye
ALA	α-Linolenic acid
BQ	Background question
BUP	Tear film breakup pattern
BUT	Tear film breakup time
COI	Conflicts of interest
CQ	Clinical question
CsA	Cyclosporin A
DHA	Docosahexaenoic acid
DPA	Docosapentanoic acid
DQS	Diquafosol
EPA	Eicosapentanoic acid
GVHD	Graft versus host disease
IPL	Intense pulsed light
IVCM	In vivo Confocal microscopy
JHI	Japanese health insurance
LLT	Lipid layer thickness
MCJ	Mucocutaneous junction
MGD	Meibomian gland dysfunction
MGX	Meibomian gland expression
MINDS	Medical information network distribution service
MRKC	Meibomitis-related keratoconjunctivitis
NIBUT	Noninvasive breakup time of tear film
NMR	Nuclear magnetic resonance
oMGD	Obstructive meibomian gland dysfunction
OSDI	Ocular surface disease index
PPAR-γ	Peroxisome proliferator-activated receptor γ
RCT	Randomized controlled trial
SCL	Soft contact lens
SJS	Stevens–Johnson syndrome
sMGD	Seborrheic meibomian gland dysfunction
SPEED	Standard patient evaluation of eye dryness
SPK	Superficial punctate keratopathy
SR	Systematic review
SS	Sjögren's syndrome
TFOS	Tear Film and Ocular Surface Society
VDT	Visual display terminals

Committee members are mentioned in "Acknowledgements" section.

In 2020, Japan Dry Eye Society established the Meibomian Gland Dysfunction Clinical Practice Guideline Committee, which published Meibomian Gland Dysfunction Clinical Practice Guidelines in Nippon Ganka Gakkai Zasshi, 2023;127(2):109–228 (in Japanese). This is the English version of that Guideline. The original work is at https://www.nichigan.or.jp/Portals/0/resources/member/guideline/MGD.pdf.

Current guideline is constructed based on Minds guideline library organized by Japan Council for Quality Health Care; JCQHC.

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Preface

Functional disturbances of the meibomian gland, known as MGD, lead to chronic ocular discomfort. One disorder, dry eye, is the result of MGD, with symptoms such as ocular dryness and fatigue. In Japan, epidemiological surveys show that about 10–30% of the population aged >50 years have MGD related disorders. It is a clinically important disease that reduces the quality of life. Herein, we provide clinical practice guidelines for MGD.

In 2010, the MGD Working Group published the definition, classification, and diagnostic criteria of MGD, to aid the clinical practice of MGD in Japan, and these have been widely referred to since then. However, the list was not comprehensive. Globally, although the International Workshop on MGD comprehensively reported its findings on MGD in 2011, it was authority-based. Hence, we compiled these first evidence based comprehensive MGD clinical practice guidelines.

According to the MINDS Guide for Developing Clinical Practice Guidelines 2017 by Kojimahara et al., a clinical practice guideline is a "document that presents recommendations considered optimal to support patient and health care professional decision-making, taking into account evidence-based SR and their overall evaluation, and balancing the benefits and harms of techniques of high significance in clinical practice". According to the method stipulated by MINDS, we prepared six BQs and 30 CQs crucial for the clinical management of MGD and conducted a SR, based on which we present these recommendations. Through the development of these clinical practice guidelines, many issues with little reliable evidence were identified. We anticipate future research on issues with weak evidence and recommendations, based on which this clinical practice guidelines will be reviewed and updated.

We hope that these guidelines will be widely used by everyone associated with MGD.

Meibomian Gland Dysfunction Clinical Practice Guidelines Committee

Chairman: Shiro Amano

Explanation of Key Terms

Term	Explanation
Meibocyte	Meibomian acinar cell
Meibum	Meibomian gland discharge/secretion
Meibum grade	Score of semi-quantitative evaluation of meibomian gland secretions by their quality and expressibility. Used to determine both the severity and the therapeutic effects in MGD. According to the Shimazaki approach, meibum grades are: 0 = clear meibum, easily expressed, 1 = turbid meibum, expressed under light compression, 2 = turbid meibum, expressed under moderate compression, and 3 = meibum, not expressed even under strong compression. (Refer CQ6)
Peroxisome proliferator-activated receptor γ (PPAR-γ)	A nuclear receptor superfamily that acts as a transcription factor. Involved in lipid synthesis and adipocyte differentiation. PPAR-γ plays an important role in cell differentiation and lipid synthesis in the meibocytes. (Ref. BQ1)
Breakup time of tear film (BUT)	Time from the opening of the eyelid to the breakup of the tear film. An indicator of the stability of the tear film. The shorter the BUT, the more unstable the tear film. Commonly measured after using fluorescein eye drops. The NIBUT measures BUT from the distortion of projected light over time caused by reflection on the tear film surface. (Ref. CQ4 and CQ7)
Findings in areas surrounding meibomian gland orifices	Changes around meibomian gland orifices seen in MGD, e.g. vascularity, displacement of the MCJ, and irregularity of the eyelid margin. (Ref. CQ3)
Obstructive findings of the meibomian gland orifices	Finding of keratinized debris that has accumulated in the meibomian orifice due to hyperkeratinization of the meibomian gland ductal epithelium, following which meibum is no longer discharged. The findings include plugging (occlusion of keratinized debris and lipids in individual orifice), pouting (protuberance and occlusion of keratinized material in the shape of a pointed mouth in neighboring orifices), and ridges (ridge-like elevations of the MCJ or of tissue between the occluded orifices). (Ref. CQ3)
Obstructive meibomian gland dysfunction	A type of low-delivery MGD. Diffused occlusion of the meibomian gland orifice is observed. (Ref. BQ1 and BQ2)
Atrophic meibomian gland dysfunction	A type of low-delivery MGD. A state of diffuse atrophy of the meibomian gland acini. Acinar atrophy has a mechanism in which the intraglandular pressure increases due to keratinized material stagnation, causing keratinized materials to atrophy due to pressure, and a mechanism in which the glandular cells themselves atrophy under various influences. (Ref. BQ1 and BQ2)

Abstract of the Guidelines

BQ/CQ number	Question	Description	Strength of recommendation
BQ1	What is the pathophysiology of MGD?	The main pathophysiology of low-delivery MGD is hyperkeratinization of the ductal epithelium of the main duct and acinar atrophy. Acinar atrophy may occur as a primary disorder of the glandular cells due to aging, or as secondary to meibomian gland obstruction. The pathophysiology of high-delivery MGD is not well understood.	
BQ2	What are the definitions, classifications and severity staging of MGD?	MGD is divided into two types: low-delivery and high-delivery; however, the subclasses within them vary slightly depending on reports. Severity staging was determined based on subjective symptoms, obstruction of meibomian gland orifices, abnormalities around the orifices, morphologic characteristics, the state of expression and lipid characteristics of the meibum when eyelids are compressed, as well as meibography. There is still no global consensus on this classification.	
BQ3	What disorders are related to MGD?	MGD is associated with posterior blepharitis, meibomitis, and ocular surface epithelial disorders. These disorders are important in the diagnosis and treatment of MGD as well as related disorders. Understanding this relationship helps to clarify how MGD influences blepharitis and how meibomitis impacts on the ocular surface inflammation.	
BQ4	What is the prevalence of MGD?	The prevalence of MGD expressed in the literature so far varies with each report due to differences in diagnostic criteria. In a population-based study of residents aged 6–96 years in Japan, the prevalence according to age was 0% (6–19 years), 11.8% (20–29 years), 5.6% (30–39 years), 21.6% (40–49 years), 32.8% (50–59 years), 41.9% (60–69 years), 48.4% (70–79 years), and 63.9% (80–96 years).	
BQ5	What are the factors associated with the development of MGD?	Many studies suggest that MGD increases with age. It is widely reported in men and postmenopausal women. Asian ethnicity, rural residence, occupation related to VDT, smoking, the use of SCL, and glaucoma eye drops. All these have been noted as risk factors for MGD. The association between ocular surgery and MGD has also been reported.	
BQ6	What are the systemic factors and disorders associated with the development of MGD?	Systemic diseases such as diabetes, dyslipidemia, hypertension, and hyperthyroidism are risk factors. Rosacea that causes ocular inflammation, SS, SJS, and GVHD are likely to be associated with the development of MGD. Additionally, menopause and androgen deficiency are also related to the development of MGD.	
CQ1	What are the diagnostic criteria for MGD?	In Japan, the diagnostic criteria for low-delivery MGD proposed by the MGD Working Group in 2010 are often refered. However, there are no globally accepted diagnostic criteria.	

BQ/CQ number	Question	Description	Strength of recommendation
CQ2	What are the characteristic subjective symptoms of MGD and appropriate ways to elicit them from patients?	Symptoms of MGD include eye discomfort, foreign body sensation, dryness, pressure, pain, burning sensation, tears, ocular fatigue, blurred vision, itching, eye discharge, and photophobia. We strongly recommend interviewing the patients to discover which of these symptoms affect them. At the moment, there is no clinical evidence of symptoms to differentiate MGD from other ocular surface disorders.	
CQ3	Is anatomical observation of eyelid margins useful in the diagnosis of MGD?	Four anatomical changes in the eyelid margins are useful in the diagnosis of MGD: obstruction of the meibomian gland orifices, eyelid margin vascularity, displacement of the MCJ, and irregular eyelid margins.	
CQ4	Is the measurement of BUT useful in the diagnosis of MGD?	Many reports state that BUT is reduced in MGD compared with the normal eye. However, BUT is not a useful test to specifically diagnose MGD.	
CQ5	Is the observation of BUP helpful in the diagnosis of MGD?	Observing BUP has been found to be useful in diagnosing dry eye subtypes. Although there are no reports of a BUP specific to MGD, it has been pointed out that MGD is associated with increased evaporation in dry eye, and it may be useful as an auxiliary test for the diagnosis of MGD.	
CQ6	Is it useful to observe meibomian gland secretions in the diagnosis of MGD?	In MGD, changes occur in the quantity and quality of meibomian gland secretions (meibum). Therefore, in the diagnosis of MGD, observation of meibum using a slit-lamp microscopy is important, and its implementation is recommended.	
CQ7	Is NIBUT measurement useful in the diagnosis of MGD?	Only few studies exist on the topic. Therefore, Whether NIBUT measurement is useful for MGD diagnosis cannot be confirmed. Since cut-off value has not been specified, it cannot be currently recommended as a test for MGD diagnosis.	
CQ8	Is meibography useful in the diagnosis of MGD?	The use of meibography for the diagnosis of MGD is recommended. Meibography is a device for observing meibomian gland tissue morphology. In addition to being effective in diagnosing MGD, it is notable for its noninvasiveness and short examination time.	
CQ9	Is the observation of tear interference image useful in the diagnosis of MGD?	LLT measured by a tear interference image observation device is reportedly thin in patients with MGD. If the cut-off value is determined through future research, it may become a promising tool for diagnosing MGD.	
CQ10	Is tear evaporation measurement useful in the diagnosis of MGD?	The amount of tear evaporation may reflect the functioning of the meibomian gland. Previous studies have reported an increase in the amount of evaporation in oMGD compared with healthy individuals. However, since measuring devices and conditions are not standardized and are not commonly used in clinical practice, tear evaporation measure cannot be recommended.	

BQ/CQ number	Question	Description	Strength of recommendation
CQ11	Is IVCM useful in the diagnosis of MGD?	IVCM is reportedly effective in diagnosing MGD. However, it is necessary to reconfirm that the structure observed in IVCM is the acini of the meibomian gland. The disadvantages to patients, such as invasiveness and the burden of long examinations, must also be considered. The decision to use IVCM in a clinical examination should be left to the individual ophthalmologist.	
CQ12	Is measuring tear film osmolality useful in the diagnosis of MGD?	There is a possibility that the tear film osmolality may reflect the function of the lipid layer. However, there are contradictory reports about the effectiveness of the tear film osmolality in diagnosing MGD. Given the noninvasive nature, we do not deny its implementation; however, its clinical utility is limited at present.	
CQ13	Is lipid quantification on eyelid margins useful in the diagnosis of MGD?	Lipid mass measurement of the eyelid margin is a noninvasive test, and causes little disadvantage to the patient, with relatively high reproducibility of semi-quantitation. However, since currently reasonable cut-off value is not set, there is little benefit to the test.	
CQ14	Is a biochemical analysis of the meibomian gland secretions useful in the diagnosis of MGD?	Currently, markers and analysis methods specific to MGD have not been established, making the biochemical analysis of meibomian gland secretions not beneficial in the diagnosis of MGD.	
CQ15	Is measuring inflammatory biomarkers in tears useful in the diagnosis of MGD?	Measuring inflammatory biomarkers in tears for diagnosing MGD is not currently useful, although it provides insights into the possibility of adjunctive diagnosis.	
CQ16	Are bacteriological tests useful in the diagnosis of MGD?	Genomic sequences using culture tests and polymerase chain reaction have been used as bacteriological tests for the diagnosis of MGD. However, neither has obtained characteristic results. Bacteriological tests are currently not useful for diagnosing MGD.	
CQ17	What are the frequencies and characteristics of keratoconjunctival epithelial disorders in MGD and what are the appropriate staining methods?	Systematically analysis of the characteristics of keratoconjunctival epithelial disorder sites in MGD could not be identified in literature. Fluorescein staining is the most valuable staining method for keratoconjunctival epithelial disorders. Rose Bengal staining and Lissamine green staining are also used for conjunctival epithelial disorders.	
CQ18	Is eyelid warming effective?	Eyelid warming improves the subjective symptoms and meibum grade. Its use is strongly recommended.	Strongly recommend “implementation”
CQ19	Is eyelid hygiene effective?	Eyelid hygiene with a cotton ball moistened with water may improve subjective symptoms and BUT. Eyelid hygiene with commercially available cleansing agents may improve subjective symptoms, meibomian gland orifice/surrounding findings, meibum grade, BUT, and epithelial disorders. Depending on the type of cleansing agent used, mild adverse events may occur. Based on the above, eyelid hygiene for MGD is moderately recommended.	Marginally recommend “implementation”

BQ/CQ number	Question	Description	Strength of recommendation
CQ20	Is meibomian gland expression effective?	Meibomian gland expression treatment is effective in improving subjective symptoms and is recommended.	Marginally recommend "implementation"
CQ21	Are DQS eye drops effective?	DQS eye drops may improve subjective symptoms, meibomian gland orifice/surrounding findings, meibum grade, BUT, and epithelial disorders in patients with concurrent MGD and dry eye. However, their efficacy in MGD without dry eye is unknown. Considering that DQS eye drops for MGD alone are not covered by JHI, not implementing it as a treatment option is moderately recommended.	Marginally recommend "not to be implemented"
CQ22	Are antimicrobial eye drops effective?	Azithromycin eye drops are effective in improving subjective symptoms, meibomian gland orifice/surrounding findings, and meibum grade. Although the incidence of adverse events is relatively high, it is limited to mild adverse events. Therefore, the implementation is marginally recommended.	Marginally recommend "implementation"
CQ23	Are ophthalmic ointments (excluding corticosteroid-based ophthalmic ointment)/oily eye drops effective?	Few evidence is available on the use of either ophthalmic ointments or oily eye drops. Hence, no clear recommendations can be made.	Not recommended due to insufficient evidence
CQ24	Is topical corticosteroid administration (eye drops and ointments) effective?	Corticosteroid eye drops are used in combination with eyelid hygiene and warming to improve subjective symptoms, BUT, eyelid margin findings, and meibum quality. However, there is little evidence, and there is no JHI's coverage for their use for MGD.	Marginally recommend "implementation"
CQ25	Are CsA eye drops effective?	CsA eye drops for MGD improve subjective symptoms, eyelid findings, and properties of meibum to some extent, but their effects are limited. We do not consider CsA eye drops for MGD as the evidence based treatment, and we marginally recommend against their use.	Marginally recommend "not to be implemented"
CQ26	Are oral omega-3 fatty acids effective?	In MGD, oral administration of omega-3 fatty acids may improve subjective symptoms, reduce vascularity around the meibomian gland orifice, and increase BUT. Considering that omega-3 fatty acid preparations are not covered by JHI and are considered as supplements, their use is marginally recommended.	Marginally recommend "implementation"
CQ27	Is oral antimicrobial medication effective?	Oral administration of azithromycin and tetracycline antimicrobials (doxycycline and minocycline) is effective in improving subjective symptoms and meibomian gland orifice/surrounding findings in patients with MGD. Since neither drug is covered by insurance for MGD in Japan, their use is marginally recommended.	Marginally recommend "implementation"
CQ28	Is intense pulsed light effective?	IPL therapy is effective in improving subjective symptoms, meibomian gland orifice/surrounding findings, meibum grade, BUT, and epithelial disorders in MGD. Furthermore, adverse events are infrequent, mild, and reversible. Hence, its implementation is strongly recommended. However, IPL is not approved for MGD in Japan, and there is no JHI's coverage. From this point of view, we only marginally recommend its use.	Marginally recommend "implementation"

BQ/CQ number	Question	Description	Strength of recommendation
CQ29	Is thermal pulsation therapy effective?	Thermal pulsation therapy improves the subjective symptoms as well as objective findings in MGD (meibomian gland orifice/surrounding findings, quality of meibum, and BUT). However, given that there is no JHI's coverage in Japan, its implementation is marginally recommended.	Marginally recommend "implementation"
CQ30	Is probing effective?	Although probing in oMGD improves subjective symptoms, it hardly improves meibomian gland orifice findings, meibum grade, BUT, or keratoconjunctival epithelial disorders. Considering that it is also an invasive treatment, we marginally recommend against its implementation.	Marginally recommend "not to be implemented"

How to read and interpret the recommendations and explanations in this guideline

The guidelines

These clinical practice guidelines aim to present recommendations with high levels of evidence based on the Minds' format, whenever possible. Important clinical issues are addressed in the form of BQs and CQs, and recommendations are advanced based on systematic review (SR).

Important issues that were not suitable for inclusion in the SR are presented as a review based on literature retrieval.

Furthermore, issues at the intersection of basic research and clinical considerations are addressed as "specific topics."

BQs and CQs

In these clinical practice guidelines, among the important issues, six questions related to pathophysiology, classification, related diseases, epidemiology, and risk factors are set as BQs. Additionally, 30 issues related to diagnosis, examination, and treatment are set as CQs.

For the BQs related to pathophysiology, classification, and related diseases (BQs 1–3), responses were prepared in the form of reviews.

For the BQs on epidemiology and risk factors (BQs 4–6) and the CQs on diagnosis and examination (CQs 1–17), responses were divided into the following sections: recommendations, explanations, problem/bias, future issues, and trends.

For the CQs related to treatment (CQs 18–30), responses were divided into the following sections: recommendations, strength of recommendations, strength of evidence, basis for the development of recommendations, and summary of SR.

Recommendations

Recommendations were prepared as answers to BQs and CQs.

These recommendations were prepared based on the results of SR, the strength of evidence on outcomes, and the balance between harm and benefit.

Additionally, "patient values and hopes" and "economic perspectives" were considered.

Subjective symptoms, meibomian gland orifice/surrounding findings, meibomian gland secretion grade, BUT, epithelial disorders, and adverse events were considered as major outcomes requiring treatment.

Explanation, problem/bias, future issues, and trends

For BQs on epidemiology and risk factors (BQs 4–6) and CQs on diagnosis and examination (CQs 1–17), the responses were divided into the following sections: explanation, problem/bias, future issues, and trends.

For the CQs related to diagnosis and examination (CQs 1–17), only the efficacy for diagnosing MGD was examined; the efficacy for determining the severity and therapeutic effect in MGD was not examined.

Strength of recommendation

The strength of recommendation was determined by a vote of the 12 committee members, comprising the supervisory board and guideline preparation team.

Since those with COI in each CQ were excluded from voting for that particular CQ, the declared COI did not affect the determination of the strength of recommendation.

In principle, the following four implementation categories were used.

Strongly recommend "implementation"

Marginally recommend "implementation"

Marginally recommend "not to be implemented"
Strongly recommend "not to be implemented"

Whenever the body of evidence was insufficient and a conclusion could not be reached, the issue was presented as not recommended due to insufficient evidence.

Strength of evidence for CQ

The strength of evidence assessed for each outcome (evidence summary) was consolidated to present a summary of for CQ.

The strengths of evidence were defined as follows
A (strong): Strongly confident in estimate of effect
B (medium): Moderately confident in estimate of effect
C (weak): Limited confidence in estimate of effect
D (very weak): Little confidence in estimate of effect

Process of developing recommendations

Based on the CQ, the progress and summary leading to the recommendation were described.

The scope of the literature used for the development has also been described.

In principle, the articles covered were RCTs, and other articles were incorporated if and when deemed relevant.

SR summary

The evidence level and bias risk in the articles included in the SR were explained, and the strength of the overall evidence was evaluated. In the literature search, in addition to the meibomian gland dysfunction (MGD), posterior blepharitis and meibomitis were included if the content of the articles were determined to be equivalent to MGD. Regarding treatment, "subjective symptoms," "meibomian gland orifices/surrounding findings," "meibomian gland secretion grade," "tear film break-up time (BUT)," "epithelial disorders," and "adverse events" were considered as major outcomes. However, if improvement was reported only in "BUT" and "epithelial disorder", the recommended level was lowered. If results of supplementary assessments, such as meibography, confocal microscopy, biochemical test, bacterial test, tear interference image observation, and tear evaporation volume, were reported, these were also considered and comprehensively evaluated.

References

References cited in SR report and summaries are listed.

Chapter 1

Preparation Process

Item	Process
1. Preparation Policy	The objective was to prepare clinical practice guidelines to aid all people involved in the treatment of MGD in decision-making regarding diagnostic and therapeutic practices. In preparing this document, we followed the MINDS method as closely as possible, and efforts were made to prepare evidence-based clinical practice guidelines.
2. Precautions for use	These guidelines need to be used based on the individual judgment of the practicing medical personnel. There is no attempt to limit the discretion of on-site medical practice. The final decision in the clinical setting must be made by the attending physician in consultation with the patient. (1) The actual condition of the affected site (human/physical environment and actual clinical situation), (2) inappropriateness to apply the guidelines based on patient symptoms (specific symptoms/findings), (3) preferences and skill of the treating physician, (4) infrastructure of the facility, and (5) constraints of the insurance system; are all to be considered in deciding the appropriate treatment. The recommendations for treatment in these guidelines also include treatment methods that are not covered by JHI. However, in practice, in addition to the informed consent of patients and families, careful judgment is required, including approval by ethics committees, depending on the set-up of the facility. In addition, there are many areas in the treatment of MGD that lack established evidence and the conditions relating to examination and treatment remain fluid. We have prepared these guidelines to serve as a reference for the treatment based on the evaluation of currently existing circumstances. Medical articles published until June 2021 has been covered in these guidelines. The guidelines need to be continuously reviewed and updated. Although a vote was taken to determine the strength of the recommendation for CQs 18–30, members with COI were excluded from vote on the corresponding CQs. Hence, as such, the declared COI did not influence the determination of recommendations' strengths.

Item	Process
3. Organizational structure	MGD Clinical Practice Guidelines' Supervisory Board
	Five ophthalmologists were nominated by the directors and councilors of the Japan Cornea Society and the caregivers of the Dry Eye Research Society.
	MGD Clinical Practice Guidelines' Preparation Team
	Comprised of 12 ophthalmologists (including the five supervisory board members) selected by the MGD clinical practice guidelines' supervisory board.
	Systematic Review Team
	Comprised of 30 ophthalmologists (including the aforementioned 12 members) selected by the MGD clinical practice guidelines' supervisory board.
4. Development process	Preparation
	On October 8, 2020 the MGD practice guidelines' supervisory board confirmed (online) the level, content, and precautions for preparation of MGD clinical practice guidelines. Development included selection of the supervisory board members, preparation team members, selection method of SR members, and the role of each team member. The budget size and funding sources were determined. The schedule for preparation was finalized. On December 27, 2020 the MGD practice guidelines' preparation team discussed and confirmed (online) the views on the pathophysiology of MGD and related diseases. At the same time, methods of proceeding with SR and treatment evaluation criteria were determined.
	Scope
	January–June 2021 The preparation team members worked over email. The SR team members were selected online. COI statements were collected from the supervisory board members, the preparation team members, and SR team members. The scope of the guidelines was determined by the chairman. The BQs, CQs, and those in charge of SR were finalized.
	Systematic review
	July 1, 2021 An agreement was reached with the Japan Medical Library Association to receive support for the creation of the MGD Clinical Practice Guidelines. August 31, 2021 We received the literature search results from the Japan Medical Library Association. September 2021 – March 2022 The preparation team members and SR team members worked online to determine the recommended format. Recommendations were written and submitted by email. Questions and uncertainties were resolved by discussions over email.
	Preparation of recommendations
	April 8, 12, and 19, 2022 The preparation team discussed (online) the contents of the recommendations, and the text regarding recommendations was finalized. The strength of the recommendations in treatment-related CQs was determined according to the modified Delphi method. Twelve committee members initially submitted comments on the strengths of the recommendations, shared with other members. Subsequently, an online meeting was convened to discuss the strengths of the recommendations. Following this, each team member resubmitted comments on the strengths of the recommendations and the final decision was made by majority vote. Additionally, the definition, classification, and diagnostic criteria of MGD were discussed and finalized.
	Finalization
	May–June 2022 The draft of the prepared clinical practice guidelines was externally evaluated; it was further revised and finalized based on the opinions received. (The results of the external evaluation are published on the website of the Dry Eye Research Society.)
	Public release

Chapter 2

Definitions, classifications, and diagnostic criteria

The definition, classification, and diagnostic criteria of MGD were first published by the MGD Working Group in 2010 with the aim of supporting clinical practice and research regarding MGD [1]. These definitions, classifications, and diagnostic criteria have been utilized in many subsequent studies on MGD and have served to promote research on MGD. Since then, many basic and clinical studies on MGD have been conducted and the understanding of the pathophysiology and clinical characteristics of MGD has evolved. Therefore, in the preparation of the MGD clinical practice guidelines, the guidelines' preparation team discussed the definitions, classifications, and diagnostic criteria of MGD;

the classifications and diagnostic criteria were revised as given below.

The definition of MGD, was first published in 2010. It incorporates essential elements for defining MGD, such as multiple causes, presence of diffuse abnormalities, and subjective symptoms (e.g. ocular discomfort). Therefore, we concluded that the definition did not require revision. The same definition was adopted in this clinical practice guidelines.

In the conventional classification, MGD was first divided into two types: low-delivery type and high-delivery type, and each was further divided into primary and secondary. However, in the process of creating these guidelines, it could be seen that there are two variations in the pathophysiology of oMGD: (1) obstructive secondary to hyperkeratinization of the ductal epithelium and (2) atrophic due to abnormal meibocytes of the meibomian gland (see BQ1). Furthermore, the transition from occlusive to atrophic type has also been observed. Therefore, the current revision divides low-delivery MGD into three categories: "congenital," "obstructive," and "atrophic." Obstructive and atrophic types were further divided into "primary" and "secondary" (Table 1). Classification into obstructive and atrophic types is important in determining the indication and strategy of treatment, and this classification is more in line with clinical practice. Additionally, risk factors for secondary low-delivery MGD are listed as annotations. It is expected that examining the presence or absence of these abnormalities will make it easier to formulate a treatment policy. The pathophysiology of the high-delivery type has not yet been elucidated, and is thus set as a single independent classification category. With future research, it is expected that the high-delivery type will also be subcategorized.

The diagnostic criteria of high-delivery MGD is not provided, since the pathophysiology of high-delivery MGD is not well understood. It was, therefore, decided to establish diagnostic criteria for low-delivery MGD only. The presence of subjective symptoms as well as abnormal eyelid margins and qualitative and quantitative abnormalities of secretions are necessary and sufficient for the diagnosis of low-delivery MGD. This point was clarified in the revised diagnostic criteria (Table 2). In 2010, the diagnostic criteria included items such as eyelid marginal vascularity, eyelid marginal irregularity, and MCJ displacement. The clinical practice guidelines' committee found that although these are useful for low-delivery MGD diagnosis, severity determination, and differential diagnosis, they are not essential for diagnosis. Therefore, they were not included in the diagnostic criteria, but were included as additional findings. When evaluating abnormalities in eyelid margins and qualitative and quantitative abnormalities in secretions a diagnosis of MGD can be made if either, (1) there exists an obstruction in the orifice or (2) there are quantitative and qualitative abnormalities in secretions. If both (1) and (2) are met, a subtype of low-delivery type MGD, oMGD is diagnosed. In these circumstances, viscous lipid may be observed along with (2) instead of (1). In atrophic MGD, another subtype, lipid expression, is decreased while meeting criterion (2) instead of (1). From the findings based on (1) and (2) under item 2 of the diagnostic criteria, it is also possible to determine the exact subtype of low-delivery MGD in each patient.

Table 1 Classification of meibomian gland dysfunction (revised as per the new guideline)

	Type	Subtypes
1.	Low-delivery type	
		(1) Congenital
		(2) Obstructive (primary, secondary)
		(3) Atrophic (primary, secondary)
2.	High-delivery type	

The following are the possible secondary causes.

Ageing, allergic eye disease, blepharitis, Stevens–Johnson syndrome, pemphigus oculus, graft-versus-host disease, Sjögren's syndrome, trachoma, drug-induced disorders, chemical wounds, and burns.

Chapter 3

Scope

I Clinical features

1. Pathophysiology

The meibomian gland is an independent sebaceous gland present in the tarsal plate in both the upper and lower eyelids. Its secretions (meibum) leave the orifice at the margin of the eyelid and spread onto the surface of the tear film. There are 30–40 meibomian gland orifices in the upper, and 20–30 in the lower eyelid. The meibum contains non-polar lipids such as cholesterol esters, wax esters, and triacylglycerides, as well as polar lipids such as (O-acyl) -omega-hydroxy fatty acids, free fatty acids, and cholesterol that are amphiphilic. The lipids secreted from the meibomian gland are distributed in the superficial tear film and believed to contribute to the stability of the tear film while suppressing the evaporation of moisture. The pathophysiology of MGD, the focus of these clinical practice guidelines, is not yet fully clarified. As mentioned previously, MGD is divided into low- and high-delivery types, and it is accepted that the pathophysiology of each is different. Conventionally, in the low-delivery type MGD, the amount of keratinized material of the meibum increases due to hyperkeratinization of the meibomian gland ductal epithelium, and the meibum becomes cloudy with

Table 2 Diagnostic criteria for low-delivery type of meibomian gland dysfunction (revised as per the new guideline)

1	Subjective symptoms	
		Eye discomfort
		Foreign body sensation
		Dryness
		Pressure
		Tears
2	Abnormalities of eyelid margins and qualitative and quantitative abnormalities of secretions	
		I Obstruction of the meibomian gland orifices is diffusely seen
		II Moderate compression of the eyelid by the thumb, or eyelid compression by forceps or clamps shows reduced expression of meibum from the meibomian gland orifice, or the expression of the viscous meibum is observed.

Satisfying both 1 and 2 are considered low-delivery type meibomian gland dysfunction.

Satisfying either (I) or (II) is considered satisfying 2.

1. With regard to subjective symptoms, it is necessary to differentiate the symptoms caused by the dysfunction of the meibomian gland from those caused by other ocular surface diseases. Symptoms that are clearly due to other ocular surface diseases must be excluded in the decision-making process.

2. The following findings are useful for subtype diagnosis, severity determination, and differential diagnosis of low-delivery meibomian gland dysfunction, and it is recommended to evaluate their presence as additional findings. However, they are not included in the diagnostic criteria.

① Vascularity or reddening of the eyelid around the orifice of the meibomian gland

② Anterior or posterior displacement of mucocutaneous junction

③ Eyelid margin irregularity

④ Gland drop out observed on meibography

⑤ Corneal abnormalities (fluorescein staining abnormalities, vascular invasion, and nodules)

⑥ Abnormalities in tear film break-up time and tear-film breakup pattern

increased viscosity. It had been thought that the major part of the pathophysiology is that these changes in the meibum cause meibomian gland obstruction and reduction of secretion of meibum (Fig. 1) [2]. Other factors that cause hyperkeratinization of the ductal epithelium and changes in the meibum include aging, inflammation, hormonal imbalance, bacterial growth, eye drops, and oral medications. Based on recent research, apart from the mechanism of occlusion of the meibomian gland orifice due to hyperkeratinization of the ductal epithelium, abnormal meibocytes of the meibomian gland are proposed as a possible core mechanism [3].

On the other hand, in the high-delivery type MGD, due to inflammation of the meibomian gland and its surroundings due to seborrheic dermatitis and other causes, a large amount of qualitatively altered meibum accumulates causing increased secretions (Fig. 2). A large amount of qualitatively

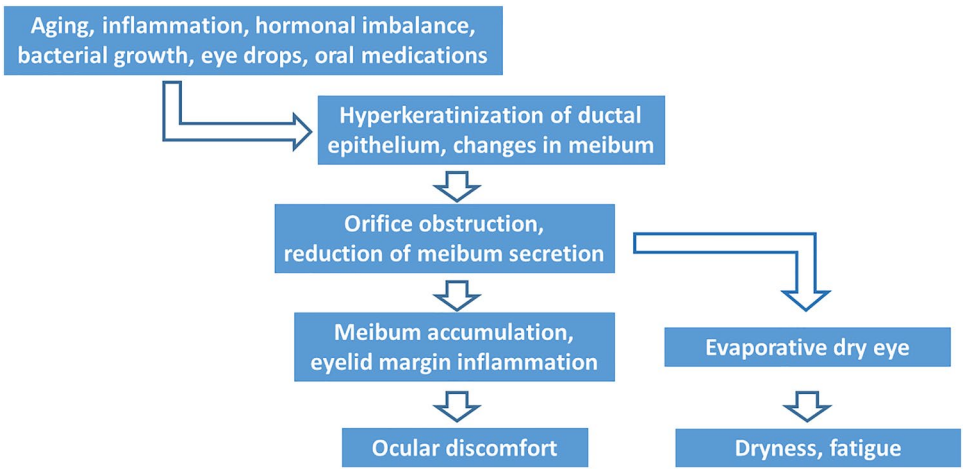

Fig. 1 Conventional theory of the pathophysiology of low-delivery meibomian gland dysfunction. (BQ1 delineates the latest theories).

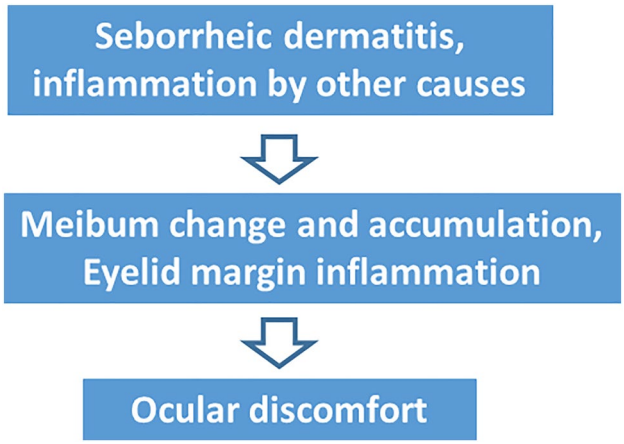

Fig. 2 Conventional theory of the pathophysiology of high-delivery meibomian gland dysfunction. (BQ1 delineates the latest theories).

altered meibum is secreted even with mild eyelid compression. Details of the pathophysiology of MGD are examined and elaborated in the review of BQ 1.

In both low- and high-delivery MGDs, meibum accumulation and inflammation of the eyelid margin occur, causing subjective symptoms such as ocular discomfort. Moreover, in low-delivery MGD, due to reduced meibum secretion, evaporative dry eye occurs, causing subjective symptoms such as dryness and ocular fatigue along with dry eye. Patients with low-delivery MGD have subjective symptoms due to pathological changes such as the occlusion of the meibomian gland orifices, and subjective symptoms due to pathological changes in the tear film and ocular surface from MGD-induced dry eye. However, the subjective symptoms from these two types of pathological changes are indistinguishable.

Posterior blepharitis and meibomitis are closely related to MGD. Inflammation in the eyelid is collectively referred to as blepharitis. In the eyelids, inflammation in the anterior skin and root of the eyelashes is called anterior blepharitis, whereas inflammation near the orifice of the meibomian gland located posteriorly in the eyelid is called posterior blepharitis. MGD often has no inflammatory findings in its early or mild stages; however, as it progresses and severity increases, it exhibits inflammatory findings such as vascularity at the eyelid margin. Posterior blepharitis may occur alone and without accompanying MGD. Therefore, although there is an overlap between MGD and posterior blepharitis, whether they are totally different diseases entities remains unclear. In many instances, the terms are used synonymously. Another term associated with MGD is meibomitis. In the correct sense of the word, whatever the cause, whenever inflammatory findings in the meibomian glands are present the condition can be described as meibomitis; however, in Japan, historically, it is used to refer to inflammation of the meibomian glands involving bacterial growth. Meibomitis is often accompanied by oMGD and may also be accompanied by corneal lesions such as corneal epithelial disorders and phlycten. Diseases associated with MGD are described in detail in BQ3.

2. Clinical Classification

The classification of MGD was proposed by the MGD Working Group in Japan in 2010 [1]. MGD was broadly classified into low and high-delivery (Fig. 3). Low-delivery type was categorized into primary (obstructive, atrophic, and congenital) and secondary (secondary to atopy, SJS, GVHD, and trachoma). High-delivery type was also considered to be either primary or secondary (secondary to ocular infections, seborrheic dermatitis). Similarly, in the classification published by TFOS MGD International Workshop in 2011 [2], MGD was broadly classified into low and high-delivery. However, it differed in that it classified the low-delivery type into hyposecretory and obstructive types.

It is believed that MGD reduces the function and secretions of the meibomian glands. However, as mentioned above, there is also a high-delivery type in MGD. In cases of high-delivery MGD, due to inflammation from various causes in and around the meibomian glands, a large amount of qualitatively altered meibum accumulates and its secretions increase. Due to qualitative changes in meibum secretion, that secretion, too is considered to be a dysfunction of the meibomian gland. High-delivery types include those associated with skin diseases such as rosacea and seborrheic dermatitis, as well as idiopathic types.

The classification and severity of MGD will be further discussed and elaborated in the review of BQ2. In addition, the present MGD practice guidelines' preparation team evaluated the classification by the 2010 MGD working group, and decided to slightly revise it. The revised version is presented in a previous chapter.

3. Definition and diagnostic criteria

The definition of MGD was published by the MGD Working Group in Japan in 2010 [1] and states: "MGD is a condition in which the function of the meibomian glands is diffusely abnormal due to various causes and involves chronic ocular discomfort." TFOS MGD International Workshop in 2011 has defined it as: "MGD is a chronic, diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion. It may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease." In content, it is similar to the definition of the Japanese group, but it differs in its reference to dry eye and ocular surface disorders caused by MGD. All present evidence on the

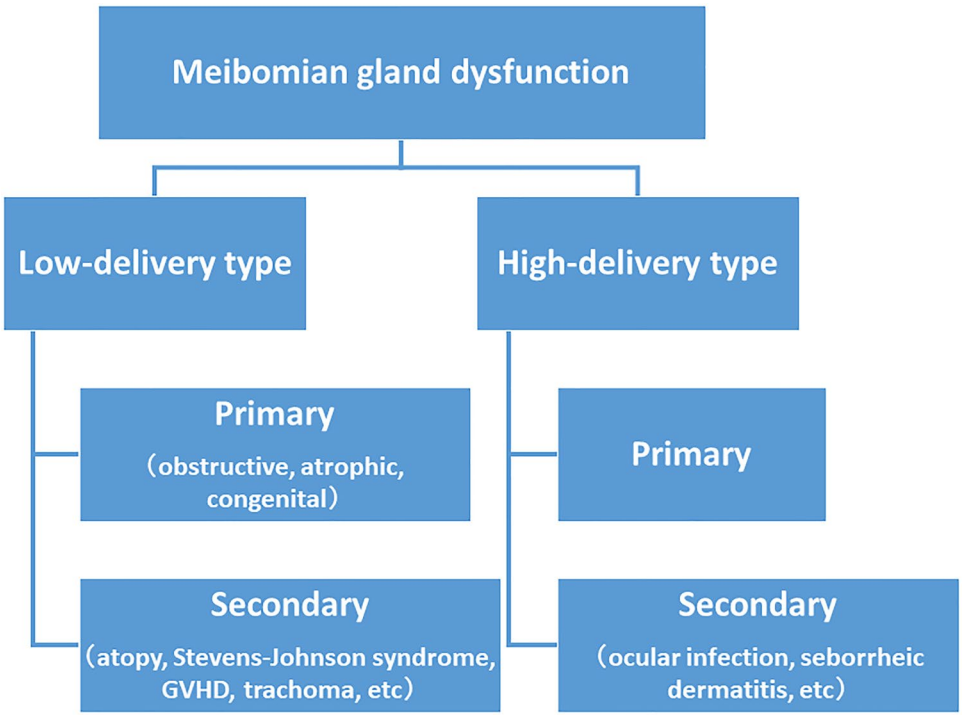

Fig. 3 Conventional classification of meibomian gland dysfunction (proposed by the meibomian gland dysfunction working group). These guidelines propose a new classification of MGD. (Chapter 2 Definitions, Classifications, and Diagnostic Criteria.)

diagnostic criteria for MGD available is examined in CQ1. To provide an overview, each group has adopted its own diagnostic criteria in various studies to date covering MGD and has recruited patients according to such diagnostic criteria. Diagnostic criteria ranges from only vascularity of the eyelid margins to a combination of vascularity of the eyelid margins, occlusion of the meibomian gland orifices, and decreased secretion of meibum. In 2010, the MGD working group [1] in Japan defined the diagnostic criteria of the low-delivery type that makes up the majority of domestic MGD cases as satisfying all three criteria as follows: subjective symptoms (ocular discomfort, foreign body sensation, dryness, and pressure), abnormal findings around the meibomian gland orifices (vascularity, displacement of the MCJ, and irregularity of the eyelid margins), and findings of occlusion of the meibomian gland orifices. This was the first clear diagnostic criteria for MGD and has been broadly used, particularly in Japan. However, 12 years have passed since this diagnostic standards were established, and it was deemed necessary to review them as our understanding of the pathophysiology of MGD and medical treatment modalities have undergone major changes. After discussions, the MGD practice guidelines preparation team proposed the revised diagnostic criteria presented in the previous chapter.

II Epidemiological characteristics

According to epidemiological surveys in Japan, the prevalence of MGD is estimated to be about 10–30% in individuals aged ≥50 years [4–6], but the exact values are still unknown. Regionally, it is reported to be higher in Asian countries compared to Western countries. The majority of these cases in Japan are of low-delivery type whereas high-delivery is relatively high in Western countries.

Even in the absence of subjective symptoms, cases with findings such as occlusion of the meibomian gland orifices and decreased meibum secretions are considered as precursor conditions of MGD. An opinion exists that treatment and intervention should be started early before subjective symptoms occur. Studies that examined the proportion of cases without subjective symptoms but with findings such as occlusion of the meibomian gland orifices and decreased secretion of meibum [4, 5], report 11–18% of symptomatic MGD and 30–63% of asymptomatic MGD, suggesting the abundance of cases with precursor conditions of MGD. However, it is sometimes difficult to distinguish between findings in MGD cases without subjective symptoms from age-related changes, and thus early treatment for MGD without subjective symptoms is controversial.

Many factors are reported as risk factors for the development of MGD, including aging, menopause, androgen depletion, dyslipidemia, prostatic hypertrophy, the use of contact lenses, and Demodex (facial tics). The epidemiological characteristics and risk factors of MGD are examined in BQs 4–6.

III Treatment of MGD (Fig. 4)

Most patients with MGD visit an eye clinic complaining of subjective symptoms such as ocular discomfort. Following

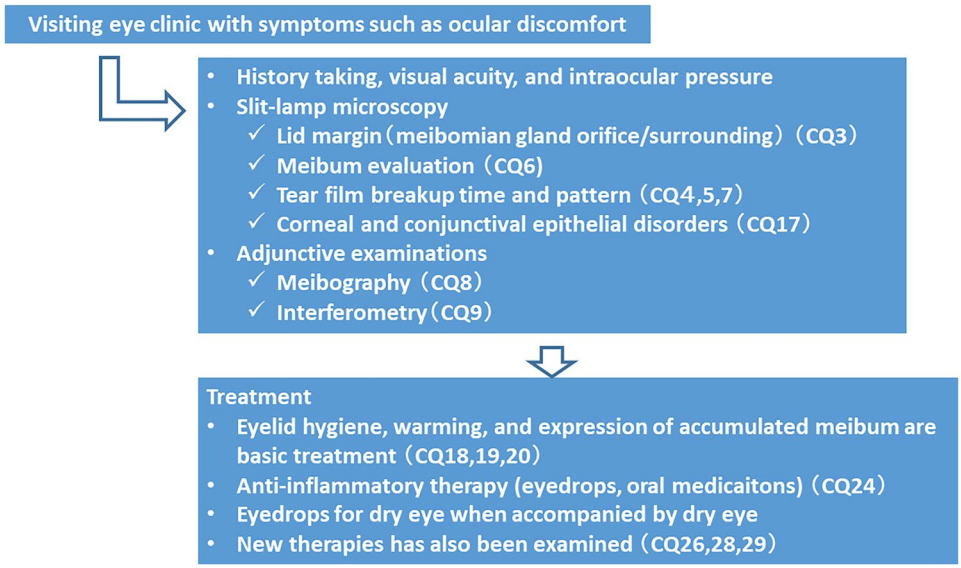

Fig. 4 Treatment flowchart of meibomian gland dysfunction.

history taking, they undergo tests such as visual acuity and intraocular pressure. In addition to subjective symptoms, MGD is diagnosed based on objective findings such as the meibomian gland orifices/surrounding findings by slit-lamp microscopy and qualitative and quantitative changes in the meibum. To confirm the presence or absence of dry eye caused by MGD, BUT, BUP, and keratoconjunctival epithelial disorders are also evaluated. Morphological observation of the meibomian glands by meibography and qualitative and quantitative evaluation of the tear film lipid layer by interferometry are also performed to support the diagnosis. Important issues in the diagnosis of MGD are examined in CQs 2–17.

The treatment of MGD is based on eyelid hygiene, eyelid warming, and expression of accumulated meibum. Whenever inflammatory findings are present, anti-inflammatory therapy using eye drops and oral medication is performed. When accompanied by dry eye, eye drops are provided according to the type and severity of dry eye. The usefulness of recently developed new therapies is also been examined. Important considerations in the treatment of MGD are examined in CQs 18–30.

IV Scope of the proposed clinical practice guidelines

1. Title

Meibomian Gland Dysfunction Clinical Practice Guidelines

2. Purpose

To provide evidence-based information and practical recommendations to assist and health care professionals as well as patients in making decisions related to treatment of meibomian gland dysfunction.

3. Topic

Meibomian gland dysfunction

4. Target users

Ophthalmologists, relevant healthcare professionals (nurses, orthoptists, and other clinic/hospital workers), and patients

5. Other existing guidelines

There are no existing clinical practice guidelines for MGD. In Japan, dry eye practice guidelines were published in 2019 [7]. Some of the contents of the dry eye practice guidelines may be helpful in the treatment of dry eye that develops concurrently with MGD. Overseas, TFOS MGD International Workshop published a report; however, it is more a review rather than evidence-based practice guidelines [2].

6. Significant clinical issues considered

1. Clarification of the pathophysiology, classification, severity staging, related diseases, epidemiological characteristics, and risk factors of MGD.
2. Identification of tests useful for diagnosing MGD.
3. Establishing the efficacy and safety of the methods proposed for treating MGD.

On this note, we examined six items: "effects on subjective symptoms," "effects on findings in and around the meibomian

gland orifices (obstructive findings such as plugging, vascularity, and MCJ displacement)," "effects on meibum grade," "effects on tear film stability," "effects on corneal and conjunctival epithelial disorders," and "adverse events."

7. Scope covered by the guidelines

All patients affected by MGD.

8. List of BQs and CQs

Draft proposals were solicited from the guideline supervisory board and the guidelines' preparation team, and the items that can be evaluated based on evidence were selected.

Among the items that were not suitable for SR, those determined to be of relevance are reviewed with a literature search.

V Systematic review

1. Implementation schedule

Election of SR team members: January–February 2021
MINDS training for SR team (including web-based training): February–March 2021
Literature Search: February–April 2021
Literature Screening: April–September 2021
Overall Evidence Assessment and Integration: April 2021–March 2022

2. Evidence search

1. For evidence search, we requested the Japan Medical Library Association's clinical practice guidelines' preparation support service (literature search) assistance.
2. Electronic databases searched and sources of evidence: PubMed, Ichushi-Web, and The Cochrane Library
3. Period of literature included: January 1995–June 2021
4. Evidence types: Primarily RCT

However, if RCTs were scarce and other relevant non-RCTs exist, they were selected following discussion by the guidelines' preparation team.

3. Literature Selection and Exclusion Criteria

RCTs that met the conditions were included.
If none or few met the conditions, non-RCTs were used.

4. Method of evidence evaluation and integration

The overall strength of the evidence was assessed based on the methodology in the MINDS Guide for Developing Clinical Practice Guidelines 2017 [8].

VI Preparation, finalization, and public release of recommendations

1. Basic Policy for Recommendation Creation

Based on the overall evidence report prepared by the SR team members, along with the guideline preparation team members, a summary of the evidence for BQs and CQs were created.

The strength of the evidence for the recommended decision was divided into four stages:

A (strong): Strong confidence in estimated effect
B (medium): Moderate confidence in estimated effect
C (weak): Limited confidence in estimated effect
D (very weak): Little confidence in estimated effect

The decision on the strength of the recommendation were discussed by the guidelines' preparation team and evaluated by the supervisory board.

In addition to the strength of the evidence, the strength of the recommendations was determined by considering the "balance of benefits and harm," "values and aspirations of patients," and "health economic perspectives."

2. Finalization

An external evaluation by the Japan Cornea Society, the Dry Eye Research Society, the Japanese Ophthalmological Society, dermatology experts, and guidelines' experts were conducted and their recommendations are reflected in the final version.

3. Specific methods of external evaluation

In response to the above external evaluations, the guidelines' preparation team and the supervisory board discussed the needs to change and amend parts of the clinical practice guidelines and decided on the the changes to be made.

4. Scheduled Public Release

After responding to the external evaluation, the supervisory board finalized the release.

Chapter 4

Recommendations - pathophysiology, classification, and related diseases -

BQ1 What is the pathophysiology of MGD?

(Hiroto Obata and Tomohiko Usui)

Introduction The meibomian gland is an exocrine gland that secretes lipids and is the main source of the lipid layer in superficial tear film. Meibomian gland secretion (meibum) is a mixture of various polar and non-polar lipids, mainly composed of wax esters 30–48%, cholesterol esters 30–40% as polar lipids, and (O-acyl) -ω-hydroxy fatty acid 1–5%, cholesterol 0.5% and free fatty acids 0.1–1% as a non-polar lipids [9, 10]. The meibum contributes to the suppression of aqueous evaporation from tear film and to tear stability. Deficiency in the tear film lipid layer is thought to cause increased aqueous evaporation, instability of the tear film, and hyperosmolality, resulting in alterations on the ocular surface [2, 11, 12].

The term MGD was coined by Korb et al. [13] in 1980. As the understanding of the pathophysiology of dry eye developed, the disease concept of evaporative dry eye MGD was formed [14, 15]. This concept prevailed globally for many years [2, 13–16]. However, research results that question the role of the lipid layer in suppressing aqueous evaporation have accumulated. The disease concept of evaporative dry eye itself has become controversial [17]. Additionally, since 2000, the association between inflammation of the meibomian gland with oMGD (meibomitis) and keratoconjunctivitis has also been considered [18–22]. It is now understood that MGD is not a single disease, but a collective term for the pathophysiology that causes various ocular surface disorders due to pathological conditions related to the meibomian gland.

Clinically, MGD is viewed as findings such as vascularity of the eyelid margin and plugging of the meibomian gland orifice (Fig. 5). The normal meibum is clear; however, in pathological conditions the viscosity changes, the color turns yellow or white, and the texture becomes turbid, granular, and toothpaste-like (Fig. 6) [23].

Although the pathophysiology of MGD is often unknown, Fig. 7 provides a schematic illustration of the mechanism of MGD as reported by the MGD International Workshop in 2011 [24]. According to this, the predominant mechanisms are: (1) hyperkeratinization of the ductal epithelium and increased viscosity of the meibum cause the meibomian gland orifice to become occluded, decreasing drainage (low delivery), (2) the occlusion of the meibomian gland orifice causes secondary atrophy of the gland, decreasing secretion (low secretion).

Since the publication of the aforementioned report, research on MGD has accelerated, and many articles and reviews have been published [3, 25–30]. Herein, we summarize the evidence on the pathophysiology of MGD to date.

Low-delivery MGD As mentioned above, the core mechanisms of MGD are divided into low delivery and low secretion. The former is sometimes referred to as oMGD.

Fig. 5 Plugging and vascularity of the meibomian gland. Plugging and vascularity in a meibomian gland orifice seen in an image from an 83-year-old woman.

Although the meibomian gland is an exocrine gland, considering the clinical classification, it is easier to unify both mechanisms into the single term of low-delivery MGD. The main pathophysiology of low-delivery MGD is hyperkeratinization of the ductal epithelium and acinar atrophy.

1. **Hyperkeratinization**

The main duct of the meibomian gland is lined with stratified squamous epithelium. The state of enhanced epithelial keratinization, i.e., hyperkeratinization, has long been thought to be the main etiology of MGD. When the keratinized materials increase in the meibum, its viscosity increases, leading to decreased secretion by and occlusion of the meibomian gland. The first report on MGD was published in 1980 and showed that the meibomian gland orifice was occluded by keratotic clusters in patients with contact lens intolerance [13]. In 1981, Jester et al. [31] reported that abnormalities of the keratinizing process in the duct and orifices of meibomian glands in humans, monkeys, and rabbits were involved in MGD. Subsequently, histopathological findings showed that keratinized material due to hyperkeratinization occlude the orifice of the meibomian gland in humans, causing ductal dilation [32–34].

Dilatation of the duct due to hyperkeratinization has also been observed in animal experiments by long-term administration of 2% epinephrine eye drops to rabbits (Fig. 8) [35–37], systemically administering polychlorinated biphenyls to monkeys [38], and systemically administering isotretinoin (a vitamin A derivative, not approved in Japan for the treatment of refractory acne) to rabbits [39]. In addition, cytological examination of turbid meibum revealed

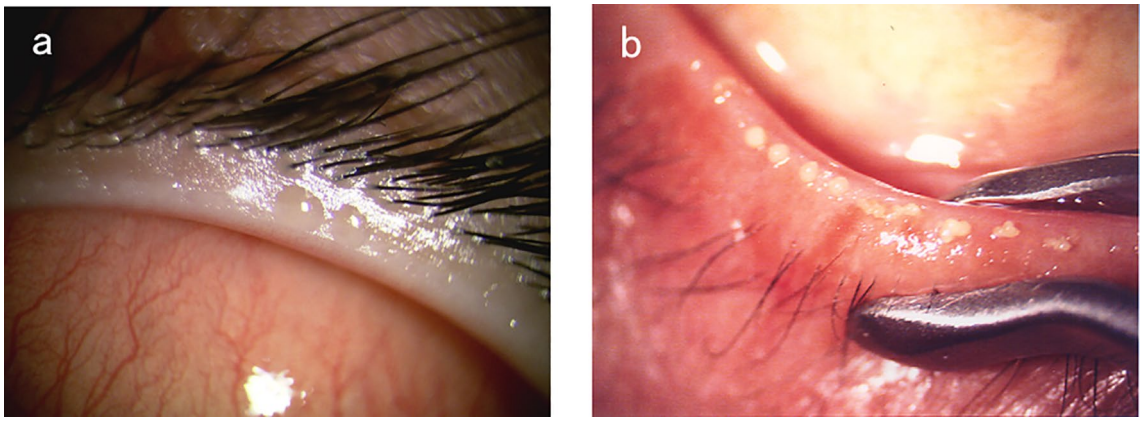

Fig. 6 Meibum quality. **a** Normal meibum is transparent (a 20-year-old woman). **b** In pathological conditions the viscosity changes, becomes cloudy in appearance and turns yellow or white, and the texture resembles that of toothpaste (a 75-year-old man).

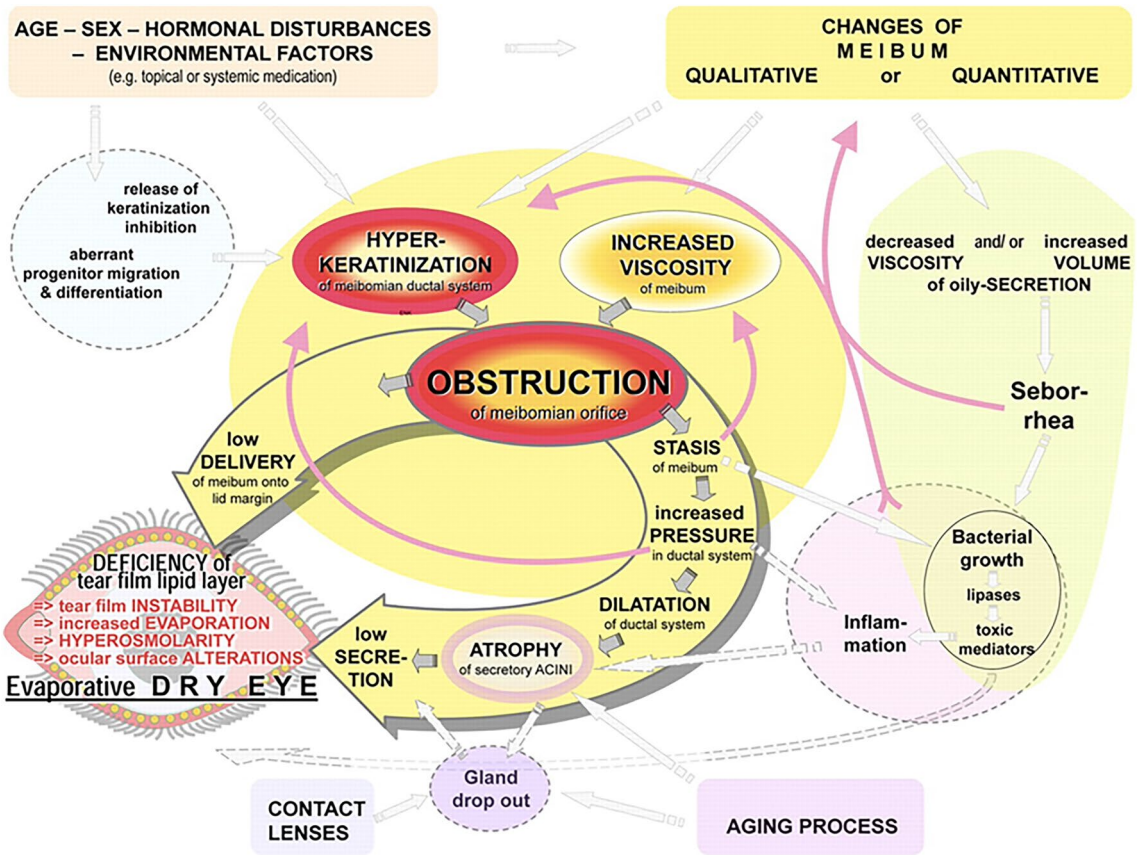

Fig. 7 Pathophysiology of MGD according to the International Workshop on MGD in 2011. The meibomian gland orifice is obstructed and drainage becomes low due to ductal hyperkeratinization and increased viscosity of the meibum. Secondary obstruction also causes atrophy of the acini, resulting in low secretion. Reprinted with permission from Springer Science and Business Media [17].

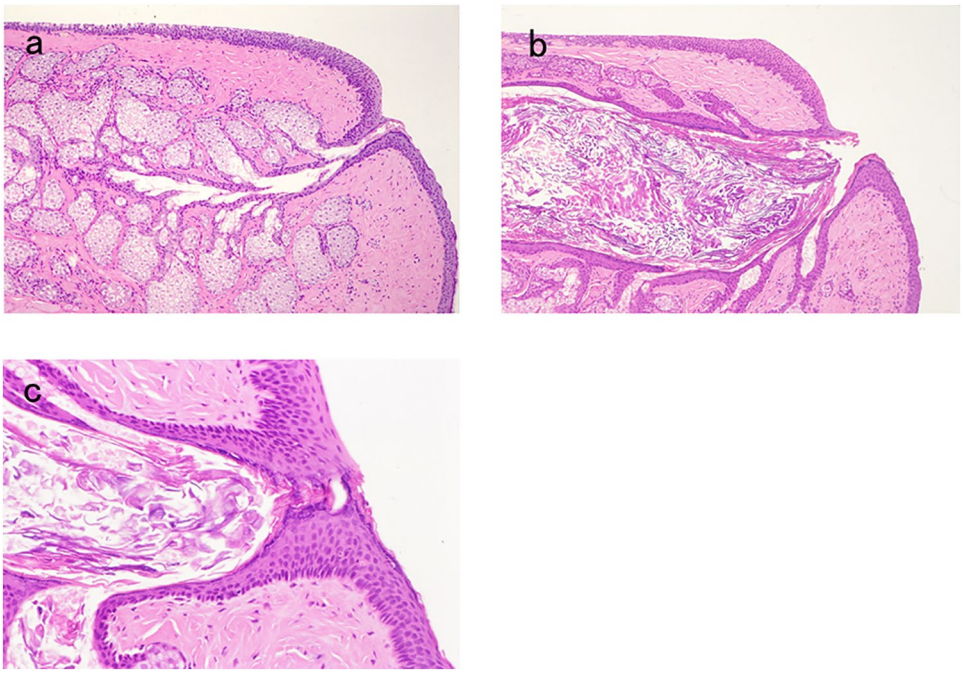

Fig. 8 Histopathological findings in rabbit MGD model following long-term use of epinephrine eye drops. **a** Normal meibomian gland as control. **b** In the MGD model, the duct is filled with keratinized material and expanded. **c** The epithelium of the ductal orifice has also undergone hyperkeratinization, causing stenosis and obstruction.

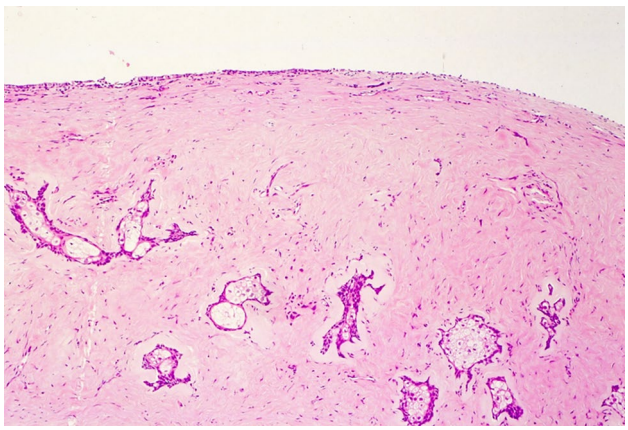

Fig. 9 Acinar atrophy of the meibomian gland. Atrophic acini show a small and irregular, not rounded shape. Histopathological image from the autopsy of a 79-year-old man.

keratinized materials; hence, hyperkeratinization is the central pathology of MGD [24].

2. Acinar atrophy

Atrophy is the shrinking of mature tissues that have already undergone normal differentiation due to various acquired causes. Atrophic acini of the meibomian gland show a small, irregular, not rounded, shape (Fig. 9). Atrophy of the acini suggests low secretion. According to a report of the MGD International Workshop from 2011, the main cause of acinar atrophy is believed to be a secondary change in which the intraductal pressure increased due to stasis of the meibum [24]. However, meibocyte may also primarily atrophy due to aging [33, 34]. Experiments in mice reveal that acinar atrophy due to aging is not associated with hyperkeratinization [40, 41]. In 2017, Hwang et al. [3] published a review on the pathophysiology of MGD centered on the meibocytes, distinct from the hyperkeratinization of the ductal epithelium. This review suggests that PPAR-γ and stem and progenitor cells of the meibocytes are modified by aging, inflammation, hormonal factors, environmental stress, neural factors, and dietary factors (Fig. 10).

PPAR-γ is a nuclear receptor superfamily that acts as a transcription factor and is a key marker involved in lipid synthesis and adipocyte differentiation. Additionally, PPAR-γ was found to play an important role in cell differentiation and lipid synthesis in the meibocytes [42, 43]. Interesting results are reported in culture experiments of immortalized meibocytes in mice; one such result indicates that the addition of rosiglitazone, an agonist of PPAR-γ and an antidiabetic agent, increased the production of wax esters and cholesterol esters [43].

Although the location of the meibomian gland stem and progenitor cells is controversial, it is now believed that they are positioned in the basal cells at the junction between the acini and the duct, and can differentiate into both the ductal epithelium and meibocytes [44]. The presence of the meibomian gland stem cells in individual acinus means that these individual acini may disappear due to stem cell dysfunction or impairment. This is believed to be consistent with the clinical observation of meibomian gland dropout seen in MGD [44].

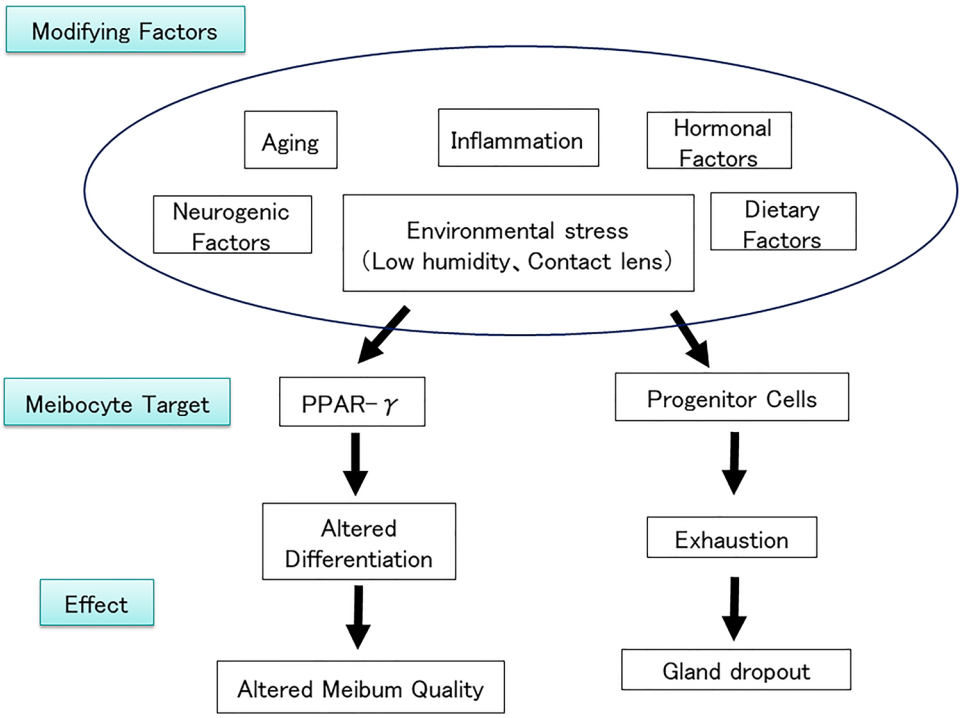

Fig. 10 Factors influencing the meibocyte. The targets of meibocyte pathology are PPAR-γ and stem and progenitor cells. These have been hypothesized as modified by aging, inflammation, hormonal factors, environmental stress, neural factors, and dietary factors. Reprinted and modified with permission from Elsevier [20].

High-delivery MGD High-delivery MGD indicates a state in which a large volume of meibum is secreted [45]. It is often associated with skin diseases such as seborrheic dermatitis, rosacea, and acne vulgaris. Unlike low-delivery MGD, the pathophysiology of high-delivery MGD is not well known. It is uncertain whether secretions actually increase or whether a state of increased secretion is indicated whenever the mild obstruction of the meibomian gland orifices is lifted [45]. It is reported that ocular symptoms and eyelid margins' abnormality are important indicators in the diagnosis of high-delivery MGD, and that few structural abnormalities could be observed by meibography [46]. The pathophysiology of acne vulgaris may be helpful in understanding the pathophysiology of high-delivery MGD. Acne vulgaris is thought to be a condition in which the sebaceous glands are activated mainly by male hormones (androgens), sebum secretion is increased, and keratinization is enhanced, resulting in clogging of the opening of the hair follicles and the accumulation of sebum, and the increased growth of *Cutibacterium acnes* (formerly known as *Propionibacterium acnes*).

It is also believed that lipases produced by bacteria degrade lipids and result in inflammation caused by free fatty acids [47]. Similarly, in the meibomian glands, increased secretion of meibum promotes the growth of bacteria that feed on lipids, and it is believed that lipases produced by bacteria degrade lipids, alter the properties of the tear film lipid layer, and cause inflammation by free fatty acids [24].

Meibum abnormality The meibum is primarily composed of lipids wax esters and cholesterol esters; however, the presence of more than 100 lipids is known [10]. Because the meibum is a blend of various lipids, its melting point has a wide range of 28–32°C. In MGD, changes in the composition and structure of lipids as well as a decrease in the amount of lipids are reported [48–50]. These factors are believed to influence the stability and fluidity of the tear film lipid layer. Free fatty acids are reported to increase because of altered lipids composition in MGD [26]. Arita et al. report that unsaturated free fatty acids were more abundant in cloudy or yellow colored meibum than in clear meibum; oxidation of fatty acids may be involved in the coloring of the meibum [23]. Free fatty acids are known to cause cytotoxicity, leading to keratinization and inflammation. In MGD patients and in elderly subjects, decreased non-polar lipids such as cholesterol esters and increased polar lipids such as (O-acyl) -ω-hydroxy fatty acid, cholesterol, and free fatty acids are reported; particularly, triglycerides were increased significantly only in MGD patients [51]. The meibum contains not only lipids, but also proteins such as keratin. Changes in proteins as well as lipids may affect the stability of the tear film. When the ratio of lipids to protein in the meibum is examined by Raman scattering microscopy, it correlates with BUT, and this is reportedly a useful test for examining the quality of the meibum [52]. The lipid composition may differ depending on the analysis method, and we expect further research to be carried out in the future on the qualitative abnormalities of the meibum.

Factors influencing MGD

1. **Aging**

Many studies point out the association of MGD with aging [33, 34, 40, 41, 53–55].

Histopathological evidence in humans and mice suggests the atrophy of acini due to aging; nonetheless, as mentioned above, hyperkeratinization of the ductal epithelium is not involved in acinar atrophy due to aging [33, 34, 40, 41, 53, 54]. In human and mice meibomian glands, the positivity rate of Ki-67, a marker of proliferating cells, decreases with aging [53–55]. When the localization of PPAR-γ is examined immunohistochemically, the cytoplasm and the nucleus in young specimens are stained, but in older specimens only the nucleus is stained, indicating a change in localization [53, 54]. It is, therefore, presumed that acinar atrophy due to aging is involved in the downregulation of PPAR-γ.

2. **Sex hormones**

Meibomian glands are affected by sex hormones, especially by the androgens [30, 56–58]. Androgens leads to expression of many genes involved in the biosynthesis, secretion, differentiation, and proliferation of meibomian glands [59]. Androgens reportedly upregulate the expression of genes related to lipid metabolism, downregulate the expression of genes that promote epithelial keratinization, and upregulate the expression of genes that suppress keratinization [30, 60]. Moreover, experiments using immortalized cultured cells of human meibomian gland epithelial cells have shown that dihydrotestosterone, the active form of androgen, suppresses the expression of many inflammatory cytokines [61].

3. **Inflammation**

Inflammation of the ocular surface, such as allergic conjunctivitis, skin diseases such as rosacea, SJS, and chemical burns, affects the structure and function of the meibomian glands [62]. In allergic conjunctivitis, distortion of the meibomian glands is seen [63]. In phlyctenular keratitis, meibomian gland loss can be observed in meibography [64]. In addition, it is known that inflammatory cell infiltration can be seen around the meibomian glands, as observed in the specimens of human autopsy and in elderly mice [33, 34, 53] (Fig. 11). In a murine model of allergic eye disease, ductal dilation and acinar atrophy were observed, suggesting that a neutrophil extracellular trap is involved [65]. In meibomitis (inflammatory form of oMGD) caused by bacterial growth in the meibomian glands resulting in keratoconjunctivitis, the causative bacteria and clinical findings change with age (MRKC) [18–22]. Clinical evaluation of the inflammation of the meibomian glands should be explored by future research to accurately define the term meibomitis.

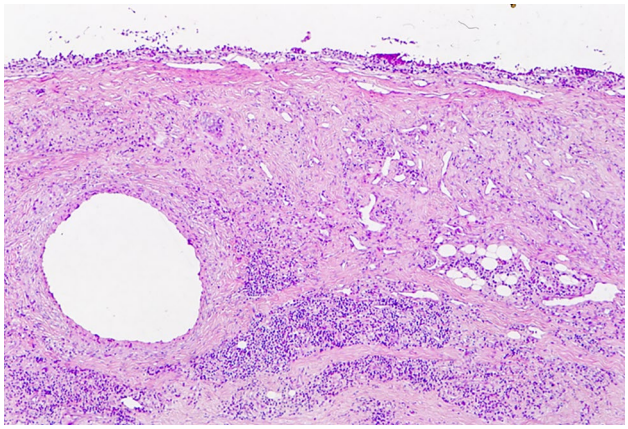

Fig. 11 Inflammatory cell infiltration of the meibomian gland. Numerous inflammatory cell infiltrations are observed in the tarsal plate. The structure of the meibomian gland is not observed. Histopathological image from the autopsy of a 67-year-old man.

4. **Microorganisms such as bacteria**

The relationship between MGD and bacteria is also complex. Bacteria can grow within the meibomian glands themselves and the growth of bacteria in the conjunctival sac may affect the meibomian glands. As mentioned above, it is believed that when bacteria such as *Cutibacterium acnes* that feed on lipids proliferate, the lipolytic enzyme (lipase) produced by the bacteria breaks down the lipids, alters the properties of the tear film lipid layer, and causes tissue inflammation by free fatty acids [11, 66, 67]. From the conjunctival sacs and meibum, normal flora such as *Staphylococcus epidermidis, Staphylococcus aureus, Corynebacterium,* and *Cutibacterium acnes* that produce lipase have been detected. In MRKC, among the phlyctenular type common in young individuals, delayed-type hypersensitive reactions to *Cutibacterium acnes* in the meibomian glands has been identified as a cause of cellular infiltration of the cornea through bacterial cultures from the meibum [18–20] and animal experiments using rats [68]. Additionally, *Staphylococcus* that produces lipase is reportedly the cause of SPK in the non-phlyctenular type, which is common in elderly individuals [21, 22].

Furthermore, one study reports that the positivity rate of bacterial culture from the meibum and conjunctival sacs was higher in patients with MGD than in controls, both for aerobic and for anaerobic bacteria, suggesting that bacteria-related cytotoxicity and/or inflammation may be involved in the pathological process of MGD [69]. In addition, one study reports that the bacterial microbiota imbalance in the conjunctival sac of patients with MGD is obvious when compared to controls,

and that *Staphylococcus, Corynebacterium*, and *Sphingomonas* may be involved in the pathophysiology of MGD [70]. The meibum is also believed to possess antimicrobial properties and to contribute to the biological defense mechanism of the ocular surface [71]. Therefore, low-delivery MGD is considered to affect the bacterial flora on the ocular surface. There is still much uncertainty about the association between MGD and bacteria. *Demodex folliculorum* is a type of mite also known as follicular mite and facial mite known to parasitize the lashes and cause marginal blepharitis [72]. *Demodex* was observed in the meibomian glands in a histopathological report published in 1982 [32]. There are also reports suggesting an association between *Demodex* and MGD [73]; however, many aspects of this issue are still unclear.

5. **Environmental stress**

In contact lens wearers, shortening and dropout of the meibomian glands was observed on meibography [74, 75]. Experiments in desiccating stressed mice report an increase in the number of Ki-67-positive cells, a dilatation of the ducts, and changes in the protein/lipid ratio of the meibum, suggesting alterations in meibocyte differentiation and lipid synthesis [76]. The effects of reactive oxygen are also reported. In Cu, Zn-superoxide dismutase-1 knockout mice, fibrosis and inflammatory cell infiltration around the meibomian glands, accumulation of lipid droplets on lipid staining, and increased apoptosis due to aging were observed [77].

6. **Neural Factors**

The meibomian glands are controlled by both sympathetic and parasympathetic nerves, as well as neuropeptides [78–80]. It is believed that these innervations control the secretions of the meibum; however, many issues are still unknown.

7. **Drugs**

As mentioned earlier, the long-term use of epinephrine eye drops [35–37], systemic administration of polychlorinated biphenyls [38] and isotretinoin [39] have long been known to cause MGD. Furthermore, the long-term use of antiglaucoma eye drops is reported to cause MGD [81, 82].

8. **Blinking**

The meibum spreads over the ocular surface through blinking. The muscle of Riolan lies around the central duct close to the meibomian gland orifices. It forms part of the orbicularis oculi and is thought to be responsible for the secretion of meibum by contracting during closure and relaxing during eyelid opening. Incomplete blinking is reported to contribute to MGD [83].

Conclusion The core mechanism in the pathophysiology of MGD reported by the MGD International Workshop in 2011 was the obstruction of the meibomian gland orifices due to hyperkeratinization of the ductal epithelium. However, subsequent experiments in cultured cells and mice report pathophysiology related meibocytes, and we think that there exist two core mechanisms, hyperkeratinization of the ductal epithelium and alterations in the meibocytes. Therefore, we propose a revised pathophysiology for improved understanding of MGD (Fig. 12). Aging, a sex hormone (androgen), bacterial infection, inflammation/allergies, and many other factors are compositely involved in the two types of cells, ductal epithelium and meibocytes. The pathophysiology of MGD is complex and there are many unclear parts. MGD cannot be regarded as a single disease entity, and it is necessary to consider more accurate evaluation methods and classification.

Acknowledgements We would like to thank Dr. Norihiko Yokoi and Dr. Tomo Suzuki for their suggestions.

Specific Topic

Tear film lipid layer function and evaporative dry eye: Discrepancy between basic findings and clinical experience

(Norihiko Yokoi)

The tear film lipid layer is a component of the ocular surface that acts to maintain the stability of the tear film. Abnormalities in its quantity/quality may lead to the tear film breakup and cause dry eye. Therefore, it is clear that MGD, which causes quantitative and qualitative abnormalities in the tear film lipid layer, results in dry eye. However, there are differences in the basic knowledge and clinical experience explaining what mechanism results in quantitative and qualitative abnormalities of the tear film lipid layer that result in the instability of the tear film [17].

The TFOS divides dry eye into two types: ADDE and evaporative dry eye; MGD is listed as the main cause of the latter [2]. Many clinicians have adopted the dry eye classification of the TFOS based on the functional abnormality of meibum/tear film lipid layer in suppressing aqueous evaporation from the aqueous layer. However, the aqueous evaporation suppression theory of meibum/tear film lipid layer is derived from the study of rabbits [84, 85], and there is no consensus on whether it can be applied to humans as such [17]. Specifically, it is likely that the lipid layer function may be different between rabbits with a long BUT of 30 minutes and a low rate of blinking, and humans with BUT of only 15 seconds and a high rate of blinking [17].

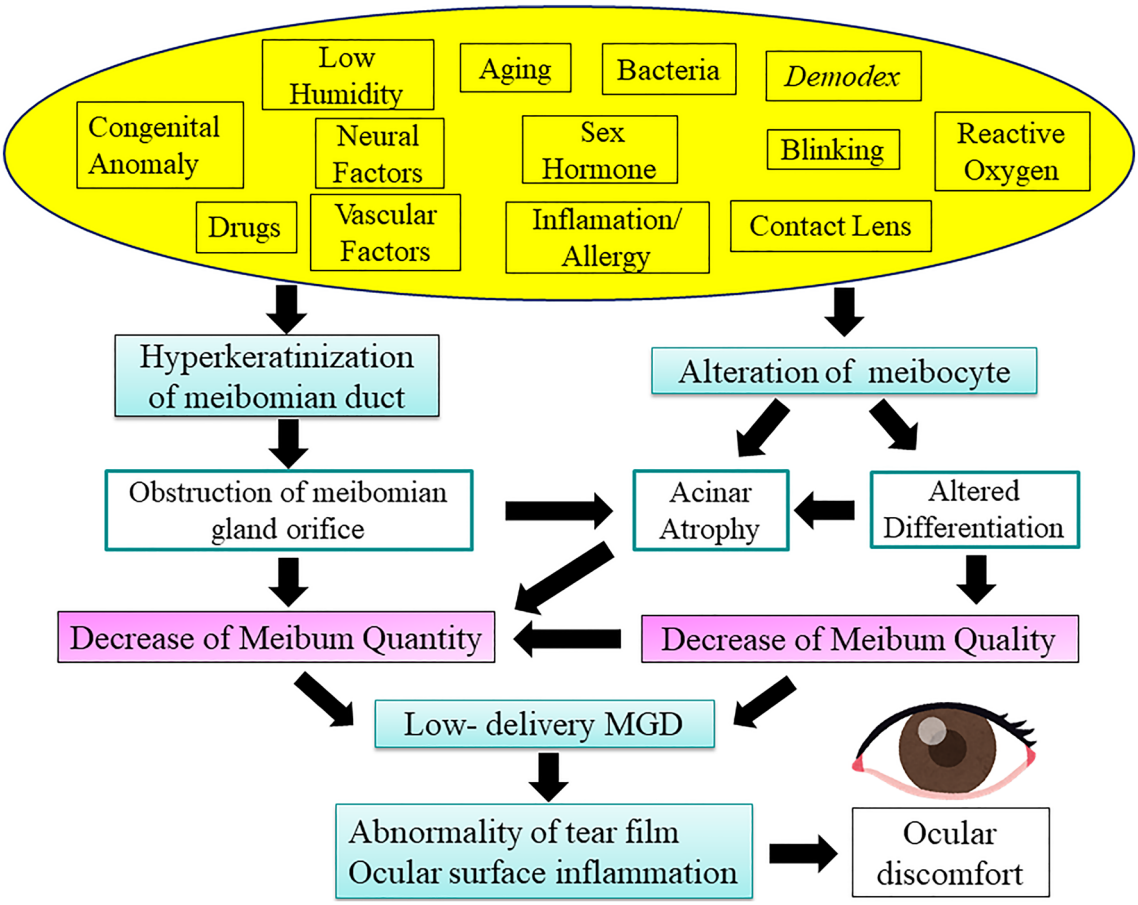

Fig. 12 The newly proposed pathophysiology of low-delivery MGD showing two core mechanisms. The pathophysiology of MGD is considered to involve two core mechanisms: hyperkeratinization of the ductal epithelium of the meibomian gland and alterations in acinar cells (meibocytes).

In rabbits with their long eyelid opening time, it is considered necessary to maintain the stability of the tear film for a longer duration. In fact, high aqueous evaporation inhibition rates (93% [84] and 75% [85]) due to the lipid layer are reported. However, in an *in vitro* model that mimics the human tear film, the aqueous evaporation suppression rate in the human lipid layer was found to be 6–8% [86], drastically different from that of rabbits. *In vivo* measurements report large aqueous tear evaporation in humans due to MGD. However, further investigation is needed regarding the function of meibum/tear film lipid layer in aqueous evaporation suppression [87].

In humans, the lipid layer plays an important role in the formation of the tear film [88]. The aqueous tear film is dragged upwards by the upward spread of the lipid layer on eyelid opening, and a tear film is formed on the cornea every time blinking occurs. However, the upward spread of the lipid layer can be described by the rheological model of Voigt, an area of physics that analyzes the behavior of viscoelastic substances [89]. The formation of the tear film involves the viscoelastic properties of the lipid layer, and the meibum has similar properties [90]. In the human meibum/tear film lipid layer, elasticity is superior to viscosity [90]. The meibum of dogs and cats with blinking rates like humans also has the same elastic dominance characteristics as humans [91]. However, in MGD, viscosity is predominant in the meibum [90], and the highly reproducible upward spread dynamics (pleated drape effect) [92] seen in healthy eyes at every blinking is lost [17, 90].

When the elasticity-dominant properties of meibum/tear film lipid layer is applied to the breakup process of the tear film, one can see functions of the tear film lipid layer other than only the suppression of aqueous evaporation. Specifically, when local thinning (with inward flexion of the lipid layer) occurs in the aqueous layer of the tear film, the lipid layer is resistant to flexion due to its elasticity, and the breakup of the tear film is prevented (Fig. 13). Hence, it is believed that the tear film lipid layer functions to cancel out fluctuations in the thickness of the aqueous layer caused by external and internal factors due to its elasticity.

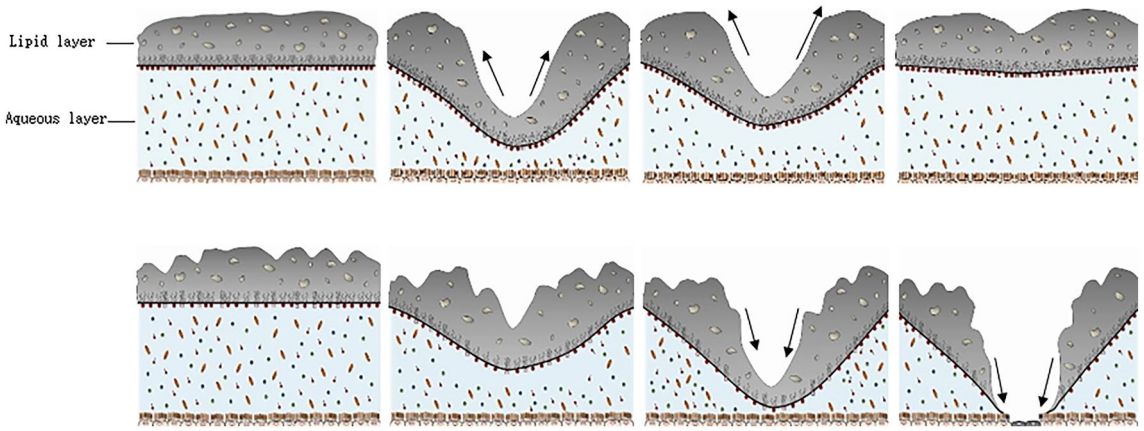

Fig. 13 Differences in tear lipid kinetics between healthy eyes (upper line) and eyes with MGD (lower line) in maintaining eyelid opening. Since a healthy meibum/tear film lipid layer has elasticity-dominant properties, it can resist local thinning of the aqueous layer (accompanied by inward flexion of the lipid layer), and thus resist breakup of the tear film. Since the meibum/tear film lipid layer in MGD has viscosity-dominant properties, it cannot resist the local thinning of the aqueous layer and leads to breakup of the tear film.

Interestingly, it is shown that when the external humidity is constant and the temperature is increased, the aqueous evaporation increases, the lipid layer thickens, and the tear film stabilizes [93]. This suggests that the increased aqueous evaporation does not necessarily lead to a decrease in the stability of the tear film, but rather that an increase in LLT leads to the stabilization of the tear film. Therefore, it is thought that the stability of the tear film is maintained by increasing the elasticity associated with the increase in the thickness of the lipid layer rather than by suppressing aqueous evaporation. Whether the primary function of the meibum/tear film lipid layer is to suppress aqueous evaporation or prevent local thinning of the aqueous layer due to its elastic properties has not yet been concluded. However, there is no difference of opinion in that the meibum/tear film lipid layer serves to maintain the stability of the tear film. However, if the latter is the primary function, it is necessary to reconsider the current dry eye classification that includes the evaporative type with MGD as its cause; this requires further research.

BQ2 What are the definitions, classifications and severity staging of MGD?

(Norihiko Yokoi and Yuka Hosotani)

Introduction The existing reports on the definitions, classification, and severity of MGD are summarized (Table 3) [1, 45, 46, 94–99]. Clear definitions are only provided in the two reports from the Japanese MGD Working Group and the TFOS MGD International Workshop [1, 45]. MGD is broadly divided into two types: low and high-delivery; how-

Table 3 Summary of articles to date on the definition, classification, and severity staging of MGD

Article	Issue Year	Main contents	Country, Region	Definition	Classification	Severity staging
Foulks et al. [94]	2003	MGD diagnosis and classification	United States, United Kingdom	×	○	×
Arita et al. [95]	2009	Diagnostic Criteria for Obstructive MGD	Japan	×	×	×
Arita et al. [46]	2010	Diagnostic Criteria for Seborrheic MGD	Japan	×	×	×
Amano et al. [1]	2010	Diagnostic Criteria for MGD in Japan	Japan	○	○	×
Nelson et al. [45]	2011	Proposal for definition and classification	International workshop	○	○	×
Geerling et al. [96]	2011	Treatment according to severity	International workshop	×	×	○
Guliani et al. [97]	2018	MGD severity and blood lipid association	India	×	×	○
Randon et al. [98]	2019	New MGD classification using confocal microscopy	India	×	○	×
Fu et al. [99]	2019	Staging of MGD severity	China	×	×	○

MGD, meibomian gland dysfunction

Table 4 Excerpt of definition and classification of MGD by the Japanese MGD Working Group in 2010 [1]

Definition of MGD	The function of the meibomian gland is diffusely abnormal due to various causes, and it is accompanied by chronic ocular discomfort.
MGD classification	1. Low-delivery type ①Primary (obstructive, atrophic, and congenital) ②Secondary (secondary to atopy, Stevens–Johnson syndrome, graft versus host disease, trachoma, etc.) 2. High-delivery type ①Primary ②Secondary (secondary to eye infection, seborrheic dermatitis, etc.)

ever, the subclasses within each vary slightly depending on the studies. The severity of MGD has been classified based on the findings related to subjective symptoms, obstruction of the meibomian gland orifices, abnormalities around the orifices, morphological characteristics, expression of meibomian gland contents on eyelid compression, properties of lipids, and meibography. However, there is no globally standardized classification and each research group independently created one for their respective studies.

Definition The term MGD was coined by Korb et al. [13] in 1980. However, the definition of MGD was specifically clarified by only by the Japanese MGD Working Group and the TFOS MGD International Workshop, with an aim to reach global consensus [1, 45]. The MGD working group 2010 defined it as "the state in which the function of the meibomian gland is diffusely abnormal due to various causes and involves chronic ocular discomfort" [1] (Table 4). The 2011 TFOS MGD International Workshop states that "MGD is 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" [45].

Classification Foulks et al. [94] published a detailed MGD classification in 2003 (Fig. 14). They classify MGD as a meibomian gland disease, and further classify it into low and high-delivery types. The low-delivery type is further divided into hyposecretory, simple, and cicatricial MGDs. Simple MGD is classified as primary and secondary (complicated by seborrheic dermatitis, rosacea, atopic dermatitis, and psoriasis), and cicatricial MGD has a secondary classification (complicated by trachoma, pemphigoid, rosacea, and atopic dermatitis). High-delivery type is almost synonymous with hypersecretion meibomian seborrhea, and is subdivided into primary and secondary (associated with seborrheic dermatitis and rosacea).

Similarly, the subsequent classification by the Japanese MGD Working Group in 2010 broadly divided MGD into the low and high-delivery types. Low delivery type is divided into primary (obstructive, atrophic, and congenital) and secondary (secondary to atopy, SJS, GVHD, and trachoma) types, and the high-delivery type into primary and secondary (secondary to ocular infections and seborrheic dermatitis) [1] (Table 4). In 2011, the MGD International Workshop classified the disease into low- and high-delivery types, same as the earlier counterparts. However, it is different from the Japanese classification in that the low-delivery type was further classified into hyposecretion and obstructive types (Fig. 15). In recent years, new classifications based on laboratory findings have also been proposed. Randon et al. [98] used IVCM to categorize meibomian glands into four types based on observations: type 0 for normal, type 1 for meibum obstruction, type 2 for inflammation, and type 3 for fibrosis [98].

In the high-delivery MGD, there are subjective symptoms and abnormal findings around the orifice of the meibomian glands (vascularity, displacement of the MCJ, and irregular eyelid margins) similar to the low-delivery type; however, lipids expressed from the meibomian glands by eyelid compression are increased [46]. In addition to the characteristic eyelid findings, Foulks et al. [94] put forward the following characteristics: normal tear dynamics, various ocular surface disorders, absence of meibomian gland dropout, quantity of meibum $\geq$0.8 mm, with normal viscosity and evaporation rate.

Severity staging The accepted severity staging of MGD is based on the one proposed by the TFOS MGD International Workshop [96, 100] (Table 5). The severity of MGD is divided into four stages based on the characteristics of the meibomian glands' secretions, subjective symptoms, and corneal epithelial disorders. Treatment for each stage has also been proposed. However, it is still not globally accepted and standardized; current researchers use the severity staging set in their own countries.

Guliani et al. [97] created a scoring system that combines subjective symptoms, findings from slit lamp microscopy, and tear test findings, to classify the severity of MGD into stages 1–4, and describe the relationship between the

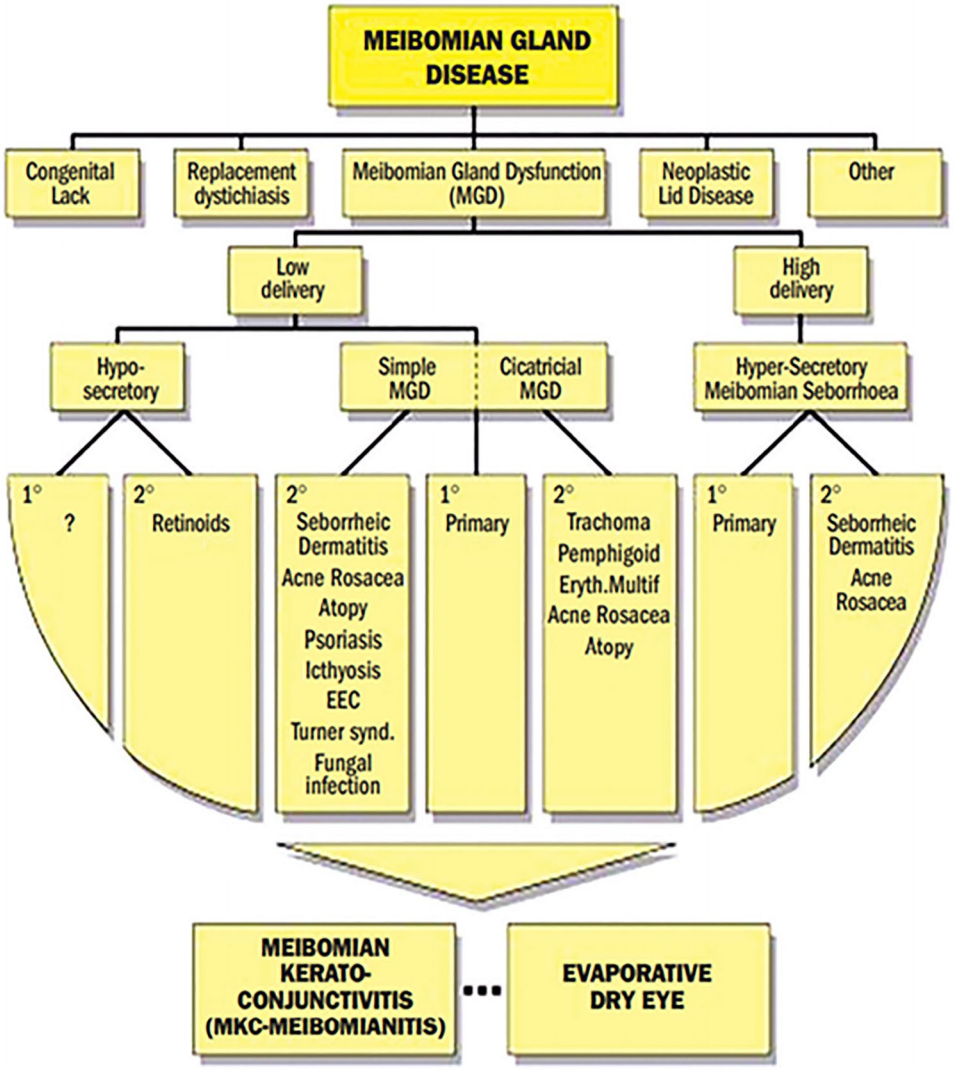

Fig. 14 MGD classification by Foulks et al. Reprinted with permission from Association for Research in Vision and Ophthalmology [1]. Foulks GN, et al.

severity of MGD and serum lipids [97]. Additionally, Fu et al. [99] created a scoring system that combines the subjective symptoms evaluated by the visual analog scale, findings from IVCM and slit lamp microscopy, meibography, BUT, and corneal staining score. The MGD severity in this system is classified into three stages, and the characteristics of each examination score are described according to severity [99]. Clinical findings related to the severity of MGD are addressed in each of the CQs described later on; they are also summarized in this section (Table 6).

Problems Although the published definitions and classifications do not vastly differ, global consistency is necessary for future research and development. Moreover, there is no globally uniform classification of the severity of MGD.

Future Challenges and Trends Although the association between MGD and dry eye has been gaining attention in recent years, it is difficult to say that universally standardized classification, severity staging, and treatment of MGD have been established. Global cooperation and collaborative research are expected in the future.

BQ3 What disorders are related to MGD?

(Aoi Komuro and Tomo Suzuki)

Introduction The meibomian glands are large modified sebaceous glands embedded in the tarsal plates of the eyelids, with their opening normally situated just anterior to the MCJ of the eyelid margin. Due to their anatomical location, MGD is often associated with marginal blepharitis and possibly even ocular surface diseases. For accurate diagnosis and treatment of MGD and its related disorders, it is important to clarify how MGD influences blepharitis and how meibomitis impacts on the ocular surface inflammation, and thereby unify the concept.

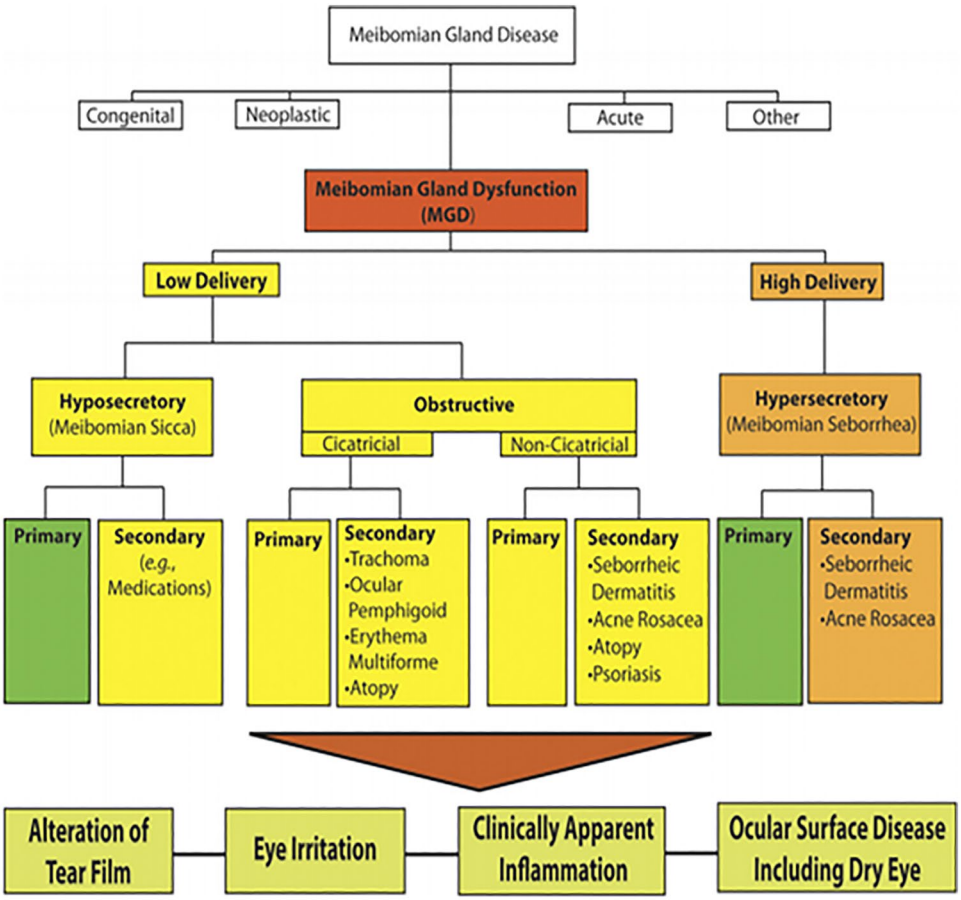

Fig. 15 Classification according to the 2011 TFOS MGD International Workshop. Reproduced with permission from Association for Research in Vision and Ophthalmology [5]. Nelson JD, et al.

Table 5 Severity staging according to the 2011 TFOS MGD International Workshop, reproduced with permission from Association for Research in Vision and Ophthalmology [96]

Stage	MGD Grade	Symptoms	Corneal Staining
1	+(minimally altered expressibility and secretion quality	None	None
2	++(mildly altered expressibility and secretion quality)	Minimal to Mild	None to limited
3	+++(moderately altered expressibility and secretion quality)	Moderate	Mild to moderate; mainly peripheral
4	++++(severely altered expressibility and secretion quality)	Marked	Marked; central in addition

"Plus" disease : Co-existing or accompanying disorders of the ocular surface and/or eyelids

MG, meibomian gland; MGD, meibomian gland dysfunction; TFOS, Tear Films & Ocular Surface Society

Explanation The term MGD was first clinically described by Korb and Henriquez in 1980; they defined it as "a dysfunction of the meibomian glands resulting in dry eye and contact lens intolerance due to decreased secretion of meibum" [13]. In 1981, Jester al. reported that MGD was histopathologically caused by the hyperkeratinization of the duct epithelium [31]. Since then, awareness regarding MGD as a cause of evaporative dry eye has increased [13]. In Japan, the definition of MGD was established 2010 [1], and by the TFOS in the following year [2] (see BQ2). This definition by the TFOS includes low-delivery oMGD with no obvious inflammatory findings. Historically, MGD has been considered an "impairment in meibomian gland function" including hypersecretory disorders with obvious findings of infection and inflammation [94, 104–106]. Based on this background, disorders related to MGD including posterior blepharitis and meibomitis, positioning of MGD in blepharitis, relationship between meibomitis and MGD, and ocular surface inflammatory diseases involved in meibomitis are described.

1. Blepharitis, marginal blepharitis (anterior and posterior blepharitis) [45] (Fig. 16)

Table 6 Summary of clinical findings related to the severity of MGD

Examination technique	Findings	Related CQ number	References
Slit-light microscopy	Characteristics of meibomian gland secretion Corneal epithelium disorder	6	Geerling et al. [96] Dogru [100]
	Eyelid margin vascularity Eyelid margin irregularity Eyelid margin thickening Plugging of the meibomian gland orifice	3	Arita et al. [101]
Keratography (Keratograph5M®)	Decrease in NIBUT	7	Ji et al. [102]
Tear osmolality measurement	Tear osmolality	12	Randon et al. [98] Fu et al. [99]
Schirmer test	Tear secretion volume		
Confocal Microscopy	Density of the acinus, area of the acinus, longest diameter of the acinus, low value of the shortest diameter of the acinus, and increased fibrosis of the interacinus space (loss of MG structure)	11	Randon et al. [98] Zhao et al. [103]
Meibography	High acinar loss score	8	Randon et al. [98] Fu et al. [99]

CQ, clinical question; MGD, meibomian gland dysfunction; NIBUT, noninvasive tear breakup time

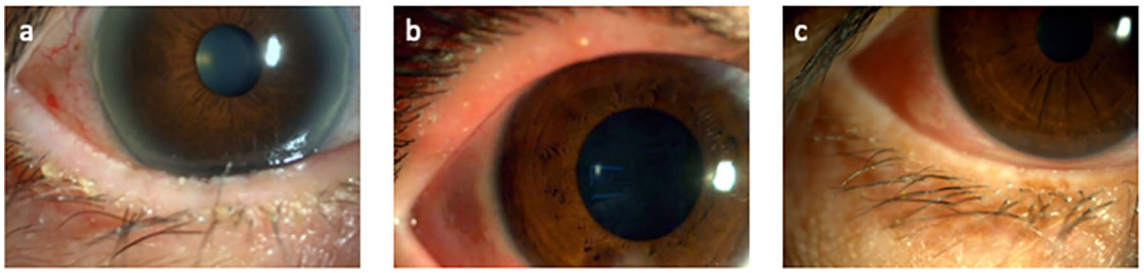

Fig. 16 Marginal blepharitis. **a** Anterior blepharitis. Staphylococcal blepharitis, which is characteristic of collarette at the root of the eyelashes, is a typical example of anterior blepharitis. MGD is concurrent, but inflammatory findings around the meibomian gland orifices are not obvious. **b** Posterior blepharitis. Meibomitis in which meibomian gland orifices are obstructed with reddish swollen surrounding area is a typical example of posterior blepharitis. **c** OMGD. Obstruction of the meibomian gland orifices is observed, but inflammatory findings are not obvious.

Blepharitis is a general term used to describe the inflammation of the entire eyelid. Marginal blepharitis represents the inflammation of the eyelid margin, including both anterior and posterior blepharitis. Anterior blepharitis is defined as an inflammation of the area anterior to the gray line of the eyelid margin, especially around the eyelash roots. Collarette often coexists in the area of the eyelash roots. Posterior blepharitis occurs posterior to the gray line of the eyelid margin, including inflammation of the posterior eyelid margin, occurring in addition to MGD, conjunctivitis (allergic and bacterial), and rosacea.

Although some articles use the terms MGD and posterior blepharitis synonymously, posterior blepharitis refers to inflammation that occurs at the posterior eyelid margin. Although MGD is one cause of posterior blepharitis, the terms MGD and posterior blepharitis are not interchangeable and can clearly be distinguished [2, 107]. As the anterior eyelid margin does not include the meibomian glands, MGD is generally not considered to be part of anterior blepharitis. However, anterior blepharitis may also spread to the posterior eyelid margin.

2. Meibomitis

The TFOS MGD International Workshop [2] states that "the terms meibomitis/meibomianitis describe a subset of disorders of MGD associated with inflammation of the meibomian glands," and "although inflammation may be considered important in the classification and therapy of MGD, these terms are not sufficiently general as

inflammation is not always present in MGD, this term is not necessarily common". In fact, the presence of noninflamed [108]/nonobvious [109] oMGD is reported, and it is widely accepted that MGD is the main cause of evaporative dry eye [13]. Whether MGD is associated with inflammation has long been discussed. Prior to 1980, it was recognized that disorders of the meibomian glands were due to hypersecretion associated with inflammation of the meibomian glands in the middle to elderly age groups, often accompanied by seborrheic blepharitis, mainly due to bacterial infections (especially *Staphylococcus aureus*) [110]. McCulley et al. [111] classified blepharitis into six categories, two of which were seborrheic blepharitis with partial meibomitis and primary meibomitis with diffuse plugging. Suzuki et al. define meibomitis as "caused by bacterial growth" and proposed the term “meibomitis-related keratoconjunctivitis” for a condition complicating ocular surface inflammation [112, 113].

3. Meibomitis and ocular surface epithelial disorders

1. Meibomian keratoconjunctivitis

A pathological condition proposed by McCulley and Sciallis in 1977 [114], characterized by SPK in a patient with chronic blepharitis which, in turn is characterized by stagnation of meibomian gland secretion”. SPK is thought to be caused by instability of the tear film. Patients were found to have anterior and posterior blepharitis along with meibomitis, and about 30% patients have accompanying rosacea and seborrheic dermatitis.

2. MRKC

The concept first proposed by Suzuki et al. [112] in 2000 was initially called "meibomitis-related keratopathy". However, in 2007, the term was renamed as MRKC [114]. In MRKC, meibomitis is defined as stagnation of the meibum at the meibomian gland orifices and the redness and swelling of the eyelid margins, especially around the orifices, as well as the palpebral conjunctiva, and is believed to be caused by bacterial growth. It is classified into two types: "phlyctenular type" with cellular infiltration and superficial vascularization in the cornea associated with meibomitis, and "non-phlyctenular type" with predominantly SPK, but without cellular infiltration [19, 112]. Since the severity of both disease types of MRKC is correlated with the severity of meibomitis and ocular surface epithelial disorders, it is essential to treat meibomitis with antimicrobial agents. The phlyctenular type is predominantly seen in young women, and reportedly caused by *Cutibacterium acnes* (*C. acnes*) [20, 112, 115]. While, the non-phlyctenular type is found in both young and elderly patients, and not only *C. acnes* but also *Staphylococcus species* involvement is presumed as the causative bacteria [21, 112]. SPK due to MRKC in the elderly can be difficult to distinguish from SPK due to dry eye, and is often overlooked [21, 22]. MRKC is often associated with oMGD along with meibomitis.

3. Ocular rosacea, blepharokeratoconjunctivitis, and phlyctenular keratoconjunctivitis.

In Europe and the United States, meibomitis is often believed to be associated with rosacea [111]. Rosacea is a skin disease characterized by facial vascularity and erythema. It is common in middle-aged and elderly people, and less common in children. Additionally, it is less common in Asians, including the Japanese [116]. Rosacea is frequently associated with blepharitis, meibomitis, and keratoconjunctivitis, and called “ocular rosacea”. Intractable conditions involving cellular infiltration and superficial vascular invasion in the corneas of children and young adults are referred to as childhood ocular rosacea (even if the cases do not involve facial rosacea), pediatric blepharokeratoconjunctivitis, or phlyctenular keratoconjunctivitis.

All of these diseases are ocular surface inflammatory diseases associated with meibomitis, and have been shown to be in the same disease category as MRKC and respond to systemic antimicrobial treatment [20].

4. Chalazion

It is widely accepted that chalazion is a "chronic inflammatory lipo-granuloma caused by stagnation of the meibum" [110]. Generally, the meibomian gland orifices associated with chalazion are obstructed and no meibum is secreted. Both the Japanese group and the TFOS define MGD as a "diffuse" abnormality of the meibomian glands. Focal abnormalities such as chalazion are not included in MGD, and are classified as other meibomian gland diseases [94]. Chalazion cannot be a cause of tear film abnormalities on the ocular surface, but it is an important sign of focal oMGD with inflammation (meibomitis). It is also important as a finding in diseases related to ocular surface inflammation such as MRKC and ocular rosacea.

Further issues As summarized in BQ2, MGD is defined by the Japanese MGD Working Group and the TFOS as “diffuse abnormalities of the meibomian glands.” However, as the definition of the TFOS suggests, MGD is a disease characterized by obstruction of the terminal duct of the meibomian glands that can affect the ocular surface. Considering this, and as the obstruction and inflammation of the focal meibomian gland orifices can cause, for instance MRKC phlyctenular type, there is a possibility that “focal MGD” may also exist.

- Epidemiology/Risk Factors -

BQ4 What is the prevalence of MGD?

(Koji Kakisu and Shiro Amano)

Recommendations The prevalence of MGD reported to date varies due to differences in the diagnostic criteria. In a population-based study of residents aged 6–96 years in Japan, the prevalences of MGD according to age groups was 0% (6–19 years), 11.8% (20–29 years), 5.6% (30–39 years), 21.6% (40–49 years), 32.8% (50–59 years), 41.9% (60–69 years), 48.4% (70–79 years), and 63.9% (80–96 years) [6].

Explanation Prevalence of MGD reported to date ranges from 3.5% to 74.5% as shown in Table 7 [4–6, 117–132]. This is likely due to differences in the diagnostic criteria used in each report and differences in the age of the participants. In addition, the prevalence rates vary greatly even if the presence of subjective symptoms is considered mandatory for diagnosing MGD. Therefore, many reports present the prevalence of symptomatic MGD, asymptomatic MGD, and the combined prevalence of MGD, separately. There are many reports covering people aged ≥50 years among whom MGD is relatively common; however, some studies consider younger age groups as well.

As mentioned earlier, a population-based study in Japan included residents aged 6–96 years and reports that the prevalence increased with age [6]. Similarly, a report from India shows that the higher the age group of the participants, the higher the prevalence [130]. Differences in the prevalence of MGD by race cannot simply be compared because the diagnostic criteria used in the studies from various countries differ. A Japanese study [4] examined the prevalence of MGD using the same diagnostic criteria as a study conducted in Spain among Caucasians [124]. Among the participants aged ≥50 years, the results in Spain showed a prevalence of 10.9% for MGD with symptoms, 21.4% for MGD without symptoms, and a combined prevalence of 32.3%. In the Japanese study, the reported prevalences was 11.2% for MGD with symptoms, 63.6% for MGD without symptoms, and a combined prevalence of 74.5% for MGD. In Japan, the prevalence of MGD without any symptoms was high, and the combined prevalence of MGD was also high.

Problems and Biases Differences in diagnostic criteria for MGD have a significant impact on the assessment of prevalence. Some studies have made a diagnosis of MGD whenever either vascularity of the eyelid margin or plugging were observed, while other studies have diagnosed MGD only whenever all subjective symptoms, eyelid margin findings, and meibomian gland orifice occlusion were observed. The stricter the diagnostic criteria, the lower the prevalence.

The diagnostic criteria include many indicators of MGD such as eyelid vascularity, plugging, and the quantity and quality of meibomian gland secretions. These indicators are not all quantitative, and the possibility exists of subjective differences in the evaluations between examiners.

Several questionnaires prepared for dry eye and ocular surface diseases have been used to examine the presence or absence of subjective symptoms in MGD. The judgment of the presence or absence of symptoms may differ depending on the questionnaire used and the judgment criteria. Moreover, in MGD, diagnosis by exclusion is crucial (to rule out the symptoms not relevant to MGD, but to other ocular surface diseases such as dry eye and conjunctivochalasis); however, few studies have applied this distinction.

Future Challenges and Trends There are no globally standardized diagnostic criteria for MGD. In Japan, the MGD Working Group proposed a diagnostic criteria for low-delivery MGD in 2010 [1]. Since then, these criteria were used in many MGD prevalence surveys. Additionally, even if the quantity of indicators used in the diagnostic criteria is low, studies have been conducted to try to standardize the indicators to ensure inter-examiner reliability [101]. Furthermore, there are several types of subjective symptoms-based questionnaires used in the diagnosis of MGD, and future evaluation of the advantages and disadvantages of eliciting subjective symptoms of MGD is anticipated. Standardization of such diagnostic criteria, as well as indicators used in these diagnostic criteria and subjective symptoms-based questionnaires, will likely be a topic for future research. Along with the development of understanding of pathophysiology, diagnostic criteria, indicators used for diagnosis and subjective symptoms-based questionnaires should be continuously updated.

BQ5 What are the factors associated with the development of MGD?

(Motoko Kawashima, Koji Kakisu, and Sayaka Sumazaki)

Recommendations Numerous studies suggest that MGD develops and worsens with age. It is reportedly more common in men and postmenopausal women. Additionally, Asian race, rural residence, occupation related to VDTs, smoking, the use of SCLs, and glaucoma eye drops are noted risk factors. The association between ocular surgery and MGD has also been pointed out.

Explanation Various studies have explored the risk factors for MGD, among which, many have identified age as a risk factor (Table 8). According to the Hirado–Takushima study conducted in Japan, the prevalence increased with age in

Table 7 Previous studies on the prevalence of meibomian gland dysfunction

Study	Year	Country	Study type	Sample size	Age (years)	Proportion of women	Index used for MGD diagnosis	MGD morbidity rate
Salisbury Eye Study [117]	1997	United States	Population-based	2,482	65–84	57.7%	Collarettes or plugging	3.5%
Shihpai Eye Study [118]	2003	Taiwan	Population-based	1,361	65–91, Average 72.2	39.6%	Telangiectasia or plugging	MGD in total: 60.8%; with symptoms: 20.8%; without symptoms: 40.0%
Lekhanont et al. [119]	2006	Thailand	Hospital-based	550	40–78, Average 58.8	72.5%	Telangiectasia, collarettes, and plugging	46.2%
Uchino et al. [120]	2006	Japan	Population-based	113	≥60, average 67.5	56%	Gland dropout, meibum expressibility, and meibum quality	61.9%
Han et al. [121]	2011	South Korea	Population-based	139	≥65	51.8%	Plugging	51.8%
Basak et al. [122]	2012	India	Hospital-based	3,023	≥30	51.9%	Plugging	MGD in total: 31.7%; with symptoms: 19.0%; without symptoms: 12.7%
Singapore Malay Eye Study [123]	2012	Singapore	Population-based	3,271	40–80, Average 58.7	51.8%	Telangiectasia or plugging	56.3%
Viso et al. [124]	2012	Spain	Population-based	619	40–96, Average 63.4	63%	Meibum quality, telangiectasia, and plugging	MGD in total 30.5%; with symptoms: 8.6%; without symptoms: 21.9%
Shah et al. [125]	2015	India	Hospital-based study	400	≥40, average 58.6	52%	Plugging	18.0%
Alghamdi et al. [126]	2016	United States	Hospital-based	233	27–89, average 63	9.0%	Telangiectasia or meibum quality	59.0%
Martinez et al. [127]	2016	Mexico	Hospital-based	338	16–85, average 45.0	55%	Meibum quality	68.0%
Amano et al. [5]	2017	Japan	Hospital-based	510	50–93, average 71.1	59.8%	Eyelid margin abnormality, plugging	MGD in total: 47.5%; with symptoms: 18.0%; without symptoms 29.5%
Amano et al. [4]	2017	Japan	Hospital-based	510	50–93, average 71.1	59.8%	Meibum quality, telangiectasia, and plugging	MGD in total: 74.5%; with symptoms: 11.2%; without symptoms: 63.6%
Asiedu et al. [128]	2018	Ghana	Hospital-based	212	17–40	50.5%	Meibum expressibility	MGD in total: 25.5%; with symptoms: 15.4%; without symptoms 10.1%
Cochener et al. [129]	2018	France	Hospital-based	180	36–92, average 69.0	56.0%	Meibum quality and expressibility	54.0%

Table 7 (continued)

Study	Year	Country	Study type	Sample size	Age (years)	Proportion of women	Index used for MGD diagnosis	MGD morbidity rate
Hirado-Takushima Study [6]	2019	Japan	Population-based	616	6–96, average 55.5	62.6%	Subjective symptoms, lid margin abnormality, and plugging	0% (6–19 years); 11.8% (20–29 years); 5.6% (30–39 years); 21.6% (40–49 years); 32.8% (50–59 years); 41.9% (60–69 years); 48.4% (70–79 years); 63.9% (80–96 years)
Chatterjee et al. [130]	2020	India	Hospital-based	570	20–84, average 49.3	47%	Meibum quality and expressibility	48.4% (all ages); 37.3% (20–39 years); 57.1% (40–59 years); 71.0% (≥60 years)
Gao et al. [131]	2020	China	Population-based	4,404	19–85, average 42.2	49.9%	Subjective symptoms, lid margin abnormality, plugging, meibum quality, and meibum expressibility	32.3% (all ages); 25.3% (≤29 years); 30.5% (30–39 years); 33.3% (40–49 years); 36.0% (50–59 years); 33.3% (≥60 years)
Tehran Geriatric Eye Study [132]	2021	Iran	Population-based	3,284	60–97, average 68.2	57.8%	Subjective symptoms, meibum quality, and meibum expressibility	71.2% (in total); 64.4% (60–64 years); 69.0% (65–69 years); 74.3% (70–74 years); 78.7% (75–79 years); 82.4% (≥80 years)

both men and women, and was the highest in individuals aged ≥80 years [6]. MGD is often seen in men [6, 123, 132] and postmenopausal women [123, 133, 134], suggesting an association with hormonal activity. However, other studies report no significant differences based on sex [5, 128, 131, 135]. A comparison between Asians and Caucasians in New Zealand indicates decreased meibomian gland function in the Asians. Although the cause remains uncertain, a relationship with blinking has been pointed out [136]. Furthermore, a study that investigated regional differences in China suggests decreased meibomian gland function in the northern regions of that country [134]. However, it was suggested that this could be related to environmental pollution, and results of similar studies could differ outside China. In a study comparing urban and rural areas, the results show that the meibomian gland function was decreased in the rural areas [137]. Abnormalities of the meibomian gland orifices and properties of meibum were found to be worse in smokers compare with non-smokers [138]. However, other studies indicate that there is no significant difference between smokers and non-smokers [123, 133, 135] in this aspect. In a study of VDT workers, MGD was observed in 74.3% of the sample, and there was a significant correlation between ocular discomfort and working time in workers with MGD [139]. Ophthalmic surgery is known to be related to MGD, and it is reported that MGD worsened after cataract surgery [140–145], refractive surgery [19], transconjunctival orbital floor fracture repair [146], and full-thickness corneal transplantation [147]. Other local factors including glaucoma eye drops [148–151], ocular demodicosis [152–154], use of SCL [155–157], radiotherapy [158], prosthesis [159], and eyeliners [160] are associated with significantly high MGD findings.

Problems and Biases The definition and diagnostic criteria of MGD differs depending on the study, the age and sex ratio of the patients. All of these may have influenced the results related to risk factors.

Future Challenges and Trends Reports are scarce on regional and racial differences. Investigations using common diagnostic criteria of MGD will prove useful in illucidating these differences.

BQ6 What are the systemic factors and disorders associated with the development of MGD?

(Takashi Suzuki, Miki Uchino, and Hiroko Iwashita)

Recommendations Systemic conditions such as diabetes, dyslipidemia, hypertension, and hyperthyroidism are asso-

Table 8 Previous studies on the risk factors for the development of MGD

Study	Year	Country	Sample	MGD diagnostic criteria	Risk factors identified
Hom et al. [161]	1990	United States	398 individuals	Absence of meibum expression or highly viscous meibum	Age
Singapore Malay Study [123]	2012	Singapore	3,271 Malay individuals (mean age, 58 years)	Vascularity/occlusion of the meibomian gland orifice	Male sex, postmenopausal women, pinguecula, diastolic hypertension, and oral ARB administration
Jang et al. [159]	2013	South Korea	30 individuals having one prosthetic eye (mean age, 46 years)		Prosthetic eye
Machalińska et al. [155]	2015	Poland	SCL users, 82 eyes (mean age, 34 years old); non-SCL users, 62 eyes (mean age 34 years old)		SCL use
Alghamdi et al. [126]	2016	United States	233 individuals; mean age, 63 years (91% men)	Abnormal vascular findings at the meibomian gland orifice; quality of meibum	Age
Mocan et al. [148]	2016	Turkey	70 glaucoma eye drop users (mean age; 65 years) and 45 healthy individuals		glaucoma eye drops
Woo et al. [158]	2017	South Korea	40 patients who underwent radiotherapy (mean age, 46 years) and 60 healthy individuals (mean age, 45 years)		Radiotherapy
Amano et al. [5]	2017	Japan	510 patients scheduled for cataract surgery, mean age 71 years	Abnormal/obstructive findings around the meibomian gland orifice	Age
Luo et al. [152]	2017	China	60 patients with ocular demodex disease and 45 patients with dry eye, aged ≤35 years		Ocular demodicosis
Lee et al. [150]	2018	South Korea	45 patients (mean age, 60 years) with normal intraocular pressure glaucoma and 40 healthy individuals (mean age, 60 years old)		Prostaglandin-associated glaucoma eye drops
Wong et al. [149]	2018	New Zealand	33 patients with open-angle glaucoma or ocular hypertension in one eye aged ≥18 years		Glaucoma eye drops
Rabensteiner et al. [153]	2018	Austria	92 patients with ocular demodicosis (mean age, 59 years) and 137 healthy individuals (mean age, 54 years)		Ocular demodicosis
Li et al. [156]	2018	China	116 SCL users, 4 HCL users, 21 orthokeratology lens users, mean age 28 years		CL-use
Hirado–Takushima study [6]	2019	Japan	356 individuals, mean age 55 years (range: 6–96)	Subjective symptoms, abnormal/obstructive findings around the meibomian gland orifice	Male sex, age, and hyperlipidemia treatment
Chatterjee et al. [130]	2019	India	570 individuals, mean age 49 years	Meibum quality and expression	Age (symptomatic MGD decreases with age)
Lee et al. [151]	2019	South Korea	30 patients with unilateral glaucoma with normal intraocular pressure, mean age 61 years		Glaucoma eye drops

Table 8 (continued)

Study	Year	Country	Sample	MGD diagnostic criteria	Risk factors identified
Wu et al. [154]	2019	China	28 individuals (mean age, 24 years) with ocular demodicosisand 22 (mean age, 20 years) individuals with non-ocular demodicosis		Ocular demodicosis
Gao et al. [131]	2020	China	4040 individuals (university staff)	Obstruction/abnormal findings of the meibomian gland orifice, subjective symptoms	Age
Hassanzadeh et al. [162]	2020		Meta-analysis		Male sex, Age, and Asian race
Li et al. [134]	2020	China	2,900 individuals; average age, 44 years	Subjective symptoms, quality of LMS, and meibum expression	Northern regions in China
Wang et al. [163]	2020	New Zealand	372 individuals, mean age 39 years	Diagnosis of dry eye, tear lipid layer, and meibography findings	Age, East Asian race, migraine, thyroid disorders, and oral contraceptives
Gu et al. [157]	2020	China	85 CL users (mean age, 26 years) and 63 non-CL users (mean age, 23 years)		CL use
Prabhasawat et al. [160]	2020	Thailand	21 eyeliner users and 21 non-users		Eyeliner
Tulsyan et al. [133]	2021	Nepal	400 individuals	Abnormal periocular findings, subjective symptoms, blinking rate, BUT, and Schirmer test	Age, hypertension, diabetes mellitus, postmenopausal women, and high LDL

ARB, angiotensin II receptor blocker; BUT, break-up time of tear film; CL, contact lens; HCL, hard contact lens; LDL, low density lipoprotein; LMS, lid margin abnormality score; MGD, meibomian gland dysfunction; SCL, soft contact lens.

ciated with the development of MGD. Additionally, rosacea causing inflammation in the eye area, SS, SJS, and GVHD are likely to be associated with the development of MGD. Menopause and androgen deficiency that are influenced by sex hormones are also related to the development of MGD.

Explanation Diabetes [124, 135, 164, 165], hypertension [123, 133, 135], and hyperlipidemia [6, 133, 166–168] are reported as risk factors for MGD (Table 9). In particular, there is much evidence to support the involvement of hyperlipidemia in the development of MGD [167]. It is also possible that lipid metabolism in the body, affecting the lipid composition in the meibomian glands may be involved in the development of MGD. Thyroid disorders [163, 169–173] are also reported to be related to MGD development. Hyperthyroidism and thyroid eye disease are particularly involved in the development of MGD; ocular protrusion is likely to result in physical effects on the meibomian glands. Furthermore, MGD is highly prevalent in inflammatory diseases that also cause inflammation of the ocular area, and it is presumed to influence MGD development. Particularly, SS [174–178], GVHD [179–181], rosacea [124, 182–184], and SJS [185] have a strong association with MGD, and it is presumed that inflammation of the meibomian glands is related to the development of MGD. Systemic events related to increased or decreased sex hormones (menopause [123, 133, 186], androgen reduction [187, 188], and prostatic hypertrophy [126]) are also reported as risk factors for the development of MGD.

Problems and Biases In literature, the diagnostic criteria for MGD varies in different studies, and the definition of MGD is inconsistent. Therefore, diagnosis can be biased. In addition, many reports suggest an overlap with dry eye, and it is not clear whether systemic diseases and conditions are directly involved in the development of MGD, or whether they indirectly mediate MGD through the development of dry eye. Many studies have examined the association of MGD with single systemic diseases; only a few studies have included multiple diseases. Therefore, much uncertainty remains about the systemic factors involved in the development of MGD.

Future Challenges and Trend Prospective studies that analyze systemic risk factors in different ways, based on a standardized definition, pathophysiology, and diagnostic criteria of MGD, are necessary.

- Examination and Diagnosis -

CQ1 What are the diagnostic criteria for MGD?

(Jun Shimazaki, Yuri Sakane, and Shizuka Koh)

Recommendations Although there are no globally consistent diagnostic criteria for low-delivery type MGD, the criteria used in Japan were proposed by the MGD working group in 2010. Most studies use criteria that independently combine subjective symptoms, abnormal eyelid margins, qualitative and quantitative changes in meibomian glands' secretion (meibum), and meibography findings. It is desirable that common diagnostic criteria be used in epidemiological studies on prevalence and in studies comparing the efficacy of treatment and assessment methods. It is crucial to establish internationally uniform diagnostic criteria, including other subtypes such as high-delivery MGD.

Explanation We studied 33 articles dealing with the diagnosis of MGD in the secondary screening, and selected 10 [1, 12, 45, 46, 95, 189–193] (Table 10). In Japan, the MGD Working Group proposed in 2010 the diagnostic criteria which specify that to conclude low-delivery MGD, three subjective symptoms, abnormal findings around the meibomian gland orifices, and obstructive findings of the meibomian gland orifices need to be positive [1] (Table 11). Since then, these criteria have often been used in Japan in studies on low-delivery MGD [5, 101, 194]. The report of the TFOS MGD International Workshop [189] does not present clear diagnostic criteria. However, the main characteristics of MGD stated include subjective symptoms, meibomian gland dropout, changes in the meibum, and changes in eyelid morphology, and the method of evaluation for each is explained. Procedures for examination and diagnosis of MGD in outpatient settings have also been proposed. It is recommended that to diagnose MGD and dry eye in general as well as dry eye related to MGD, the following assessments need to be conducted: (1) subjective symptoms, (2) blinking velocity and spacing, (3) lower tear meniscus height, (4) tear film osmolality (if possible), (5) BUT assessed by fluorescein staining, (6) staining score of cornea/conjunctiva, (7) Schirmer test or phenol red thread test, and (8) finally by quantitatively evaluating the morphological changes in the eyelid associated with MGD, the quality and quantity of the expressed meibum, and the degree of meibomian glands' dropout. Additionally, they propose staging based on test results and treatment methods according to stage (Table 12); many subsequent clinical studies refer to the methods included in the TFOS report for diagnosis [195–197]. However, it has been pointed out that there are multiple diagnostic assessment methods, such as meibum and meibography grade classification; therefore, further discussions are required in this regard. Globally standardized diagnostic criteria for MGD has not yet been established. Currently, a number of unique criteria combining several aspects, such as subjective symptoms, eyelid morphology, quantitative and qualitative changes in the meibum, and meibomian gland dropout, are referred to

Table 9 Studies on systemic factors and diseases that are risk factors for MGD

Study	Year	Country	Sample	Risk factors assessed	Findings
Zengin et al. [182]	1995	Turkey	43 rosacea patients (ocular, n=28 and skin, n=15) vs. 50 healthy individuals	Ocular rosacea	In ocular rosacea, Schirmer value, BUT, and meibomian gland function were significantly lower than in the healthy group.
Shimazaki J et al. [174]	1998	Japan	27 eyes of 27 patients with SS vs 27 eyes of 27 patients with dry eye disease	SS	In patients with SS, meibomian gland dropout was significantly higher than others.
Cermak et al. [187]	2003	US	Nine patients with CAIS vs 10 women and 21 men without CAIS	CAIS	CAIS was significantly associated with changes in meibomian glands and increased dry eye findings and symptoms.
Tamer et al. [188]	2006	Turkey	64 patients with MGD vs 64 patients with dry eye disease and without MGD vs healthy individuals	Androgen	Androgen was drastically decreased in patients with MGD and non-autoimmune dry eye compared with patients having non-MGD dry eye disease and healthy individuals.
Ban et al. [179]	2011	Japan	17 eyes of nine patients with cGVHD-associated dry eye vs 16 eyes of eight patients with hematopoietic stem cell transplant without dry eye	GVHD	The cGVHD-related dry eye group had a significantly lower meibomian gland acinar density.
Viso et al. [124]	2012	Spain	619 Spanish Caucasian individuals (men, n=229; women, n=390)	Diabetes, cardiovascular disease, rosacea, and RA	Asymptomatic MGD was associated with diabetes, cardiovascular disease, and symptomatic MGD was associated with rosacea and RA.
Siak et al. [123]	2012	Singapore	3,280 Malay 40–80-year-old individuals living in Singapore (data of 3,271 were analyzed)	Male sex, postmenopausal women, and hypertension	High prevalence of MGD in men of all ages, postmenopausal women, and those with hypertension.
Kim et al. [169]	2015	South Korea	51 patients with thyroid eye disease vs. 31 healthy individuals	Hyperthyroidism	The prevalence of MGD was high in patients with thyroid eye disease, and there was a significant difference in the meibography score, OSDI, and BUT.
Shamsheer et al. [164]	2015	India	100 patients with diabetes vs healthy individuals (men, n=116; women, n=84)	Diabetes mellitus	The frequency of MGD severity was significantly higher in patients with diabetes.
Palamar et al. [183]	2015	Turkey	18 patients with rosacea vs. 19 healthy individuals	Rosacea	OSDI, Oxford scale score, lower eyelid and upper eyelid meiboscores were high in the rosacea group.
Engel et al. [180]	2015	Germany	86 patients with ocular GVHD vs. 30 healthy individuals	GVHD	Meibomian gland deterioration was significantly higher in the ocular GVHD group than in healthy individuals.
Machalińska et al. [184]	2016	Poland	41 patients with rosacea vs. 44 healthy controls	Rosacea	There was a significant correlation between abnormal eyelid margin scores and meibomian gland deterioration in the rosacea group.

Table 9 (continued)

Study	Year	Country	Sample	Risk factors assessed	Findings
Alghamdi et al. [126]	2016	US	233 (mean age, 63 years; 91% men)	Sleep apnea and prostatic hyperplasia	Abnormal vascular distribution of the eyelids in Caucasians than in African Americans. Sleep apnea syndrome and prostatic hypertrophy were associated with abnormal vascular distribution.
Hashemi et al. [135]	2017	Iran	4,700 (Men, n=1,931; women, n=2,769)	Hypertension, high HDL, and diabetes	Hypertension, HDL, diabetes, and education correlated with MGD.
Golebiowski et al. [186]	2017	Australia	46 postmenopausal women with dry eyes; 13.7 ± 6.4 years after menopause	Menopause	E2 (17β-estradiol) and eyelid vascularity were associated with worsening of the quality of meibomian gland secretion.
Chen et al. [166]	2017	Taiwan	1,329 individuals	High LDL and triglycerides	LDL cholesterol and fasting triglyceride level were risk factors for asymptomatic MGD.
Park et al. [170]	2018	South Korea	30 patients with thyroid eye disease (men, n=8; women, n=22)	Hyperthyroidism	Significant correlation between clinical activity score and meiboscore.
Sullivan et al. [175]	2018	US	Patients with primary SS (n=11), secondary SS (n=16), non-SS-MGD (n=14), and healthy controls (n = 17).	SS	Primary SS and secondary SS were associated with MGD.
Kuriakose et al. [167]	2018	Systematic review	Four articles on dyslipidemia and MGD	Dyslipidemia	Strong positive correlation between MGD and dyslipidemia. Total cholesterol, LDL, HDL and triglycerides also significantly correlated with MGD.
Wang et al. [171]	2018	Taiwan	31 eyes of 17 patients with thyroid eye disease	Hyperthyroidism (thyroid eye disease)	MGD severity was higher in patients with thyroid eye disease having high clinical activity score.
Zang et al. [176]	2018	China	22 eyes of 22 patients with SS vs 22 eyes of 22 patients with non-SS evaporative ADDE	SS	NIBUT, upper eyelid meibomian gland dropout and corneal staining were high in the SS group, but was weakly associated with symptoms.
Kang et al. [177]	2018	South Korea	31 patients with SS dry eye vs 30 patients with non-SS dry eye vs 35 healthy controls	SS	In the SS and non-SS groups, NIBUT was lower than that in the healthy control group; however, the meiboscores, meibomian gland secretion capacity, and secretion quality were higher.
Sandra Johanna et al. [165]	2019	Spain	37 men over 40 years of age with type 2 diabetes vs. 36 non-diabetic men aged over 40 years	Diabetes mellitus	MGD was present in 52 patients with diabetes mellitus (71.23%); the prevalence was significantly different from the control group (66.6%)
Park et al. [172]	2019	South Korea	98 patients with thyroid eye disease vs 62 patients with dry eye	Hyperthyroidism (thyroid eye disease)	In thyroid eye disease, the upper eyelid meiboscore was significantly higher than that in dry eye.

Table 9 (continued)

Study	Year	Country	Sample	Risk factors assessed	Findings
Choi et al. [178]	2019	South Korea	30 patients with cGVHD-related dry eye, 35 patients with SS, 35 patient with MGD, and 35 healthy controls	SS, GVHD	In the cGVHD-related dry eye group, the meiboscores, meibomian gland expression score, and meibum quality score were significantly higher.
Arita et al. [6]	2019	Japan	356 residents of Hirado–Takushima (men, n=133 and women, n=223)	Patients taking hyperlipidemia medications, elderly age, and male sex	The risk factors for MGD (Japanese diagnostic standard) were hyperlipidemia treatment, elderly age, and male sex.
Lekhanont et al. [185]	2019	Thailand	32 patients with SJS (15 men and 17 women, aged 42.2±17.7 years)	SJS	Meibum secretion was absent in 23 patients (71.9%) and partial or total meibomian gland loss was seen in all patients.
Wang et al. [163]	2020	New Zealand	372 individuals (150 men and 222 women) aged ≥16 years (21–85 years), residing in Auckland for more than 15 years.	Thyroid disorders and oral contraceptive therapy	95 patients (26%) had MGD; age, East Asian ethnicity, presence of migraine or thyroid disease, and oral contraceptive therapy were significant risk factors.
Irfan et al. [168]	2020	India	116 participants (58 patients with MGD without dyslipidemia and 58 healthy controls without dyslipidemia)	Lipid metabolism disorder	Elevated cholesterol and triglyceride levels were significantly associated with MGD severity. There was a significant association between LDL levels and MGD severity.
Tulsyan et al. [133]	2021	Nepal	400 patients with MGD aged ≥30 years	Hyper-LDL cholesterolemia, hypertension, and menopause	Hypertension, menopause, and hyper-LDL cholesterolemia were significant risk factors for MGD.
Altin Ekin et al. [173]	2021	Turkey	210 eyes of 105 patients with Hashimoto's disease vs. 105 controls	Hashimoto's disease	In patients with Hashimoto's disease, a significant decrease in meibomian gland secretion and a significant increase in eyelid abnormality score, meibography score, and dropout area were observed.
Dikmetas et al. [181]	2021	US	22 patients with dry eye secondary to cGVHD vs 28 healthy controls	GVHD	Significant worsening of meibography score and corneal subbasal plexus density, decreased Schirmer value and BUT, and increased corneal staining score were observed in the cGVHD group.

ADDE, aqueous-deficient dry eye; CAIS, complete androgen insensitivity syndrome; cGVHD, chronic GVHD; GVHD, graft versus host disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NIBUT, noninvasive breakup time of tear film; OSDI, ocular surface disease index; RA, rheumatoid arthritis; SJS, Stevens-Johnson syndrome; SS, Sjögren's syndrome

Table 10 Articles selected at secondary screening

Study	Country/ Organization	Contribution
Amano et al. [1]	Japan	Definition and diagnostic criteria for low-delivery MGD by the MGD Working Group.
Tomlinson et al. [189]	TFOS	TFOS workshop report on MGD diagnosis and evaluation methods.
Nelson et al. [45]	TFOS	TFOS workshop report on the definition and classification of MGD.
Shimazaki et al. [12]	Japan	Examined the relationship between the percentage of patients with ocular discomfort with MGD findings and other clinical findings.
Arita et al. [190]	Japan	Investigated the parameters useful for differentiating between low-delivery MGD and aqueous-deficient dry eye.
Mathers et al. [191]	US	Evaluated the assessment parameters useful for differentiating dry eye, blepharitis, MGD, and rosacea-like dermatitis by cluster analysis.
Arita et al. [95]	Japan	Studied the assessments useful for the diagnosis of low-delivery MGD, and reported sensitivity and specificity.
Giannaccare et al. [192]	Italy	Examined the assessments useful for the noninvasive diagnosis of low-delivery MGD, and reported sensitivity and specificity.
Xiao et al. [193]	Norway	Reported the usefulness, sensitivity, and specificity of morphological evaluation using meibography in the diagnosis of low-delivery MGD.
Arita et al. [46]	Japan	Examined the assessments useful for diagnosing high-delivery MGD, and reported sensitivity and specificity.

MGD, meibomian gland dysfunction; TFOS, Tear Film and Ocular Surface Society; US, United States

Table 11 Diagnostic criteria for low-delivery type of meibomian gland dysfunction by the Japan MGD working group proposed in 2010. Reprinted with permission [1]

Low-delivery MGD is diagnosed when three of the following items are positive:
1. Subjective symptoms Ocular discomfort, foreign body sensation, dryness, and pressure.
2. Abnormal findings around meibomian gland orifice I Eyelid margin vascularity II Anterior or posterior displacement of the mucocutaneous junction III Eyelid margin irregularity Those that satisfy one or more of I–III are considered positive for 2.
3. Obstructive findings of the meibomian gland orifice I Meibomian gland obstruction findings (plugging, pouting, and ridge) II Moderate pressure on the eyelid by the thumb decreases meibum expression Those that satisfy both I and II are considered positive for 3.

in different studies. This lack of uniformity in diagnosis dissuades the comparison of outcomes between different studies. Nonetheless, several attempts to propose new criteria that are useful for diagnosing MGD and differentiating it from other diseases based on the conventional diagnostic criteria have been reported.

Of the papers we selected, seven [12, 46, 95, 190–193] were clinical studies that explore new criteria useful for diagnosing and differentiating MGD (Table 13). Shimazaki et al. [12] report that low-delivery MGD was seen in 64.6% of the patients with symptoms of ocular discomfort; that patients with meibomian gland obstruction and dropout in meibography had significantly more epithelial disorders than those without, and that in these patients the evaporation of tears was increased. Arita et al. [190] examined the distinction between ADDE and low-delivery MGD. They report that when low-delivery MGD was diagnosed with the presence of all three abnormalities including subjective symptoms, abnormal eyelid margins, and loss of area of meibomian glands (meiboscore) as observed in meibography, the sensitivity and specificity of the distinction with ADDE was 68% and 80%, respectively [190]. Mathers et al. [191] investigated tests useful for differentiating dry eye, blepharitis, MGD, and rosacea-like dermatitis by cluster analysis and suggest that meibomian gland dropout, changes in quality and quantity of expressed meibum, Schirmer test value, and the amount of tear evaporation were useful. In Mathers' study [191], they set cufoff values in glanddrop out, lipid viscosity, evaporation, Schirmer test value, and lipid volume to classify low-delivery MGD and high-delivery

Table 12 MGD staging by the international workshop on MGD by TFOS. Reprinted with permission [189]

Disease Stage	Frequency and severity of symptoms	OSDI* Grade (0–100)	Changes associated with MGD	Meibum quality score† (0–24)
Level 0 Normal	No symptoms	0	No abnormality	0
Level 1 Asymptomatic	Asymptomatic or occasional symptoms	0–12	Asymptomatic non-obvious MGD, change in quality of meibum only when expressed, and no loss of meibomian glands	1–5
Level 2 Minimally symptomatic	Occasional symptoms; induced by environmental factors	0–12	Minimal change in quality of meibum expressed from scattered glands, and no or minor loss of meibomian glands	6–10
Level 3 Mildly symptomatic	Often symptomatic; some restrictions on activities	13–22	Mild change in quality of meibum, occasional eyelid margin symptoms, and mild loss of meibomian glands	11–15
Level 4 Moderately symptomatic	Symptoms present most of the time; frequent restriction in regular activities	23–32	Moderate increase in turbidity and viscosity of meibum, plugging, hypervascularity of eyelid margins, loss of orifice, and moderate loss of meibomian glands	16–20
Level 5 Severely symptomatic	Symptoms present all the time; severe impairment with constant restriction in regular activities	33–100	Significant diffuse MGD, scarring or non-scarring, multiple eyelid margin symptoms, deformity and marked vascularity of eyelid margins, and severe meibomian gland loss	21–24

MGD, meibomian gland dysfunction; OSDI, Ocular Surface Disease index; TFOS, Tear Film and Ocular Surface Society.

*OSDI. Rated 0–100 with a 12-item questionnaire on subjective symptoms.

† Meibum quality score. Eight glands in the middle 1/3 of the lower eyelid were scored from 0–3 to obtain the total score (0–24). 0 = clear, 1 = cloudy, 2 = cloudy with debris, 3 = thick, like toothpaste.

MGD. Furthermore, many studies report the sensitivity and specificity of MGD diagnosis. Arita et al. [95] determined that when low-delivery MGD was diagnosed based on two abnormal findings among subjective symptoms, eyelid margin score, and meiboscore, the sensitivity was 84.9% and the specificity, 96.7% [95]. Giannaccare et al. [192] examined tests useful for noninvasively diagnosing low-delivery MGD. They report that the sensitivity was 86.2% and the specificity was 38.5% when low-delivery MGD was diagnosed with either BUT $\leq$ 9.6 seconds or an area of loss of meibomian glands by meibography > 20%. The sensitivity was 39.3% and the specificity was 85.6% when both criteria were met. Xiao et al. [193] report that morphological evaluation by meibography was useful for the diagnosis of low-delivery MGD. The sensitivity was 93% and the specificity was 97% when diagnosis was based on the area of meibomian gland dropout. When based on the distortion of six or more meibomian glands, the sensitivity was 93% and the specificity was 90%. Although there are few reports on the diagnostic criteria of subtypes other than low-delivery MGD, studies by Mathers et al. [191] and Arita et al. [46] examined tests specifically useful in diagnosing high-delivery MGD. The diagnostic sensitivity was 100% and the specificity was 96.7% when subjective symptoms were $\geq$ 2 and abnormal eyelid margins were $\geq$ 2 [46]. However, many uncertainties remain regarding the diagnosis and classification methods of the subtypes of MGD other than the low-delivery type; the current evidence seems insufficient for setting a clear diagnostic standard.

Several new standards have been proposed that show good sensitivity and specificity as described above, which may be utilized in the future. However, since the number of studies is limited, more research needs to be performed and carefully reviewed.

Problems and Biases Diagnostic criteria for MGD are not uniform, and although a general trend is followed, different studies have used various criteria. Studies have used many assessment methods including meibum expression and several scoring methods, making comparison among studies difficult. Furthermore, the diagnostic criteria for subtypes other than the low-delivery type are unclear.

Future Challenges and Trends The absence of internationally standardized diagnostic criteria is one of the constraints in comparing prevalence, assessment methods, and efficacy of treatment methods among studies. It is desirable to

Table 13 Studies on assessments useful for MGD diagnosis

Study	Focus	Diagnostic criteria at recruitment	Assessments	Diagnostic Results
Shimazaki et al. [12]	Differentiation between patients with low-delivery MGD having ocular symptoms and healthy controls	Subjective symptoms, obstruction of the meibomian gland orifice or gland dropout	Subjective symptoms, abnormal eyelid margin, and meibography	MGD findings were seen in 64.6% of the people with ocular discomfort. In the presence of orifice obstruction and gland dropout, the epithelial injury was strong and the quantity of evaporation was increased.
Arita et al. [190]	Differentiation between low-delivery MGD and ADDE	Diagnostic criteria for MGD in Japan and ADDE if Schirmer value ≤ 5 mm	Subjective symptoms, abnormal eyelid margin, and meibography	When diagnosed with low-delivery MGD based on positivity on all three criteria of subjective symptoms, eyelid margin score, and meiboscore*, the sensitivity of differentiation from ADDE was 68%, and the specificity was 80%.
Mathers et al. [191]	Differentiation among dry eye, blepharitis, MGD, and rosacea-like dermatitis	No detailed criteria for patients diagnosed with the aforementioned diseases	meibography, meibum quality, Schirmer value, and quantity of tear evaporation	Classified the patients into nine groups based on the quality of meibum, meibomian gland dropout, expressed meibum and lipid volume, Schirmer value, and quantity of tear evaporation amount, and reported the cut-off values.
Arita et al. [95]	Tests useful for the diagnosis of low-delivery MGD	Subjective symptoms, eyelid margin abnormalities ≥ 1, and decreased meibum expression	Subjective symptoms, abnormal eyelid margin, and meibography	When low-delivery MGD was diagnosed due to the presence of two abnormal symptoms, eyelid margin score, and meiboscore*, the sensitivity was 84.9%, and the specificity was 96.7%.
Giannaccare et al. [192]	Tests useful for the noninvasive diagnosis of low-delivery MGD	Subjective symptoms, MGD signs (abnormalities of the eyelid margin or meibum) ≥ 1	BUT and meibography	The sensitivity was 86.2% and the specificity was 38.5% when diagnosed with low-delivery MGD, on conforming to either BUT ≤ 9.6 seconds or with meibomian gland loss > 20%. When both were met, sensitivity was 39.3% and specificity was 85.6%.
Xiao et al. [193]	Usefulness of morphological evaluation for the diagnosis of low-delivery MGD	Qualitative and quantitative changes of meibum	Meibography	When the cutoff value of meibograde† was considered to be 1.5, the diagnostic sensitivity of low-delivery MGD was 93%, and the specificity was 97%. When the cutoff value was ≥6 for gland distortion, the sensitivity was 93% and specificity was 90%.
Arita et al. [46]	Tests useful for the diagnosis of high-delivery MGD	Subjective symptoms, eyelid margin abnormalities ≥ 1, and increased secretion of meibum	Subjective symptoms and eyelid margin abnormalities	Sensitivity was 100% and specificity was 96.7% when diagnosed with high-delivery MGD based on both abnormalities in symptoms and eyelid margin score.

ADDE, aqueous-deficient dry eye; BUT, tear film break-up time; MGD, meibomian gland dysfunction.

*meiboscore: 0 = area of meibomian gland loss 0, 1 = less than 1/3, 2 = more than 1/3 and less than 2/3, 3 = more than 2/3; this is considering the total score in the upper and lower eyelids.

† meibograde: 0 = area of meibomian gland loss 0–25%, 1 = 26–50%, 2 = 51–75%, 3 = >75%; this is considering the total score in the upper and lower eyelids.

unify diagnostic criteria and evaluation methods for further research.

CQ2 What are the characteristic subjective symptoms of MGD and appropriate ways to elicit them from patients?

(Yukiko Nagahara and Masaki Fukui)

Recommendations Symptoms of MGD include ocular discomfort, foreign body sensation, dryness, pressure, pain, burning sensation, tears, eyestrain, blurred vision, pruritus, discharge, and photophobia. These need to be elicited when suspecting MGD. However, there is currently no convincing evidence to specify characteristic subjective symptoms that differentiate MGD and other ocular surface disorders.

Explanation The characteristics of MGD subjective symptoms and the appropriate method to elicit them were confirmed by the diagnostic criteria. In Japan, according to the definition and diagnostic criteria proposed in 2010 [1], MGD is defined as "a disease in which meibomian gland function is diffusely abnormal, due to various causes, with accompanying chronic ocular discomfort." Additionally, among the diagnostic criteria for low-delivery MGD, subjective symptoms such as ocular discomfort, foreign body sensation, dryness, and pressure are included. Moreover, based on the diagnostic criteria proposed by the International Workshop on Meibomian Gland Dysfunction in 2011 [189], it is assumed that subjective symptoms are also included in international standards. However, international diagnostic standards mention that the absence of symptoms is a preclinical stage of MGD. In a survey of patients aged ≥50 who underwent cataract surgery years in Japan, the prevalence of MGD with symptoms was 18.0% and without symptoms was 29.5%; it is reported that the dry eye symptoms were stronger in symptomatic MGD than in asymptomatic MGD [5]. This strengthens the view that an asymptomatic condition could be a pre-clinical stage of MGD. The possibility that subjective symptoms related to the eyelids (itchiness, foreign body sensation, and pain) may indicate MGD has been investigated in symptomatic cases. However, it is difficult to distinguish MGD from other ocular surface diseases by distinctive subjective symptoms alone. Questionnaires for assessing subjective symptoms include McMonnies Questionnaire [198], Schein Questionnaire [117], OSDI [199], Dry Eye Questionnaire [200], Ocular Comfort Index [201], and SPEED [202]. Details have been discussed under CQ1: What are the diagnostic criteria for MGD?. Some studies on the diagnostic criteria of MGD do not include subjective symptoms [191–193].

In studies that have evaluated the assessments and treatment of MGD, the aforementioned questionnaires, specifically developed for these studies, and in addition, Japan's own dry eye questionnaire, the Dry Eye Related Quality of Life Score [203], have been used. The questionnaire studies show significant differences in the degree of subjective symptoms before and after MGD treatment [204, 205].

There are few reports that have examined the association between subjective symptoms and MGD. And the results vary in the way the original questionnaire scores, BUT, and corneal fluorescein staining score correlate with MGD [119]; OSDI was related to confocal microscopic findings [98]; the LLT correlated with SPEED but not OSDI [206]; and the original questionnaire and meiboscores were not correlated [207].

As a study that examined the degree to which subjective symptoms are useful in the diagnosis of MGD, Arita et al. [95] created a receiver operating characteristic curve of MGD diagnosis with each of the following: ocular symptoms' scores, lid margin abnormality scores, meiboscores, meibum scores, SPK scores, BUT, and Schirmer values. They report that the area under the curve of the ocular symptoms' score was the highest at 0.948 (95% confidence interval: 0.912–0.984). Fu et al. [99] examined what correlation the items : dryness, foreign body sensation, pain, burning sensation, tears, nystagmus, blurred vision, itching, eye discharge, photophobia showed with tears meniscus height, BUT, corneal fluorescein staining, eyelid margin findings, meibum expression, meibum quality, meiboscores, meibomian gland dropout rate, meibomian gland score, and confocal microscopy findings. However, they did not arrive at an identification of characteristic symptoms, and only suggest the association between subjective symptoms and inflammation. Paugh et al. [208] explored the development of a questionnaire for subjective symptoms specific to MGD. The Schein questionnaire was revised, and a Rasch analysis was performed with a total of 24 items divided into frequency and degree of the following 12 symptoms: dryness, grittiness, burning, redness, vision fluctuation/blurred vision, tiredness, sensation of discomfort, foreign body sensation, itching, irritation, soreness, and scratchiness. Subsequently, a 14-item questionnaire was prepared, divided into frequency and degree of the following seven symptoms: dryness, grittiness, burning, vision fluctuation/blurred vision, itching, soreness, and scratchiness. This questionnaire correlates with the original Schein questionnaire, is able to identify the effects of MGD treatment, is not correlated with BUT (to differentiate it from dry eye), and is considered to be specifically designed for MGD diagnosis.

Problems and Biases There are no reports that a specific single subjective symptom can be used for diagnosing MGD, and there are few reports on subjective symptoms that are highly sensitive and specific to MGD. Arita et al. [95] show that subjective symptoms are important in MGD diagnosis. Fu et al. [99] show the subjective symptoms that correlate with the test results of MGD, and Paugh et al. [208] report

which items on subjective symptoms can be combined to form a specific questionnaire for MGD diagnosis. Although some progress was made, at present, it is not clear how useful this information is for MGD diagnosis.

Future Challenges and Trends It has been shown that eliciting subjective symptoms is crucial for diagnosing MGD, and that there is a possibility of distinctive subjective symptoms and their combinations in MGD. In the future, it is necessary to verify the reproducibility and effectiveness of this information in the diagnosis and treatment evaluation.

CQ3 Is anatomical observation of the eyelid margins useful in the diagnosis of MGD?

(Yuri Sakane and Masahiko Yamaguchi)

Recommendations The meibomian gland orifice is located at the eyelid margin. MGD causes various anatomical changes to the eyelid margin. Anatomical changes in the eyelid margins that are useful in the diagnosis of MGD include: meibomian gland orifices' findings (plugging, pouting, capping, and ridge formation), eyelid margin vascularity, displacement of MCJ, and eyelid margin irregularity (Fig. 17). These anatomical changes in the eyelid margin are scored by the presence or absence and extent of each finding, and are used for diagnosis and severity classification of MGD. The usefulness of eyelid marginal anatomy in the diagnosis of high-delivery MGD has not yet been sufficiently substantiated.

Explanation Five main anatomical findings of eyelid margins are considered in the diagnosis of MGD; eyelid margin vascularity, displacement of MCJ, eyelid margin irregularity, eyelid margin thickness, and meibomian gland orifices' findings (plugging, pouting, capping, and ridge formation). Studies on MGD diagnosis have used multiple combinations of these abnormal eyelid findings. Among the studies that we analyzed in the secondary screening, a combination of four factors (eyelid margin irregularities, eyelid margin vascularity, plugging, and MCJ displacement) are reported in seven articles [4, 5, 95, 130, 190, 209, 210], a different combination of four factors (eyelid margin irregularities, eyelid margin vascularity, eyelid margin thickness, and plugging)

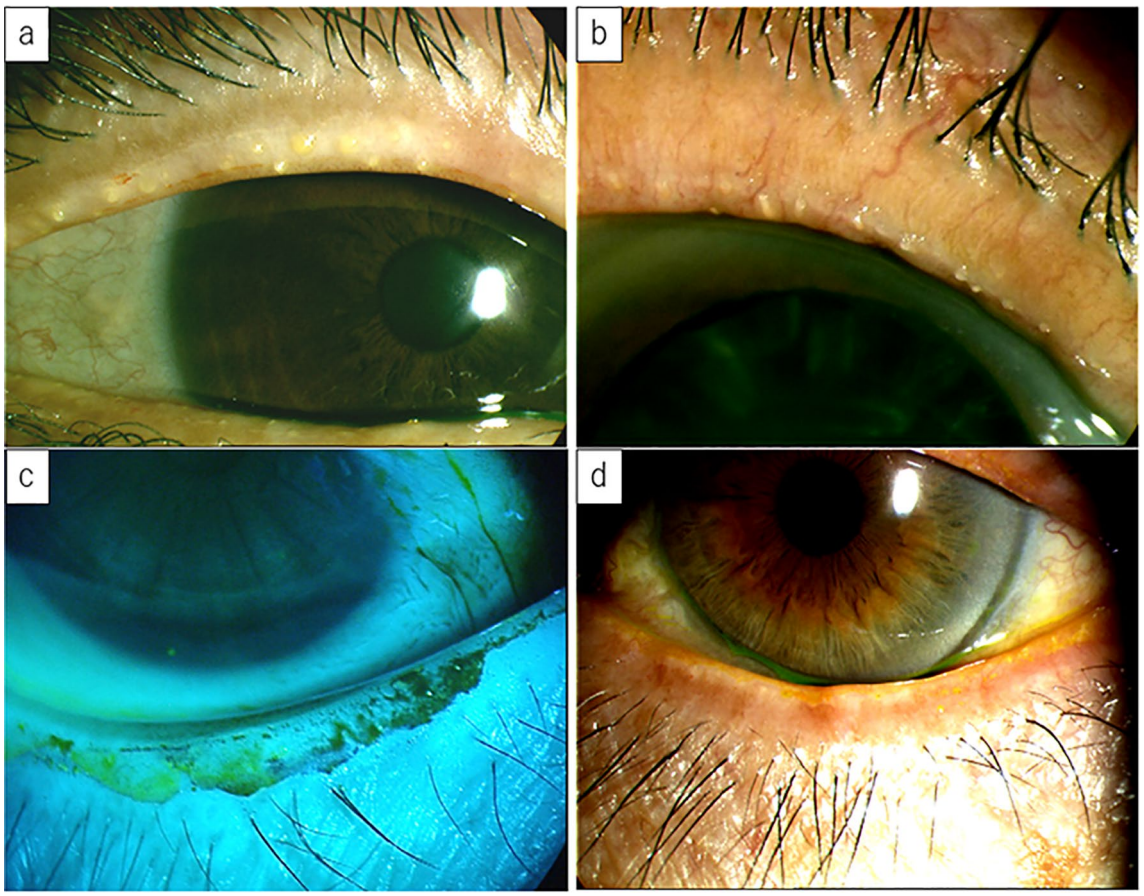

Fig. 17 Anatomical findings of the eyelid margins in MGD. **a** Obstructive findings of the meibomian gland orifice (plugging and capping). **b** Eyelid margin vascularity. **c** Anterior displacement of the MCJ (fluorescein staining). **d** Eyelid margin irregularity.

is reported in one study [101], a combination of three factors (eyelid margin irregularities, eyelid margin vascularity, and plugging) are reported in two studies [99, 134], and a combination of two factors (eyelid margin vascularity and plugging) is reported in two studies [124, 211].

In a study comprising a large sample (=510), Amano et al. [4] performed MGD diagnosis using the same diagnostic criteria used in an epidemiological study of MGD in Spain [124]. They compared the scores of eyelid margin irregularities, MCJ anterior displacement, eyelid margin vascularity, and plugging in individuals with and without MGD and report significant differences ($p < 0.0001$ for all four factors). In addition, when MGD diagnosis was performed at the same facility using the 2010 Japanese diagnostic criteria for low-delivery MGD [1], a significant difference ($p < 0.0001$) was observed in all four factors between individuals with and without MGD. In a multicenter study in China [134] that included 2,900 participants, the diagnostic criteria for MGD from China [212] and Japan [95] were combined. This study shows that the lid margin score (total score of eyelid margin irregularity, eyelid margin vascularity, and plugging) correlated with unique oMGD grading ($p < 0.001$). In a study of 570 people in a facility in India [6], the diagnosis was made using the diagnostic criteria proposed by the MGD international workshop in 2011 (diagnosis by scoring the quality of meibum and the extent of expression) [189]. They examined the four factors of eyelid margin irregularities, eyelid margin vascularity, MCJ displacement, and plugging and show that there was a significant difference in scores between MGD and non-MGD groups for all four factors ($p < 0.001$, respectively). However, when the MGD group was divided by the presence or absence of symptoms, a significant difference was observed only in plugging. Although the sample size was small, Arita et al. [101] compared 30 patients with oMGD diagnosed according to 2010 Japanese diagnostic criteria for low-delivery MGD [1] with 20 healthy controls without MGD. They advocate the grading of MGD including the anatomical changes in the eyelid margins and report on the usefulness of MGD diagnosis and severity determination. In this study, the five factors of eyelid margin vascularity, MCJ anterior displacement, eyelid margin irregularity, eyelid margin thickness, and plugging were compared between patients with MGD and healthy controls. Of the above, four factors, excluding MCJ anterior displacement, were used for MGD grading. Although the results suggest a significant difference between the two groups on MCJ anterior displacement, only four factors excluding MCJ displacement, were used as factors associated with eyelid abnormality in MGD grading.

There remains a controversy whether, when assessing its positional abnormality, the MCJ moves anteriorly (towards the skin) or posteriorly (towards the palpebral conjunctiva) in MGD when assessing its positional abnormality. Bron et al. [104] hypothesize that the displacement of MCJ in MGD and blepharitis happens both anteriorly and posteriorly, and that elevated tear film osmotic pressure and changes in tear composition of tear meniscus due to dry eye and ocular surface inflammation lead to cellular injury at the eyelid margin, causing abnormal positioning of the MCJ [213]. Yamaguchi et al. [214] compared the degree of anterior displacement of the MCJ using the grading of meibomian gland function and morphological tests and report that the MCJ moves anteriorly in MGD. In addition, Hirotani et al. explored the association between MCJ anterior displacement and conjunctivochalasis at the lower eyelid margin [215]. The anterior displacement of MCJ was found associated not only with MGD but also with conjunctivochalasis and other ocular surface diseases; this whole issue needs further research.

The above-stated research evidence is predominantly related to low-delivery MGD. An anatomical observation of eyelid margins in high-delivery MGD with variations in pathophysiology was reported only by Arita et al. [46]. They suggest that the total score of four factors, eyelid margin irregularity, eyelid margin vascularity, foaming at the outer canthus, and anterior or posterior displacement of MCJ, is useful to calculate lid margin abnormalities for diagnosing high-delivery MGD. At present, as the diagnostic criteria for high-delivery MGD remains indeterminate, it can be considered as a future topic of research.

Problems and Biases Subtle differences in the diagnostic criteria for MGD used across countries is an issue. Among the anatomical changes in the eyelid margins, meibomian gland orifices' obstruction findings, including plugging, can easily be seen as a direct change associated with MGD. However, eyelid margin vascularity, eyelid margin irregularity, eyelid margin thickness, and MCJ displacement, may also be observed in other ocular surface and eyelid diseases. Whether or not these are changes specific to MGD is not sufficiently explored in literature.

Future Challenges and Trends Although anatomical observation of eyelid margins is useful in MGD diagnosis, it is desirable to conduct multicenter studies and therapeutic intervention studies using unified MGD diagnostic criteria. It is also necessary to compare these observations in MGD with the ocular surface diseases that cause anatomical changes to the eyelid margin as well as those with healthy controls. In addition, anatomical changes in eyelid margins in high-delivery MGD need to be investigated.

CQ4 Is the measurement of BUT useful in the diagnosis of MGD?

(Masahiko Yamaguchi, Minako Kaido, and Masaki Fukui)

Recommendations Numerous reports state that BUT is reduced in MGD compared with a normal eye. However,

it is debatable whether dry eye associated with MGD or whether meibomian gland abnormality is the cause, nor is there a uniform view regarding histological changes in the meibomian glands, and, therefore, BUT is not a useful test for specifically diagnosing MGD.

Explanation Two types of tests are used for evaluating the stability of the tear film: fluorescein staining BUT and image analysis without fluorescein staining (NIBUT). The former is discussed in this section, while the latter is discussed under CQ7.

Evidence on BUT in MGD is broadly divided into: 1) studies comparing MGD with normal eyes, 2) studies comparing MGD with non-MGD, 3) studies comparing MGD with various dry eye types, and 4) studies on the relationship between histological findings in the meibomian glands and BUT. Table 14 shows a summary of these methods.

A number of reports state that BUT in MGD is significantly shorter than in the normal eye [4, 216–220]. However, other reports claim that there is no significant difference from the normal eye [102, 221].

Some studies show the BUT is significantly lower in cases with MGD than in cases without MGD [128, 130], while others show no significant difference [222]. However, the variations in the results may be due to the differences in the participants. While the former results were derived

Table 14 Summary of tear film break-up time measurement in MGD diagnosis

Comparison	BUT	Study	Year	BUT cut-off value in DE
MGD vs Normal Eye	MGD< Normal	Pflugfelder et al. [216]	1998	N/A
		Tung et al. [217]	2014	≦ 7
		Napoli et al. [218]	2014	<10
		Amano et al. [4]	2017	≦5
		Ye et al. [219]	2019	≦10
		Xiao et al. [220]	2020	<5
	No Difference	Lee et al. [221]	2017	<5
		Ji et al. [102]	2017	<10
MGD vs non-MGD	MGD < non-MGD	Asiedu et al. [128]	2018	-
		Chatterjee et al. [130]	2020	≦10
	No Difference	Robin et al. [222]	2019	<10
MGD vs DE subtypes	MGD < DE subtypes	Vu et al. [223]	2018	≦5
		Ye et al. [219]	2019	≦10
		Li et al. [134]	2020	≦5
	MGD > DE subtypes	Pflugfelder et al. [216]	1998	N/A
		Horwath-Winter et al. [224]	2003	< 10
		Tung et al. [217]	2014	≦7
		Napoli et al. [218]	2014	< 10
		Lee et al. [221]	2017	<5
		Ji et al. [102]	2017	<10
		Rabensteiner et al. [153]	2018	N/A
			2018	——
Association of BUT with MGD grade	Correlation observed	Uchino et al. [120]	2006	< 5
		Moore et al. [225]	2009	< 7
		Viso et al. [226]	2011	≦10
	No correlation	Nichols et al. [233]	2003	N/A
		Eom et al. [234]	2013	——
		Sullivan et al. [235]	2014	N/A
		Ji et al. [102]	2017	<10
		Daniel et al. [229]	2020	≦7
Association of BUT with histological changes in MG	Association observed	Feng et al. [207]	2014	——
		Randon et al. [98]	2019	——
		Adil et al. [196]	2019	——
		Jie et al. [227]	2019	<10
		Gulmez et al. [228]	2020	——
		Daniel et al. [229]	2020	≦7
		Rashid et al. [230]	2020	<5
		Lin et al. [231]	2020	——
		Zhang et al. [232]	2020	<10

BUT, tear film break-up time; DE, dry eye; MGD, meibomian gland dysfunction.

by studies of patients with dry eye symptoms, and of dry eye-related diseases, as well as other conditions; the latter were observed in patients with dry eye symptoms only. Specifically, although there is a relationship between MGD and decrease in BUT, it is hard to say that MGD is the cause of this decrease and the resulting symptoms.

Furthermore, BUT was significantly lower in patients having MGD with dry eye than in those without dry eye [134, 223]. On comparing the MGD with various dry eye types, studies suggest that BUT is significantly longer in MGD than in ADDE (including SS-ADDE, non-SS-ADDE, non-SS-ADDE with MGD, SS with MGD, and SS without MGD) [102, 153, 216, 217, 221, 224]. However, one study reports that BUT in MGD was significantly shorter than ADDE [219], while another reports no significant difference [218]. On the association between meibomian gland morphological findings and BUT, some reports state that such association exists [98, 120, 196, 207, 225–232] whereas others state that it is absent [102, 229, 233–235]. Viso et al. [226] and Gulmez Sevim et al. [228] report that the higher the MGD grade, the shorter the BUT; conversely, Nichols et al. [233], Sullivan et al. [235], and Ji et al. [102] report that the MGD grade was unrelated to BUT. Feng et al. [207] and Jie et al. [227] assume that the higher the meibomian gland loss, the lower the BUT, while Eom et al. [234] deny any association of BUT with meibomian gland loss. Rashid et al. [230] report that the higher the meiboscore, the lower the BUT. Lin et al. [231] suggest that, in addition to the meiboscore, meibomian gland tortuosity, eyelid margin findings, and a lower meibum expression influenced a decrease in BUT. However, Daniel et al. [229] report that only the tortuosity of the meibomian glands is related to BUT.

Arita et al. [95] studied the parameters relevant for diagnosing MGD by calculating the area under the curve from the receiver operating characteristic curve. According to their study, the most effective parameters to distinguish oMGD from a normal eye in a single examination are (in the order of significance) symptoms, abnormal eyelid margins, meiboscore, and BUT. This indicates that several parameters need to be considered when diagnosing MGD.

Problems and Biases Since the diagnostic criteria of MGD differ from study to study, a consistent evaluation is difficult. Pflugfelder et al. [216] used meibomian gland orifices and surrounding findings and Schirmer values, whereas Uchino et al. [120] used meibum expression alone to classify MGD. In addition, there are reports evaluating MGD based on both upper and lower eyelid findings [98, 228, 234], as well as those evaluating only the lower eyelid [196, 225], and those evaluating only the central part of the eyelid [230]. Another consideration is the cut-off value of BUT in dry eye. Although it is ≤5 seconds in Japan, some studies indicate a cut-off value of 7 or 10 seconds (Table 14).

Future Challenges and Trends Factors that affect BUT vary widely, such as decreased tear volume, tear mucin, tear lipid layer, and corneal epithelial disorders. Therefore, the relationship between these factors and MGD needs to be verified. It is reported that VDT workers are at risk for developing MGD and may have a decreased BUT [236]. It is hoped that the impact of environmental factors of this type will be substantiated.

CQ5 Is the observation of BUP helpful in the diagnosis of MGD?

(Shizuka Koh and Yuri Sakane)

Recommendations Observation of BUP has been found to be useful in diagnosing dry eye subtypes [88, 237, 238]. Although there are no reports on a BUP specific to MGD, it has been pointed out that MGD is associated with evaporative dry eye [12, 26, 106]. BUP may be useful as an auxiliary examination for diagnosis. However, due to the little evidence and lack of clarity, it is not possible to determine whether it should be recommended.

Explanation According to the Asia Dry Eye Society, dry eyes are classified into three types: aqueous-deficient, decreased wettability, and increased evaporation [239]. This suggests that the problem lies with the moisture content of tears, membrane-associated mucin, lipid layer, or secreted mucin. BUP is a method for diagnosing problems in the tear film by observing the disruption pattern of tear fluid, seen on staining with fluorescein. It is reported to be useful in the diagnosis of dry eye and for treatment strategies [88, 237, 238]. BUP includes the basic patterns of area break, line break, spot break, dimple break, and random break. Area break and line break are aqueous-deficient types, spot break and dimple break are decreased wettability types, and random break is a pattern typical of evaporative dry eye. It has been pointed out that low-delivery MGD can impair the tear lipid layer and cause evaporative dry eye [12, 26, 106], and Shigeyasu et al. [240] report that, on assessing BUP in 867 eyes 16.9% of 117 eyes exhibiting random break had MGD. However, since random break is a pattern seen in healthy individuals as well, and even disorders associated with secretory mucin that works to retain moisture in the aqueous layer can result in evaporative dry eye, it is difficult to state that random break is a characteristic finding of low-delivery MGD. In high-delivery MGD, the BUP is unknown.

Problems and Biases BUP is mainly used in diagnosis or research on dry eye, and there are no studies that specifically assessed BUP in patients with MGD. In addition to the evaporative type, MGD may occur in combination with any other type of dry eye, and may indicate a BUP other than random break.

Future Challenges and Trends The usefulness of BUP in MGD diagnosis has not been reported and established. BUP is useful for diagnosing dry eye associated with MGD because it enables an estimation of the impairment of the tear lipid layer, and can also be used to support MGD diagnosis. However, since the evidence is scarce on this topic, further studies are necessary.

CQ6 Is it useful to observe meibomian gland secretions in the diagnosis of MGD?

(Masahiko Yamaguchi and Yuri Sakane)

Recommendations In MGD, the function of the meibomian glands is disturbed, and the quantity and quality of secretions change. Therefore, in the diagnosis of MGD, observation of the meibum by slit-lamp microscopy is important, and its implementation is recommended. The meibum is mainly evaluated by semi-quantitatively grading the quality and expressibility.

Explanation Although MGD is predominantly classified into low-delivery and high-delivery, it is important to observe the properties, color, and quantity of the secreted meibum in each of the types. As evidence is unclear regarding the high-delivery type, no clear evaluation method for the meibum in that type reported. In the low-delivery type, a method for semi-quantitative determination of the expressibility and quality (color and viscosity) of the meibum by compressing the eyelid has been proposed [104, 174, 189, 216, 241]. The diagnostic criteria for low-delivery MGD in Japan [1] includes decreased expression of meibum on eyelid compression. Table 15 shows the prominent evaluation methods of the meibum.

To evaluate the quality of meibum, Bron et al. [104] graded the meibum released by applying digital pressure on the eyelid as: 0 = clear liquid, 1 = cloudy fluid, 2 = cloudy particulate fluid, and 3 = inspissated (like toothpaste). Two methods for scoring may be considered; one utilizes the highest grade from the eight expressed meibomian glands (total score range: 0–3), while the other sums the scores from all eight glands (total score range: 0–24). Although a summed score is generally recommended [189], it is important to note that if the meibomian gland obstruction progresses to the point that meibum expression ceases in some glands, the total score will decrease.

Pflugfelder et al. [216] propose a method to evaluate the expressibility of the meibomian glands. Meibum expression from five glands on compressing the eyelids are observed; the grading is: 0 = all glands expressible; 1 = 3-4 glands expressible; 2 = 1-2 glands expressible; and 3 = no glands expressible. Additionally, Korb and Blackie [241] scored the number of expressed glands that yield a liquid secretion, regardless of its qualitative appearance, using a device capable of applying constant pressure to the eyelids and simultaneously express meibum from eight meibomian glands (meibomian glands yielding liquid secretion score). This is measured on the nasal, central, and temporal sides of the eyelids; it is reported that, even among healthy controls the temporal side has less secretion than the nasal side [241]. Other evaluation methods include a classification that combines the expressibility according to the response to digitally applied pressure and the quality of meibum, proposed by Shimazaki et al. [174]. This method divides

Table 15 Evaluation method of meibum by slit lamp microscope

Study	Expression method	Factor evaluated	Grading/Classification
Bron et al. [104]	Digital pressure	Quality of meibum from eight glands	0: Clear fluid 1: Cloudy fluid 2: Cloudy particulate fluid 3: Inspissated, like toothpaste
Plfugfelder et al. [216]	Digital pressure	Number of glands with expression out of five glands	0: All glands expressible 1: 3-4 glands expressible 2: 1-2 glands expressible 3: No glands expressible
Korb and Blackie [241]	Expression device	Number of glands with expression out of 8 glands	Number of meibomian glands expressed yielding liquid secretions regardless of their quality (MGYLS score)
Shimazaki et al. [174]	Digital pressure	Levels of digitally applied pressure and quality of meibum	0: Clear meibum, easily expressed 1: Cloudy meibum, easily expressed 2: Cloudy meibum expressed with moderate pressure 3: Meibum not expressed, even with hard pressure

MGYLS, meibomian glands yielding liquid secretion

meibum expression into the following four grades: 0 = clear meibum easily expressed; 1 = cloudy meibum expressed with mild pressure; 2 = cloudy meibum expressed with more than moderate pressure; 3 = meibum not expressed even with hard pressure.

Of the 23 articles that were considered during the secondary screening in our review, 17 were clinical research articles that included observation of the meibum. The breakdown of evaluation methods used in these articles is: 10 articles [99, 130, 134, 155, 193, 195, 196, 220, 242, 243] utilized the methods by both Bron et al. [104] and Pflugfelder et al. [216], one article utilized the method by Bron et al. [244] alone, and six articles [23, 46, 95, 190, 209, 245] used the method by Shimazaki et al. [174].

As mentioned above, there are several evaluation methods for observing the meibum, but there is currently no internationally standardized method. In addition, there are various studies that evaluated the lower eyelid alone [155, 193, 195, 196, 220, 242], upper eyelid alone [46, 95, 134, 245], or both [23, 243, 244]. Considering that the secretion is different on the nasal and temporal sides in the same eyelid, it is desirable to have a common method of expression, such as by compressing, and uniformity in the areas studied in the upper and lower eyelids.

Problems and Biases There is no standardized uniform criterion for the evaluation of the meibum or the areas studied on the eyelids. The lower eyelid reportedly has a significantly higher rate of meibomian gland secretion than the upper eyelid, and the quality of meibum is poorer [244]. Additionally, it is suggested that even if the eyelid is normal, the expression of the meibum on the temporal side is less than on the nasal side [241]. As such, results may differ depending on where the compression is applied.

Future Challenges and Trends It is desirable that common evaluation methods be used to compare the efficacy of treatment and testing methods in the studies. To achieve this, it is necessary to unify the methods of meibum expression and evaluation.

CQ7 Is NIBUT measurement useful in the diagnosis of MGD?

(Fumika Oya and Shizuka Koh)

Recommendations Whether NIBUT measurement is useful in the diagnosis of MGD cannot be determined because of the small number of related studies and inconsistent results. Although it is noninvasive, only very few facilities can perform the test. Furthermore, a standardized cut-off value has not been set. Therefore, currently it cannot be recommended as a test for the diagnosis of MGD.

Explanation BUT measurement using fluorescein is widely used to test the stability of the tear film. The test is convenient and cost-effective with an added advantage that it can be performed at any medical institution. However, several issues have been pointed out, including that the stimulation by fluorescein may affect tear film stability, measurement results vary depending on the examiner and the amount of fluorescein used, poor reproducibility of the test and temperature, humidity, and air conditioning may influence the results [246]. To overcome these issues, NIBUT measurement assessments have been developed. The devices which can assess NIBUT mainly observe the pattern of projected light generated by the reflection on the surface of the tear film, and measure NIBUT by assessing the distortion over time [246]. Examples of commercially available devices in Japan include Keratograph5M ® (Oculus Optikgeräte GmbH), ICP Tearscope ™ (SBM Sistemi), idraTM (SBM Sistemi), and DR-1αTM (Kowa).

Many studies have been conducted on NIBUT in patients with dry eye, and there is a certain consensus on its usefulness in the diagnosis of dry eye disease. It has been adopted as a diagnostic criteria in the TFOS Dry Eye Workshop II [246]. Conversely, there is scarcely any literature that examined NIBUT in patients with MGD.

Giannaccare et al. [192] used ICP Tearscope™ to compare NIBUT in patients with MGD and healthy controls, and report that NIBUT in MGD patients was significantly shorter than in healthy controls. The cutoff value of NIBUT for MGD diagnosis was 9.6 seconds, with a sensitivity of 65.8% and a specificity of 63.0%. Although NIBUT alone could not accurately diagnose MGD, they believe that the diagnostic accuracy could be improved by combining it with other parameters such as the meibomian gland dropout score. However, Kim et al. [247] used Keratograph 5M ® to compare NIBUT in patients with MGD and healthy controls and report no significant difference. These studies [192, 247] excluded patients with ADDE, likely minimizing the effect of dry eye on NIBUT. It remains unclear whether the contrasting results are due to the differences in the test equipment; additionally, Kim et al. [247] did not clarify whether the participants were age and sex matched.

Qi et al. [248] measured NIBUT in patients with dry eye having MGD and healthy controls using Keratograph 5M ®, and show that NIBUT was significantly shorter in the MGD group than in the control group. Contrarily, Abdelfattah et al. [249] measured NIBUT in patients with ocular surface diseases such as MGD and dry eye as well as in healthy individuals using Keratograph 5M ®. They report no difference in NIBUT between the two groups. These results are also inconsistent and need further exploration in the future.

In addition, Ji et al. [102] report that NIBUT shortens with the increase in the severity of MGD in patients with dry

eye having MGD, while Robin et al. [222] report no difference in NIBUT between patients with MGD and those with allergic conjunctivitis and primary/secondary SS.

As mentioned above, the usefulness of NIBUT in MGD diagnosis has been assessed in only a few studies, and these results are inconsistent. Therefore, it is not possible to determine whether NIBUT is useful for diagnosing MGD.

Problems and Biases All related articles identified were observational studies [102, 192, 222, 247–249]. In the study by Kim et al. [247], the allocation of patients and controls was inappropriate, and therefore significant selection bias was observed. Diagnostic criteria for MGD and equipment used for measuring NIBUT varies with each study, and hence serious indirectness is observed in the study population and outcome measurements. Some studies [192, 248] found shorter NIBUT in patients with MGD than that in controls, while others [247, 249] found no difference between the two groups, showing serious inconsistency. Since MGD may cause evaporative dry eye, it is necessary to carefully determine whether the reduction in NIBUT observed in MGD [192, 248] is due to MGD directly or indirectly through dry eye.

NIBUT measurement requires a dedicated device, and only a limited number of medical institutions can currently offer the test. Although it has the advantage of being noninvasive, there is little benefit in diagnosis because the cut-off value in MGD is not specified.

Future Challenges and Trends Since dry eye is often associated with MGD, it is difficult to diagnose MGD by NIBUT measurements alone. However, the diagnostic accuracy of MGD can reportedly be improved by considering NIBUT with other parameters [192]. With more such studies, it would be possible to develop the noninvasive laboratory equipment programmed to automatically diagnose MGD by simultaneously evaluating NIBUT and meibomian gland function. It is believed that if such equipment is brought to widespread use, MGD can be properly diagnosed and treated in a general facility without a corneal specialist.

CQ8 Is meibography useful in the diagnosis of MGD?

(Jun Shimazaki and Minako Kaido)

Recommendations Meibography is a method of observing the morphology of meibomian glandular tissues using a meibograph. It is effective in the diagnosis of MGD, with the advantages of being noninvasive and requiring only a short time. Therefore, the use of meibography for the diagnosis of MGD is recommended.

Nonetheless, there are differences in functionality and mismatches in image analysis results depending on the model; there is room for further investigation regarding which parameters obtained by meibography are effective in diagnosing MGD. It should also be noted that the morphology of the meibomian glands does not necessarily represent the function of the ocular surface.

Explanation Meibography is a non-invasive method of examining the morphological characteristics of the meibomian glands, first reported by Tapie in 1977 [250]. Originally, transmitted light was observed from the conjunctival side by shining light from the surface skin of the eyelid. However, in recent years, the development of non-contact meibography by infrared light enables the wide use of meigography in clinical practice [251]. Using meibography, many studies have explored meibomian gland drop-out by analyzing the glandular structure semi-quantitatively (such as using meiboscores) or quantitatively. Additionally, studies have assessed meibomian gland tortuosity, fishhook morphology of the eyelid margins, shortening, changes in the meibomian gland course such as thickening and tapering, diameter of the meibomian gland orifices, and number of meibomian glands [252, 253]. Studies of MGD using meibography may be broadly divided into 1) studies comparing two groups, such as normal and dry eyes, 2) studies examining the relationship of meibomian gland morphology with ocular surface findings and tear function, and 3) studies on the diagnostic ability of meibography in MGD (Table 16).

1. Comparison of two groups, such as normal eye and dry eye

In MGD, the dropout score of meibomian gland structure was significantly higher than in normal eyes [95, 234, 248, 254], and the meibomian glands were shorter or tortuous [252]. The meibomian gland orifices reportedly expanded due to the filling up of contents [252]. Compared with dry eye, MGD showed significant dropout of meibomian gland structures [46, 190, 255]. In addition, Robin et al. [222] compared MGD with non-MGD having ocular symptoms, and McCulley et al. [256] compared dry eye with MGD and dry eye without MGD, both report significantly more common structural loss in meibomian glands in the presence of MGD. On comparing the presence and absence of symptoms, Shimazaki et al. [12] report that in cases with ocular symptoms, the meibomian gland structure had a higher dropout than in cases without symptoms. Lin X et al. [231] suggest that in MGD with symptoms, the tortuosity of the meibomian glands was increased when compared with the glands in MGD without symptoms.

2. Relationship between meibomian gland morphology and ocular surface findings and tear function

Table 16 Studies on meibography in MGD

Focus	Findings	References
MGD vs Normal Eye	MG dropout: MGD > Normal eye	[95, 234, 254]
	MG length and width: MGD > normal eye; MG orifice brightness: MGD > Normal eye	[252]
MGD + DE vs Normal eye	MG dropout: MGD with DE vs Normal eye	[248]*
Symptomatic MGD vs symptomatic non-MGD	MG dropout: MGD > nonMGD	[261]
	However, the lower eyelid had more findings than the upper eyelid.	[222]
MGD vs DE	MG dropout: MGD > ADDE	[46, 190, 255]
MGD with DE vs MGD without DE	MG dropout: MGD with DE > MGD without DE	[256]
Symptoms: Present vs absent	MG dropped out: Symptomatic > asymptomatic	[12]
	MG tortuosity: symptomatic > asymptomatic, but all participants had MGD	[231]
Meibography findings vs symptoms, ocular surface, tear findings, and other findings	MG dropout: correlated with BUT	[120, 207, 257, 258]*, [259]*, [261]†, [229]‡
	MG dropout: meibum-related	[196]†[244]*†
	MG dropout: correlated with Schirmer value	[196, 207]†, [229]‡
	MG dropout: correlated with corneal fluorescein staining score	[196, 207, 260]*,†, [229]‡
	MG dropout: correlated with expressibility	[196, 257]*,†
	MG dropout: correlated with OSDI	[248]*, [261]*, [196]*, [229]
	MG dropout: correlated with DE diagnosis	[261]
	MG dropout: correlated with tear film osmotic pressure	[260]
	MG dropout: correlated with NIBUT	[248]*, [222]
	MG dropout : no correlation with symptoms	[222, 229, 259, 260]
	MG dropout: no correlation with NIBUT or BUT	[259]
	MG dropout: no correlation with BUT	[222, 260]
	MG dropout: no association with Schirmer value	[222, 260]
	MG dropout: no correlation with expressibility	[260]
	MG tortuosity: correlated with eyelid margin findings, meiboscore, meibum expressibility, and BUT	[231]
	Length of MG: correlated with symptoms	[252]
	Width of MG: correlated with BUT	[252]
Reliability of meibography/ diagnostic capability in MGD	Mutual relationship between the two grading methods of images and intra- and inter-reliability with diagnosticians.	[263]
	AUC values: Symptoms > eyelid margin findings > meiboscores > BUT	[95]
	Three-dimensional OCT and two-dimensional infrared meibography findings not always consistent	[262]
	Observation of the upper eyelid showed little differences between examiners	[259]
	Sensitivity and specificity on using meibograde for MGD diagnosis were 96.7% and 85%, respectively	[196]
	Reproducibility likely with almost no difference between evaluators and between evaluations.	[253]
	The Oculus Keratograph 5M could be used to measure automatically; however, no results consistent with conventional models obtained.	[222]

* Studies on upper eyelid, † studies on lower eyelid, ‡ studies that considered overall MG score

ADDE, aqueous–deficient dry eye; AUC, Area Under the Curve; BUT: break-up time of tear film; DE, dry eye; MG, meibomian gland; MGD, meibomian gland dysfunction; NIBUT, noninvasive BUT; OCT, Optical Coherence Tomography; OSDI, Ocular Surface Disease Index.

The association of meibomian gland dropout and BUT is reported in some studies [120, 207, 257–259] while others report no association [222, 260]. In addition, the loss of meibomian gland structure is associated with increases in subjective symptoms [196, 248, 261], fluorescein staining scores [196, 207, 260], Schirmer values [196, 207], tear evaporation rates [260], and alterations in expressed meibum quality and quantity [196, 244, 257]. On the other hand, some report that there is no association between the loss in meibomian gland structure and subjective symptoms [222,

259, 260], tear Schirmer value [222, 260], and meibomian gland secretion quality [260]. Furthermore, Lin et al. [231] describe the relationship between meibomian gland tortuosity as being related to the severity of anatomical abnormalities at the eyelid margin, meibomian gland dropout by meiboscores, and the meibum expressibility score. Liang et al. [252] state that the length of the meibomian glands correlated with the subjective symptoms and the width of meibomian glands with BUT. Daniel et al. [229] examined the relationship between ocular surface findings and tear function using meibography findings as a comprehensive score. They indicate that although there is no relationship with the intensity of symptoms, both the upper and lower eyelids have an association with the corneal staining score. In addition, the overall score of the upper eyelid was related to BUT and Schirmer values, but not that of the lower eyelid, suggesting more significant findings in the upper eyelid than in the lower eyelid. Dogan et al. [259] recommend an upper eyelid examination because the matching of the analysis results between the participants can be obtained in a more meaningful manner in the upper eyelid.

3. Diagnostic ability of meibography in MGD

Adil et al. [196] show that the sensitivity of the diagnostic ability of meibography findings was 96.7% and the specificity, 85%. Arita et al. [95] report meibography findings to be effective in diagnosing MGD; they rated the efficiency of the diagnostic criteria to be in the following order: subjective symptoms, abnormal eyelid margins, and meibomian gland structure loss by meiboscores.

Problems and Biases It should be noted that the diagnosis of MGD and the criteria for patient recruitment are not consistent among the studies. Many used the three criteria of subjective symptoms, anatomical abnormalities of the eyelid margin (abnormalities of the meibomian gland orifice and vascularity), and meibum expressibility as indicators; but the criteria were not always uniform. Different meibographs were used in the studies. Images obtained do not necessarily match due to differences in the equipment [222, 262, 263]. Especially when performing semi-quantitative analysis, matching and reproducibility among the participants become an issue [253, 263]. There is no clear conclusion as to what histological changes are reflected in the meibomian gland dropout in the meibography. Among the studies that report these findings, one used IVCM to observe the glandular structure [98]. In one, glandular structure was not observed in cadavers [264]. If the meibomian gland structural loss observed in meibography is an irreversible change, the efficacy of this test in determining the therapeutic effect in MGD may be limited.

Future Challenges and Trends It is important to decide which parameters in meibography are useful for diagnosing MGD, determine severity, and select treatment methods. Cut-off values for each device used in the diagnosis of MGD need to be set.

CQ9 Is the observation of tear interference images useful in the diagnosis of MGD?

(Fumika Oya and Shizuka Koh)

Recommendations LLT measured by a tear interference imaging device is reportedly thin in patients with MGD. It may be useful in diagnosing MGD provided the cut-off value is determined through further research. However, LLT is influenced by the tear reservoir volume, changes in the tear lipid layer dynamics and the delay in clearance due to decreased tear reservoir volume. Therefore, precautions in the interpretation are necessary. Whether the interferometric pattern is useful for diagnosing MGD cannot be currently concluded.

Explanation Analysis of tear interference images was developed as a noninvasive technique for evaluating the tear film in studies of dry eye [89, 265–267]. Typically, this involves observing the interference images of the tear lipid layer located on the external tear surface; however, LLT can also be measured depending on the device. Devices currently available in Japan include LipiView II® (Johnson & Johnson Vision), DR-1αTM (Kowa), Keratograph 5M™ (Oculus Optikgeräte GmbH), and idraTM (SBM).

Goto et al. [266] used DR-1™ (old model of DR-1α™) to report for the first time that LLT was significantly reduced in eyes with MGD compared with healthy eyes. Eom et al. [234] report that LLT significantly thinner in eyes with MGD compared with healthy eyes using LipiView® (older version of LipiViewII®), and that LLT decreased with the increase in the extent of meibomian gland dropout. Finis et al. [268] report a significant positive correlation between LLT measured using LipiView® and the number of expressible meibomian glands in a retrospective study on dry eye. When the cut-off value of LLT of ≤75 nm was considered, sensitivity of MGD detection was 65.8%, and specificity was 63.4%.

Nonetheless, Arita et al. [255] classified tear interferometric patterns observed in DR-1α™ into pearl-like appearance (monotonous gray interferometric fringe) suggested to apply to healthy eyes, Jupiter-like appearance (multicolored interferometric fringe) for ADDE, and crystal-like appearance (grayish amorphous interferometric fringe) for evaporative dry eye (including MGD).

As mentioned above, observation studies [234, 266], report that LLT in patients with MGD measured by

analyzing the tear interference image is thinner than in normal eyes. The number of published articles is small, and the validity of the cut-off value [268] needs to be further investigated. However, it may be useful for diagnosing MGD. Only a single classification of interferometric pattern on tear interference images [255] is reported, and hence, its usefulness in MGD diagnosis cannot be currently concluded.

Problems and Biases All related articles were observational studies [234, 255, 266, 268]. In one study [255], the participants were all employees of the same company; this may have influenced the direction of the discussion. Focus areas were limited in the studies and differences in race and region of residence were not considered. The evaluation and diagnostic criteria of MGD and/or accompanying dry eye were not uniform, and the equipment used varied. Serious indirectness in the study population and outcome measurements were identified. Additionally, LLT changes under the influence of the tear fluid reservoir, the changes in the tear lipid layer dynamics and the delay in clearance due to decrease in the tear fluid reservoir. Therefore, precautions in interpretation are necessary [89, 265, 269].

Dedicated measuring equipment is required to analyze tear interference images, and only a limited number of medical institutions can perform this test. Although this technique has the advantage of being noninvasive, there are currently no criteria for diagnosing MGD with this technique. Therefore, it is not beneficial in MGD diagnosis. Furthermore, some devices allow the observation of only the inferior portions of the cornea and do not allow evaluation of the whole cornea; this is a disadvantage.

Future Challenges and Trends Analysis of tear interference images enables estimation of impairments in the tear lipid layer. This may aid the diagnosis of MGD. However, many areas lack clarity, making further research necessary. Since commercially available tear interference imaging devices are expensive and difficult to handle in general examinations, some researchers are attempting to build applicable devices themselves

CQ10 Is tear evaporation measurement useful in the diagnosis of MGD?

(Jun Shimazaki and Yasuhito Hayashi)

Recommendations The amount of tear evaporation may reflect the function of the meibomian gland. Many reports have found an increase in the amount of evaporation in oMGD in comparison with healthy individuals. However, measuring devices and conditions are not standardized and not commonly used in clinical practice. Hence, tear evaporation measurement cannot be recommended for the diagnosis of MGD at present.

Explanation It is speculated that the lacrimal lipid layer secreted from the meibomian glands suppresses tear evaporation. Therefore, the amount of tear evaporation may reflect the function of the meibomian glands; previous studies have focused on this aspect [84, 85]. The principle behind the measurement is to prepare a closed space in the ocular area, inject dry air with a constant humidity, have patients blink at regular intervals, measure the increase in humidity in the chamber over time, and calculate the weight of evaporated water per unit eye surface area and per unit time as the amount of evaporation. The amount of evaporation on eyelid closing is set at 0, and $g/cm^2/sec$ is often used as the measurement unit.

Our SR identified eight articles on the measurement of tear evaporation in oMGD [12, 256, 270–275]. The majority of these studies used healthy individuals as controls and indicate a significant increase in tear evaporation in oMGD. For example, Goto et al. [271] report a significant increase ($5.8 \pm 2.7x10^{-7} g/cm^2/$ sec in patients with oMGD; $4.1 \pm 1.4x10^{-7} g/cm^2/sec$ in healthy individuals) using a ventilated chamber system and a microbalance sensor ($p = 0.0008$). On the other hand, McCulley et al. [256] report that in patients with dry eye having MGD, there was no significant increase in tear evaporation compared with patients having dry eye alone, and the evaporation amount fluctuated depending on the ambient humidity. However, this study did not measure evaporation in patients with MGD alone. McCann et al. [273] conducted measurements in healthy individuals and patients with blepharitis (defined as significantly lower stability of thin-film interference compared with healthy controls, significant loss of meibomian glands, and significant increase in viscosity and turbidity of secretions). They report a significantly higher tear evaporation rates in patients with blepharitis ($46.3 \pm 22.9 g/m^2/hr$) compared with $18.0 \pm 10.7 g/m^2/hr$ in healthy controls ($p < 0.001$); with a cutoff value of $32.3 g/m^2/hr$, the evaporation measurement showed 73% sensitivity and 86% specificity. Khanal et al. [272] also studied various parameters that distinguish between ADDE and evaporative dry eye, and report significantly different tear turnover rate and tear evaporation amounts between the two groups. However, the amount of tear evaporation had a large overlap between the two groups, and the diagnostic sensitivity was only 77% and the specificity 55%.

Problems and Biases The lack of a uniform diagnostic criteria for MGD in the studies makes it difficult to compare the studies. Moreover, the evaluation methods use for individual parameters are also different among the studies. No standard equipment has been used for measuring the amount of evaporation, with different methods being used in each

study. The units used to express the evaporation amounts also tended to differ in the studies, and the cut-off values separating normal and abnormal values are unclear. Furthermore, there is no consensus regarding the changes in the amount of tear evaporation in ADDE, and it is difficult to say that the amount of tear evaporation reflects only the function of the meibomian glands.

Future Challenges and Trends Tear evaporation measurement is noninvasive with no patient burden, and may be a useful tool for diagnosing oMGD, and determine its severity and the effects of treatment. To achieve this, it is necessary to popularize commercially available measuring devices. Additionally, to improve the diagnostic accuracy of this technique in MGD, future studies should focus on identifying the cut-off value in tear evaporation of MGD and other related disorders.

CQ11 Is IVCM useful in diagnosing MGD?

(Minako Kaido and Yasuto Hayashi)

Recommendations IVCM is a device that can observe meibomian glandular tissues at the cellular level. Since IVCM shows characteristic findings in MGD, it has often been reported to be effective in diagnosing MGD. However, all related studies to date have been observational. It is pointed out that it may not be clear whether the structure seen as the acini of the meibomian glands is actually correctly identified. Therefore, it is necessary to reconfirm that the structure observed in IVCM is the acini of the meibomian gland. Since IVCM requires contact with the epithelium, it is necessary to consider the disadvantages to the patient of invasiveness and burden due to prolonged examination. Currently, it is not possible to determine whether IVCM can be recommended.

Explanation The application of IVCM to MGD diagnosis started with the observation of the tear lipid layer [276]; however, images obtained were coarse and the features unclear. There have been no follow-up studies. Subsequently, the equipment was improved and the Heidelberg Retina Tomograph II - Rostock Cornea Module (HRT II RCM, Heidelberg Engineering GmbH) was introduced. Since then, it has been used in specialized corneal clinics to observe the cornea and conjunctiva at the cellular level [99, 277].

In addition to the acinar density of the meibomian gland, longest and shortest acinar diameter, inflammatory cell density, cell density of the superficial epithelium and basal epithelium of the eyelid margin, meibomian gland orifices, and color tones of the meibum, acinar space, and acinar wall can be evaluated by IVCM. Table 17 shows the findings specific for MGD. Matsumoto et al. [278] show a significant decrease in acinar density and a significant increase in acinar diameter in MGD compared with the normal eye. These were reportedly associated with a decrease in lipid expression from the meibomian gland orifices [278]. Additionally, Ibrahim et al. [279] show that meibomian gland acinar density, shortest and longest acinar diameter, and inflammatory cell density were significantly associated with BUT, fluorescein staining score, Rose Bengal staining, decreased lipid expression from the meibomian gland orifices, meibomian gland dropout, and ocular surface tear evaporation rate. In addition, they show that acinar density, shortest and longest acinar diameter, and inflammatory cell density were useful for MGD diagnosis. When the acinar density was 70 glands/mm^2, longest diameter of the acini was 65 µm, shortest diameter was 25 µm, and inflammatory cell density was 300 cells /mm^2; the sensitivity and specificity were 81% and 81%, 90% and 81%, 86% and 96%, and 100% and 100%, respectively [279]. Villani et al. [280] obtained similar results in comparison with the normal eye. They additionally identified enlarged meibomian gland orifices and high secretion reflectivity of the color tone of the meibum as well as of acinar space; however, the secretion reflectivity of the acinar space color tone was lower in MGD than in SS. They suggest that the enlargement of the meibomian gland orifice and enhancement of the secretion reflectivity of the meibum color tone may be due to increased viscosity of the meibum due to glandular ductal obstruction.

Attempts at severity classification by MGD symptoms has shown a negative correlation between symptom intensity and confocal microscopy parameters. Specifically, the stronger the symptoms, the smaller the acinar density, acinar area, and longest and shortest diameter of the acini, and the stronger the acinar space fibrosis and loss of meibomian gland structure. In addition, the acinar area and the longest and shortest diameter of the acini are believed to be small because of the strong fibrosis of the glandular space and loss of meibomian gland structure [103]; detailed verification is still necessary. Further,

Table 17 Specific findings on *in vivo* confocal microscopy in meibomian gland dysfunction

No	Finding
1	Enlarged acini (longest and shortest diameter) of the meibomian gland
2	Reduced acinar density
3	Increase inflammatory cells in the acini, with an uneven color tone
4	Fibrosis and increased inflammatory cells in the acinar space of the meibomian gland
5	Enlargement of the meibomian gland orifice

a study on severity classification based on IVCM findings reports that a significant relationship of severity exists with symptoms, ocular surface tear evaporation rate, tear secretion, BUT, MGX, and meibography findings [98].

A study involving conjunctival immune cells identified more intraepithelial immune cells, intraglandular immune cells, and periglandular immune cells in MGD compared with normal eyes [281]. On observing corneal nerves, it is reported that the stronger the symptoms, the lower the subbasal nerve density, and the higher the reflectivity [99].

Problems and Biases Zhou et al. [282] studied the oval epithelial structure observed on IVCM of the upper eyelids in cadavers. Through laser scanning microscopy of the frozen section of the upper eyelids, they show that the oval epithelial structure corresponds to the reticular protuberance (intermastoid process) present at the dermis-epidermal junction, rather than the acini of the meibomian glands. The meibomian gland acini is located 300 µm or deeper, measured from the epithelium. Because the HRT II RCM can observe to a depth of up to 100 µm, the meibomian gland acini is not observable using the HRT II RCM [282]. The cross-sectional area of the acini in HRT II RCM was more than one order of magnitude larger than the one observed by laser scanning microscopy, indicating that the studies that report observations of the meibomian gland acini were incorrect. However, since IVCM is performed in patients by compressing the eyelid conjunctiva, we cannot say with absolute certainty that the meibomian gland acini is not observable. Other problems include the expensive equipment and the skills required for performing the procedure, making IVCM difficult to use widely for MGD diagnostics.

Future Challenges and Trends Although most studies report on the meibomian glands in the lower eyelid, the histological differences between the upper and the lower eyelids in MGD should be elucidated, and the association between subjective symptoms and ocular surface findings should be examined.

Since the HRT II RCM allows only observation of the reflection of the laser light at 670 nm, the examiner makes a record of any image that may resemble a familiar structure. Since the composition of the imaged object is not always understood, additional external evidence is necessary to support the identity of the observed objects. It is imperative to reconfirm that the structure reported in the conventional IVCM observation as the acini of the meibomian gland are indeed so. However, the current IVCM does not reach sufficient depth to capture the full extent of the meibomian gland. To deepen the observation depth, the development of a device that uses a near-infrared laser is also needed [282].

CQ12 Is measuring tear film osmolality useful in the diagnosis of MGD?

(Yasuhito Hayashi and Jun Shimazaki)

Recommendations Tear film osmolality may reflect the function of the lipid layer. Some studies report effectiveness while others report ineffectiveness in diagnosing MGD. Although performing the test is not discouraged because of its minimally invasive nature, its clinical relevance is limited at present.

Explanation Elevated tear film osmolality has been widely used as an objective sign in dry eye, especially in Europe and the United States. There are reports that it is the most useful of all dry eye test assessment methods, but there are also reports [283, 284] that issues regarding reproducibility exist. In MGD, the tear film osmolality may increase due to the increased occurrence of evaporative dry eye. In the past, tear film osmolality measurements were limited to research purposes due to the need for laboratory-level equipment. However, since the launch of the TearLab® Osmolality System (TearLab Corporation), it has become widely used because of ease in measurement using small tear samples. Most of the articles we reviewed used the TearLab® system.

Contradictory findings have been obtained in studies on the usefulness of tear film osmolality measurement in the diagnosis of MGD. Rico-Del-Viejo et al. [260] report that osmolality increased when the proportion of the area of meibomian gland loss exceeded 50% on infrared meibography. Xiao et al. [220] divided patients with MGD into four groups based on meibum expression, meibum quality, and degree of meibomian gland loss on meibography images. They found that osmolality was significantly increased in the low-delivery MGD groups (low-delivery and oMGD) compared with high-delivery MGD groups (hypersecretory and nonobvious MGD). Furthermore, tear LLT and tear osmolality were significantly related. Diagnosing MGD with a cutoff value of 308 mOsm/L tear osmolality had 68.6% sensitivity and 55.2% specificity [227]; moreover, this was reportedly more useful than the OSDI in diagnosing MGD [285].

On the other hand, Giannaccare et al. [192] conducted a study on patients with MGD having subjective symptoms (OSDI≥ 13) and at least one clinical sign of MGD, such as terminal ductal obstruction, plugging of the meibomian glands, turbid secretions, inflammation and swelling of the eyelid margins, or poor meibum secretions. They compared this group with sex and age-matched healthy controls and report that there was no significant difference in the mean value of tear osmolality between the two groups. Adil et al. [196] contradicted the results of Rico-Del-Viejo et al. [260] and note that there was no relationship between the rate of

meibomian gland loss and tear osmolality [196, 260]. Furthermore, Randon et al. [98] studied the meibomian glands with confocal microscopy and report no significant relationship between the stage of MGD and tear osmolality.

Measurement of tear osmolality by TearLab ® is minimally invasive and can be performed in a short time; therefore, patients are not inconvenienced. However, the current system costs about US$10 per eye, and since it is not covered by JHI, there is a financial burden on the patients. Therefore, the test is not used broadly in Japan at present; also, this test is not easy to administer.

Problems and Biases Literature regarding the usefulness of tear osmolality measurements in MGD diagnosis shows mixed results, making it impossible to recommend it. A major reason for these mixed results lies in the inconsistency between studies on diagnostic criteria of MGD, based on which patients have been recruited. Many studies have used the following three abnormalities as criteria: subjective symptoms, anatomical abnormalities of the eyelid margin (abnormalities of the meibomian gland orifice and eyelid margin vascularity), and difficulty in expressing the meibum; however, the criteria are not always consistent. Selection bias may have been present in all studies that were reviewed.

Future Challenges and Trends There are no conclusions regarding the usefulness of tear osmolality measurements in the diagnosis of dry eye. Since the increase in tear osmolality reflects both the decrease in tear turnover and the increase in evaporation [272], it is impossible to evaluate the function of evaporation suppression by the tear lipid layer in MGD patients using tear osmolality. Barna et al. [286] report that tear osmolality increases when the tear clearance decreases in MGD, and it may be necessary to reconsider the idea that the increase in tear osmolality in MGD indicates a decrease in the function of evaporation of the tear lipid layer. Conversely, its usefulness may be enhanced by future improvements in the equipment usede to measure tear osmolality.

CQ13 Is lipid quantification on eyelid margins useful in the diagnosis of MGD?

(Yasuhito Hayashi and Fumika Oya)

Recommendations Lipid quantification on the eyelid margins could be essential in the diagnosis of MGD considering the pathophysiology of the disease; however, it is difficult to determine whether lipid quantification is useful in diagnosing MGD. Eyelid margin lipid quantification has few disadvantages for patients due to the minimally invasive technique, and it allows relatively reproducible semi-quantitative measurements. However, as the cut-off value has not been determined, there is little benefit in performing the test in the diagnosis of MGD.

Explanation Meibometry involves eyelid margins' lipid quantification devised as a method that applies sebum measurements [287, 288]. Meibometer® (MB550 and the successor MB560) is a commercially available medical device for measuring lipid amounts on the eyelid margin. The principle behind the instrument is to increase transparency by penetrating lipids into the material of translucent plastic tape. In the MB550, the test value is presented at the 690 nm laser transmittance of the most transparent part. Yokoi et al. [269] measured the resting amount of lipids on the eyelid margin (casual oil level) in patients with MGD, patients with ADDE, and healthy controls, and report that casual oil levels were significantly reduced in patients with MGD compared with controls, and that these levels tended to increase in ADDE. To better measure casual oil levels, a couple of improvements have been made. First, the method of collecting lipids has been improved so that the meibum is not expressed by eyelid compression. Second, measurements using all the lipids attached to the plastic tape are made possible using a handheld scanner and a computer equipped with densitometry analysis software [269]. Using this method, we can avoid the overestimation of the quantity secreted due to the uneven secretion often present in patients with MGD. Komuro et al. [289] also measured casual oil levels in patients with oMGD, patients with seborrheic MGD, and healthy controls using a Meibometer®. They report that casual oil levels decreased in patients with oMGD and increased in patients with seborrheic MGD. Ashraf et al. [290] measured casual oil levels in patients with MGD and healthy controls using SEBUTAPE® (Evalulab) and Fourier transform infrared spectroscopy for sebum secretion. They report that casual oil levels in patients with MGD patients were twice as high as the controls.

The differences in the results of Yokoi et al. [269], Komuro et al. [289] and Ashraf et al. [290] may be related to differences in the sampling methods of lipids and differences in the measurement methods of the sampled lipids. Additionally, the sex and age of the patients with MGD and controls were not matched in the study by Ashraf et al. [290] and this probably influenced the results. The amounts of lipids on the eyelid margin are reportedly affected by age/sex [287], menstrual cycle [291], and eyelid temperature [292], and detailed data analysis based on these factors is necessary.

The number of studies comparing the amounts of lipids on the eyelid margins in patients with MGD and controls is small; they are all observational with small sample sizes [269, 289, 290]. The quantification of lipid secretions is considered essential in discussing the dysfunction of

the meibomian glands, but it is not possible to determine whether lipid quantification is useful in the diagnosis of MGD at this time.

Problems and Biases The studies [269, 289, 290] were unmasked, old, and without any records on COI. In the study of Ashraf et al. [290], the allocation of patients and controls was inappropriate, and, therefore, significant selection bias existed. In addition, serious inconsistencies were observed in the outcomes reported by Yokoi et al. [269], Komuro et al. [289], and Ashraf et al. [290].

The measurement of lipid amounts on the eyelid margins using the Meibometer ® has no JHI's coverage and it is not prevalent in general hospitals, posing problems of accessibility. Although it is reported to be relatively reproducible [293], it is not widespread. Since it is a noninvasive test, there is little disadvantage to the patient; nonetheless, the cut-off values for the Meibometer® testing are not specified, and therefore, there is little benefit in performing the assessment.

Future Challenges and Trends In patients with MGD, lipid quantification on the eyelid margins using a Meibometer® have shown a significant decrease in lipid amounts compared with a control group without MGD [269, 289]. If cut-off values for the Meibometer® are determined according to age and sex by future research with large samples and consistent techniques, the assessment may be useful in the diagnosis of MGD. Furthermore, it is believed that the utilization values of the device could be improved if a system can be developed to simultaneously analyze all the components of the collected meibomian gland secretions [290].

CQ14 Is a biochemical analysis of the meibomian gland secretions useful in the diagnosis of MGD?

(Masahiko Yamaguchi and Fumika Oya)

Recommendations Various analyses have been performed to identify lipid components and structures that alter the properties of the meibum in patients with MGD. However, since related literature is sporadic and markers and analysis methods' specific to MGD have not been established, biochemical analysis of the meibum is not useful in the diagnosis of MGD. Considering the time and cost burden of lipid analysis, poor access to tests, and burden on patients when sampling, biochemical analysis poses disadvantages to patients. Although clinical application of meibum lipid analysis is not practical at present, further research on the topic would be beneficial to understand the pathophysiology of MGD and establish new treatment methods.

Explanation The meibum is composed of non-polar and polar lipids, which, in turn, are composed of various components such as wax esters, cholesterol esters, diesters, free cholesterol, free fatty acids, diglycerides, triglycerides, sphingolipids, phospholipids, and (O-acyl) ω-hydroxy fatty acids [294]. In MGD, the color and viscosity of the meibum are altered, and various biochemical analyses have been conducted to study the changes in lipid composition and lipid structure that result in these changes.

Borchman et al. [295] used NMR spectroscopy to demonstrate that the cholesterol ester/wax ester ratios were significantly lower in patients with MGD than in healthy individuals; additionally, the quantity of cholesterol ester was found to be low in patients with MGD [295, 296]. However, age-specific surveys report that cholesterol ester increases due to aging and that the cholesterol ester /wax ester ratios are almost the same in patients with MGD and newborns, suggesting that the quantity of cholesterol ester is not the only factor involved in changing the properties of the meibum [296].

Arita et al. [23] used liquid chromatography to investigate changes in the composition of free fatty acids and suggest that both white and yellow meibum contain many unsaturated fatty acids. Additionally, it is reported that the amount of linoleic acid among the free fatty acids correlates with the severity of clinical findings in MGD, such as eyelid margin vascularity and plugging [297]. Since the proportion of free fatty acids among the lipid components that make up the meibum is very small, it is not certain to what extent the changes in the composition of free fatty acids are related to the changes in the properties of the meibum in MGD.

Shine et al. [298] used gas chromatography to show that unsaturated fatty acids comprise only a small percentage of the meibum in MGD, while in seborrheic MGD this percentage was higher. They report that the percentage of unsaturated fatty acids was related to the viscosity of the meibum. Later, Borchman et al. [299] used infrared spectroscopy and indicate that the meibum in MGD had fewer unsaturated fatty acids and more saturated fatty acids compared with healthy individuals. However, Joffre et al. [300] report that gas chromatography revealed significantly less saturated fatty acids in patients with MGD than in healthy individuals, contradicting the two previous studies. Differences in these results need to be further verified.

Additionally, using gas chromatography, Joffre et al. [300] report that branched-chain hydrocarbons were more abundant in the meibum of patients with MGD than in healthy individuals. Borchman et al. [50] report that using NMR spectroscopy, the proportion of linear hydrocarbons was lower in patients with MGD than in healthy controls, while the proportion of iso-branched hydrocarbons was higher. However, using infrared spectroscopy, Borchman et al. [299] demonstrate that branched-chain hydrocarbons were less common in patients with MGD than in healthy

individuals. These results are also inconsistent and require future verification.

Regarding the composition of the polar lipids in the meibum, Shine et al. [301, 302], in investigations using liquid chromatography and gas chromatography, found that only the phospholipids and sphingolipids contained unbranched unsaturated fatty acids; hydroxy fatty acids of sphingolipids were low and there were many phosphatidylethanolamine derivatives in patients with MGD. Paranjpe et al. [303] analyzed sphingolipids by liquid chromatography and suggest that the amounts of ceramide, hexosyl-ceramide, and sphingosine 1-phosphate are low in poor quality meibum, whereas sphingomyelin and sphingosine are high.

Shine et al. [304] examined the composition of triglycerides in meibum using gas chromatography and report that patients with MGD have more unbranched saturated C20-28 fatty acids compared with healthy individuals. In an analysis using Raman spectroscopy, Oshima et al. [305] determined that the components containing carotenoid-like bands were significantly lower in patients with MGD. Butovich et al. [306] used a hot stage cross-polarized light microscopy and an immunohistochemical approach and argue that protein-like substances are increased in the meibum of patients with MGD, and that this protein-like substance may increase the melting point and change the properties of the meibum.

As mentioned above, various analytical methods have been used to investigate the lipid components of the meibum; nonetheless, the markers specific to MGD diagnosis have not yet been identified. Since reports using the same methods, approaches are limited and sample sizes were small, and, therefore, results are inconsistent.

Problems and Biases All the studies comparing the meibum of patients with MGD and healthy individuals were cross-sectional in nature. Diagnostic methods for MGDs of interest varied among the studies that used the Japanese diagnostic criteria [23, 297], Foulks and Bron diagnostic criteria [50, 295, 296, 299, 305], unique diagnostic criteria [298, 300–304], and unknown [306]. Serious inconsistencies were identified in participants' selection. Various lipid analysis methods have been used including NMR spectroscopy [50, 295, 296], infrared spectroscopy [299], gas chromatography [298, 300, 301, 304], liquid chromatography [23, 297, 302, 303], Raman spectroscopy [305], and hot stage cross-polarized light microscopy with immunohistochemical approach [306]. These variations among the studies make it difficult to directly compare the obtained results. There are many sporadic studies from the same facility on the analyzed lipid components, and inconsistent results were obtained regarding the components analyzed at multiple facilities (percentage of unsaturated fatty acids [298–300], percentage of branched hydrocarbon [50, 299, 300]).

Lipid analysis using any methods is time-consuming and expensive, and can only be performed at specialized facilities. Therefore, currently, it is hard to apply meibum lipid analysis in a clinical setting as a diagnostic method. In addition, a large amount of meibum samples is required for the identification of lipids, and it is necessary to strongly compress the eyelids using a conformer or swab. These can be detrimental to the patient as it can result in severe discomfort.

Future Challenges and Trends The properties of the meibum are clearly different in patients with MGD than in healthy individuals. It is essential to identify the lipid components that are a product of this change to enhance the depth of understanding regarding the pathophysiology of MGD and establish new treatment methods. There is hope that MGD diagnosis can be simplified if research progresses in the future to discover the specific markers for MGD and develop kits that can be easily used in clinical settings.

CQ15 Is measuring inflammatory biomarkers in tears useful in the diagnosis of MGD?

(Yukiko Nagahara and Masaki Fukui)

Recommendations Measurement of inflammatory biomarkers in tears for the diagnosis of MGD is not currently useful, although it sheds light on the possibility of an adjunctive diagnostic method.

Explanation Seven studies were identified that measured inflammatory biomarkers in the tears of patients with MGD and considered their usefulness in MGD diagnosis [307–313]. Of these, two studies [310, 311] discovered only single biomarkers. These were Acidic Mammalian Chitinase [310] and IL-17 [311]. The biomarkers considered in the other five studies included TNF-α [307, 309, 312, 313], IFN-γ [309, 312, 313], EGF [307, 309, 312], Lactoferrin [308], MMP-9 [308], MIP-1α [309, 312], RANTES [309], IL-1α [307–309, 312], IL-1β [308, 309, 312], IL-1RA [308], IL-2 [313], IL-4 [313], IL-6 [309, 312, 313], IL-8 [309, 312], IL-10 [309, 312, 313], IL-12 [309], IL-12p70 [312], IL-13 [309], and IL-17α [313].

Table 18 shows a summary of the results. The participants in the studies included patients with MGD and patients with MGD having dry eye symptoms. The comparison groups also varied; different studies considered different groups such as healthy controls, patients with SS, patients with dry eye without MGD, and patients with MGD without dry eye symptoms. That could have been due to the fact that the biomarkers being examined have not yielded consistent results. For example, on assessing TNF-α, one study reports no significant difference [307], while two other studies identified an increase in MGD

Table 18 Studies on inflammatory biomarkers in tears in meibomian gland dysfunction

	Barton et al. [307]	Solomon et al. [308]	Lam et al. [309]	Zhao et al. [312]	Li et al. [313]	Musumeci et al. [310]	Kang et al. [311]
Comparison	MGD vs Normal	MGD vs SS vs Normal	DES + MGD vs DES - MGD vs Normal	MGD vs SS vs Normal	DES + MGD vs DES - MGD	MGD vs SS vs Normal	MGD vs DES vs Normal
TNF-α	No significant difference		DES + MGD > Normal, DES - MGD > Normal	SS > MGD > Normal	DES + MGD > DES - MGD		
IFN-γ			No significant difference	MGD > Normal	No significant difference		
EGF	MGD > Normal		DES - MGD < Normal	No significant difference			
Lactoferrin		SS > Normal and MGD					
MMP-9		MGD > Normal, SS > Normal					
MIP-1α			No significant difference	SS > MGD and Normal			
RANTES			DES + MGD > Normal and DES (-) MGD				
AMCase						MGD > SS > Normal	
IL-1α	MGD > Normal	MGD > Normal, SS > Normal	No significant difference	SS > Normal			
IL-1β		MGD > Normal, SS > normal	No significant difference	MGD > normal			
IL-1RA		No significant difference					
IL-2					No significant difference		
IL-4					No significant difference		
IL-6			DES + MGD > Normal, DES - MGD > Normal	MGD and SS > normal	DES + MGD > DES - MGD		
IL-8			DES + MGD > Normal, DES - MGD > Normal	SS > MGD > Normal			
IL-10			No significant difference	No significant difference	No significant difference		
IL-12			DES + MGD > DES - MGD				
IL-12p70				MGD and SS > Normal			
IL-13			No significant difference				
IL-17							MGD > Normal, DES > Normal
IL-17α					No significant difference		

AMCase, acidic mammalian chitinase; DES, dry eye syndrome; EGF, epidermal growth factor; IFN, interferon; IL, interleukin; MGD, meibomian gland dysfunction; MIP, macrophage inflammatory protein; MMP, matrix metalloproteinase; RANTES, regulated on activation, normal T cell expressed and secreted; SS, Sjögren's syndrome; TNF, tumor necrosis factor.

[309, 313]. TNF-α reportedly increased in dry eye, regardless of the presence or absence of MGD; moreover, significantly higher increases were seen in SS than in MGD [312]. Therefore, results were inconsistent and not specific for MGD. Similarly, even for other biomarkers no findings that could lead to the implementation in MGD diagnosis were obtained. Specifically, no single biomarker has been identified that is significantly different in patients with MGD in comparison with either healthy individuals or patients with dry eye.

Acidic Mammalian Chitinase is a Th2-dependent cytokines, activated by IL-13 and involved in allergic diseases. According to Musumeci et al. [310], the protein concentration in tears was significantly higher in MGD compared with SS and healthy individuals. However, such a finding on Acidic Mammalian Chitinase is only available in a single report, whereas in another study [309] no increase in related IL-13 has been observed; therefore, the evidence is insufficient.

In addition to inflammatory cytokines, lipid analysis [314–317] had recently identified an increase in lacrimal contents; moreover, the composition of the lipids contained in the lacrimal fluid shows that it is possible to distinguish between MGD, dry eye, and normal eyes [315].

Problems and Biases Few reports have examined biomarkers in tears that are specific for MGD. The results cannot be compared because the target diseases do not match. The two studies that assessed a single biomarker each may have publication bias. Furthermore, the numbers of examined subjects were small and the results do not provide much evidence.

Future Challenges and Trends Studies on the biomarkers in tears specific for MGD may increase in the future. It would be useful to show a relationship between the severity of MGD and certain biomarkers, identify the cut-off values using receiver operating characteristic curve, and show which biomarkers are useful for diagnosis and what are their diagnostic reference values in MGD. If it is difficult to diagnose MGD with a single biomarker, we hope that combinations specific to MGD may be identified. As shown in the explanation, the possibility of diagnosing MGD has been shown by the constitutive analysis of lipid molecules by lipidomics. Yet the evidence is not high; therefore, future accumulation of data is required.

CQ16 Are bacteriological tests useful in the diagnosis of MGD?

(Yukiko Nagahara and Masaki Fukui)

Recommendation Bacteriological tests performed for the diagnosis of MGD include bacteriological culture and genome sequencing using polymerase chain reaction. However, neither of these tests could obtain any results characteristic to MGD. Therefore, at present, bacteriological tests are not useful for diagnosing MGD.

Explanation Based on previous studies, bacteriological examination has been accepted for blepharitis and rosacea, and some of these concepts seem to match MGD. We identified seven studies that combined bacteriological tests with the diagnosis of MGD and provide clarifications of diagnostic criteria.

Studies on bacteriological examination in MGD may be broadly divided into two types: those using bacteriological culture [69, 318] and genome sequencing [70, 319–322]. Sample collection methods vary in these studies; methods include scraping the eyelid margins, eyelid skin, conjunctival sac, and caruncle, and collection of meibum. No difference in the culture results of eyelid margin samples before and after meibum expression is reported in one study [318]. Another study reports lower positive culture of conjunctival sac samples compared with the meibum [69], while a different study identified no difference in the type of bacteria between the meibum and eyelid margins' skin samples [321]. The test results may differ depending on the location of the samples.

In bacteriological culture, the bacteria with the highest detection rate in both MGD and non-MGD were coagulase-negative *Staphylococcus* [69, 318, 319, 321]; however, they cannot be considered characteristic to MGD as they were detected in both the presence and absence of MGD. The bacteria reported to have a significant difference in the positivity rate both in the presence and in the absence of MGD are *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The positivity rate of *Staphylococcus aureus* reportedly decreases with the severity of MGD [318], and *Pseudomonas aeruginosa* positivity decreases in MGD [321]. However, other studies did not find significant differences with these bacteria, whichm makes a conclusion difficult (Table 19).

The composition of the flora is studied using genome sequencing. Herein, a brief explanation of the test is provided for a better understanding. There are two types of metagenomic analyses: whole genome metagenomic analysis for the entire genome of the bacterial flora, and *16S rRNA* metagenomic analysis for the *16S rRNA* gene. However, 16S rRNA metagenomic analysis is more common because of the analysis unit price. The *16S rRNA* metagenomic analysis extracts DNA from specimen samples and amplifies a portion of the *16S rRNA* gene using polymerase chain reaction. The base sequence data is analysed by a computer, and the results are visualized and displayed using a stacked bar chart[a.] Dong et al. [70] show phylum and genera. Furthermore, they examined bacteria that are significantly different

Table 19 Positivity rate of ocular surface bacterial cultures in patients with MGD

Study	Variable assessed	Sampling site	Detection method	Study groups	C-NS	*S. aureus*	*P. acnes*	*Corynebacterium*	*Pseudomonas* sp.	*Streptococcus*	None
Watters et al. [318]	Percentage of cases	Lower eyelid margin	Culture	Normal	64.1	48.7*	25.6	-	2.6	0	7.7
				Mild MGD	58.3	20.8*	29.2	-	0	4.2	20.8
				Moderate–severe MGD	63.6	18.2*	45.5	-	0	3	15.2
Zhang et al. [69]	Percentage of aerobic bacteria detected	Meibum	Aerobic culture	Control	48.6	0	-	6.3	0	0	-
				MGD	64.1	5.1	-	14.3	0	0	-
		Conjunctival sac		Control	71.4	0	-	6.6	0	2.4	-
				MGD	59.6	3.7	-	2.4	0.7	0.7	-
	Percentage of anaerobic organisms detected	Meibum	Anaerobic bacterial culture	Control	-	-	66.7	-	-	-	-
				MGD	-	-	75	-	-	-	-
		conjunctival sac		Control	-	-	88.9	-	-	-	-
				MGD	-	-	75	-	-	-	-
Jiang et al. [319]	Percentage of cases	Meibum	PCR of colonies after culture	Control	39.7	0	-	0*	-	-	53.4
				Mild MGD	62.5	0	-	0*	-	-	37.5
				Moderate MGD	50.9	5.5	-	0*	-	-	41.8
				Severe MGD	57.9	15.8	-	31.6*	-	-	10.5
Zhao et al. [321]	Positivity rate	Meibum	Genome Sequencing	Control	55	< 10	< 10	24.75	91*	< 10	-
				MGD	28	< 10	< 10	33.75	23*	< 10	-

*Significantly different between groups

C-NS, Coagulase-negative *Staphylococcus*; MGD, meibomian gland dysfunction

between the MGD and control groups. Using main coordinate analysis[b], Li et al. [320] show that there was no significant difference in the composition of the bacterial flora with or without MGD, and Dong et al. [70] report that there was no significant difference in the composition of the bacterial flora in non-MGD compared with mild and moderate MGD, while there was a significant difference with severe MGD. Using linear discrimination analysis[c], Li et al. [320] report that *Bacilli, Bacillates,* and *Bacillus pumilus* are common in MGD, and *Bacteroidetes* are common in non-MGD, and Dong et al. [70] indicate that *Staphylococcus* and *Sphingomonas* are common in MGD and *Corynebacterium* are common in non-MGD; however, these findings are not consistent. The findings of Li et al. [320] and Dong et al. [70] are summarized in Table 20.

Of note, a study that used genomic sequencing to analyse the bacterial flora on the ocular surface with or without *Demodex* and MGD suggests the involvement of *Demodex* in bacterial flora changes [322].

[a]Stacked bar chart: A chart created for classifying the bacteria by showing the proportion of each bacterial group.

[b]Main coordinate analysis: A method of considering bacterial flora as a single ecosystem and visualizing the differences in diversity between ecosystems. Three-dimensional diagrams with two or three axes are often presented. Each plot refers to one specimen. The closer the plots are to each other, the more similar the composition of the flora. The further apart the plots are, the more different the composition of the flora.

[c]Linear discrimination analysis: A method to find the boundary that best distinguishes the two groups. This line is called a decision boundary, and the linear discrimination analysis score indicates the extent to which the groups can be distinguished by the decision boundary.

Problems and Biases Few studies have conducted bacteriological tests for MGD; their findings do not indicate that they are effective in the diagnosis of MGD. A simple and direct comparison is difficult because the sites of sample collection and testing methods do not match.

Future Challenges and Trends In bacteriological tests, the culture of the scraped sample cannot detect all the bacteria in the sampled tissue. This is also evident from the large number of bacteria identified on genome sequencing. However, on genome sequencing, the status of the flora is known, but the number of bacteria contained in the flora is not accurately measured.

Ideally, the association of a specific bacterium with a disease is confirmed by initially detecting the bacterium and subsequently setting reference values for positivity and negativity. Unfortunately, the bacteria and flora associated with MGD have not been clearly identified following research using bacteriological culture and genome sequencing. In fact, the bacteriological analysis of MGD and flora by genome sequencing have only just commenced, and the necessary amount of accumulated data is yet to be collected. Additionally, it is necessary to investigate whether each

Table 20 Findings using genomic sequencing of ocular surface bacterial flora in patients with MGD

Studies	Participant characteristics	Sampling site	Stacked bar chart	Primary coordinate analysis	Linear discrimination analysis
Li et al. [320]	Comparison of patients having dry eye with and without MGD	Superior and inferior eyelids, lacrimal caruncle, and conjunctival sac	Not considered	No difference in bacterial flora composition	With MGD > without MGD: *Bacilli*, *Bacillates*, and *Bacillus pumilus* With MGD < without MGD: *Bacteroidetes*
Dong et al. [70]	MGD group versus non-MGD control group	Conjunctival sac of upper eyelid, and eyelid margin	With MGD > without MGD: phylum - *Firmicutes*, *Proteobacteria*, and *Deinococcus–Thermus* genus - *Staphylococcus* and *Sphingomonas*	Significant difference in composition in severe MGD only	With MGD > without MGD: *Staphylococcus* and *Sphingomonas*
			With MGD < without MGD: phylum - *Actinobacteria* genus - *Corynebacterium*		With MGD < without MGD: *Corynebacterium*

MGD, meibomian gland dysfunction

bacterium is directly related to MGD. There are reports of new bacteria being discovered in the meibum [323, 324].

Q17 What are the frequency and characteristics of keratoconjunctival epithelial disorders in MGD and what are the appropriate staining methods?

(Masahiko Yamaguchi and Minako Kaido)

Recommendation Many cases of keratoconjunctival epithelial disorders in MGD are reported; however, it is debatable whether the cause is dry eye associated with MGD or meibomian gland abnormality. Literature is unavailable on the systematic analysis of the characteristics of keratoconjunctival epithelial disorder sites in MGD. Fluorescein staining is the most versatile staining method for keratoconjunctival epithelial disorders; whereas, Rose Bengal staining and lissamine green staining are also used.

Explanation Keratoconjunctival epithelial disorders are significantly increased in MGD compared with normal eyes [4, 12, 216, 219, 278, 279]. These disorders are considered to be milder than ADDE [153, 216, 219]. However, there is no consensus on the association between the severity of MGD and keratoconjunctival epithelial disorders. Nichols et al. [233] classified the severity of MGD by the degree and properties of the expressed meibum but discounted the association between the severity of MGD and keratoconjunctival epithelial disorders. Additionally, Shimazaki et al. [12] show that epithelial damage was enhanced when both the meibomian gland dropout and obstructive findings of the meibomian gland orifices were observed, but the relationship with epithelial damage was not significant when only one of these findings was observed. In addition to a report that there is no association between the severity of MGD and keratoconjunctival epithelial disorders [281], there are reports on the absence of any relationship between keratoconjunctival epithelial disorders and the degree of meibomian gland dropout [325], subjective symptoms, eyelid margin vascularity, and degree of meibum expressibility [124, 126]. However, other studies indicate a relationship between keratoconjunctival epithelial disorders and the degree and properties of the expressed meibum and meibomian gland dropout [128, 278]; moreover, the dropout rate of the meibomian gland structure by noninvasive meibography correlated with the score of keratoconjunctival epithelial disorders [207]. Ibrahim et al. [279] report the association between confocal microscopy findings of the meibomian glands and keratoconjunctival epithelial disorders; keratoconjunctival epithelial disorders increased with the increase in inflammatory cell density, longest and shortest acinar diameter, and with the decrease in acinar unit density.

Problems and Biases It should be noted that ocular surface examinations and their evaluation methods are not internationally standardized. Fluorescein and Rose Bengal staining are used to determine keratoconjunctival epithelial disorders; the use of lissamine green staining has recently been introduced. In Japan, the evaluation by fluorescein staining is limited to the cornea [12, 278, 279]. The cornea is classified into three regions: upper, middle, and lower, each scored from 0–3 points (total: 9 points). The evaluation by Rose Bengal staining is scored from 0–3 points each for the lateral conjunctiva, cornea, and medial conjunctiva (total: 9 points) [12, 278, 279]. In Europe and the United States, the cornea is evaluated by fluorescein staining in five regions (center, lower medial, upper medial, lower lateral, and upper lateral) [126, 219, 233, 325]. In the evaluation of the conjunctiva, either the medial, lateral, and inferior conjunctiva are evaluated [216], or conjunctival sites such as the upper lateral, lower lateral, upper medial, and lower medial sites are evaluated [216, 233].

Future challenges and Trends MGD is often associated with dry eye; however, it remains unclear whether the frequency and severity of keratoconjunctival epithelial disorders are influenced by MGD alone. Moreover, studies have not systematically analyzed the characteristics of the keratoconjunctival epithelial disorder sites in MGD. Therefore, in the future, to investigate the influence of MGD on the frequency and characteristics of keratoconjunctival epithelial disorders, studies should focus on MGD without dry eye.

- Treatment -

CQ18 Is eyelid warming effective?

(Reiko Arita and Naoyuki Morishige)

Recommendation Eyelid warming reduces subjective symptoms in MGD and improves the conditions of meibomian gland secretions (meibum grade).

Strength of recommendation Strongly recommend "implementation"

Voting result: 12/12 (100%) strongly recommended "implementation"

Strength of evidence A (strong): Strongly confident in estimate of effect

Recommendation background Among the studies that examined the effects of eyelid warming, 42 that can be evaluated based on outcomes were initially selected, and the results for each outcome were assessed. In many studies subjective symptoms, meibomian gland orifices' and

surrounding findings, meibum grade, BUT, and epithelial disorders were found to improve. Many of these studies that targeted patients with MGD had a small sample size of approximately 30 patients; most of these studies have pointed that out as a limitation.

After evaluating each outcome in the 42 articles, a total of six, including three RCTs [326, 327, 330] and three observational studies [108, 328, 329] were selected for SR, so that bias because of the different eyelid warming devices (MGDRx [326], Eyebag [327], Blephasteam [328, 329], Eye mask [108], and Azuki no chikara [330]) does not occur. Improvement in subjective symptoms, the predominant issue in MGD, was achieved in all studies. Improvements in meibum grade or conditions were obtained in all studies. Arita et al. [330] observed a significant improvement in meibum grade one month after the application of eyelid warming. Other studies that evaluated the meibum conditions also determined their improvement, and thus, it was considered that eyelid warming improves meibum conditions.

Research on eyelid warming had used various devices, and developments of the method are continuing. Eyelid warming using a towel is reportedly less effective than the aforementioned devices [328, 330, 331]; therefore, eyelid warming devices should be recommended over a towel. All the devices evaluated in the SR were priced between a few US dollars to tens of dollars and were reusable. Currently, eyelid warming for MGD is not covered by JHI. Nonetheless, eyelid warming is one type of home care, often there is no need to seek insurance coverage, and the devices are inexpensive and reusable.

Eyelid warming is strongly recommended to be implemented as a treatment for MGD because it improves the subjective symptoms of MGD, meibum conditions (meibum grade), and other outcomes; it is also economical.

SR summary In Cochrane, PubMed, and Ichushi-Web databases, literature search was performed using the following keywords: meibomian gland dysfunction, posterior blepharitis, eyelid diseases, lacrimal gland diseases, warming, warmings, warm, hyperthermia, thermography, thermotherapies, and temperature. Of the 178 articles retrieved, studies on thermal pulsation (LipiFlow®, JNJ Vision), IPL, and lipid analysis, case reports, reviews, and study designs that were not RCTs were excluded. From the excluded reports, we extracted those in which, although the focus was an evaluation of other treatment methods (thermal pulsation and IPL), eyelid warming was used as a control condition, comparison was conducted before and after application, and one or more outcomes were evaluated. Only two studies [332, 333] evaluated all outcomes, making the number of articles insufficient to perform SR. Therefore, 42 articles [108, 326–366] that can be reviewed based on the outcomes were selected, and the results for each outcome were extracted and analyzed. The results based on each outcome were as follows:

1. Subjective symptoms: assessed in 33 studies; 32 reported improvement [108, 326–331, 333–357], while 1 reported no change [332].
2. Meibomian gland orifice and surrounding findings (plugging, vascularity, eyelid irregularity, and displacement of MCJ): assessed in 18 studies; 13 reported improvement [108, 326, 328, 330, 333, 334, 336, 337, 342, 344, 348, 350, 356], while 5 reported no change [327, 331, 332, 345, 357].
3. Meibum grade: assessed in 20 studies: 19 reported improvement [326–330, 332, 333, 335–339, 343–345, 349, 350, 355, 360], while 1 reported no change [342].
4. BUT: assessed in 33 studies; 25 reported improvement [108, 326, 330, 333, 334, 336, 338–346, 348, 350, 352, 353, 358, 359, 361–364], while 8 reported no change [327, 328, 331, 332, 349, 354, 356, 357].
5. Epithelial disorders: assessed in 15 studies; 10 reported improvement [108, 326, 330, 333, 334, 336, 344, 349, 352, 365], while 5 reported no change [327, 332, 342, 358, 359].
6. Adverse events: assessed in 10 studies; 1 reported adverse events [366], while 9 reported no adverse events [108, 328, 331, 333, 334, 343, 353, 356, 357].

In one SR, only one adverse event was reported [366]; it was temporary and reversible. Since improvement in subjective symptoms can be expected on application of eyelid warming, even the balance of benefits and harm does not reduce the recommendation level for eyelid warming. Although no studies mentioned patient satisfaction regarding eyelid warming, many participants responded favourably regarding comfort in one study [326] that investigated "comfort". This indicates the possibility of developing patient's satisfaction regarding treatment effectiveness.

After evaluating each outcome in the 42 articles, 6 were selected for SR including 3 RCTs [326, 327, 330] and 3 observational studies [108, 328, 329]. The subjective symptoms improved within 1 day [326], 2 weeks [108, 327], 3 weeks [328, 329], and 4 weeks [330] after the treatment. Although the reported periods varied depending on the study, the improvement in subjective symptoms was consistent after application of eyelid warming. Improvement in meibum grade or conditions following eyelid warming was reported in all RCT studies and observational studies. Hence, eyelid warming is strongly recommended to be implemented as a treatment for MGD because it improves the subjective symptoms of MGD, meibum conditions (meibum grade), and other outcomes.

CQ19 Is eyelid hygiene effective?

(Hiroaki Kato and Masatoshi Hirayama)

Recommendation Although eyelid hygiene is generally recognized as a standard treatment for MGD, few studies have verified the effectiveness of eyelid hygiene alone. In MGD, eyelid hygiene using a cotton ball moistened with water may improve subjective symptoms and BUT. Eyelid hygiene with commercial cleansing agents may improve subjective symptoms, meibomian gland orifice/surrounding findings, meibum grade, BUT, and ocular surface epithelial damage. However, depending on the type of cleansing agent used, non-serious adverse events may occur, and caution is required. Based on the above, eyelid hygiene is marginally recommended for MGD.

Strength of recommendation Marginally recommend "implementation"

Voting results: 2/11 (18%) strongly recommended "implementation" and 9/11 (82%) marginally recommended "implementation". A member with a COI was excluded from voting.

Strength of evidence C (weak): Limited confidence in estimate of effects

Recommendation background To avoid overlap with other CQs, literature search on the effectiveness of eyelid hygiene for MGD was limited to studies that used water or commercially available cleansing agents. Hence, one RCT [367] and three observational studies [368–370] were retrieved. From these, it was concluded that eyelid hygiene with cotton balls moistened with water may improve subjective symptoms and BUT, and eyelid hygiene with cleansing agents may improve subjective symptoms, meibomian gland orifice/surrounding findings, meibum grade, BUT, and ocular surface epithelial damage. However, depending on the type of cleansing agent used, adverse events [367] have occurred (30–52.5%); although none of these were serious, therefore, caution is necessary.

Among the studies selected, 1 RCT [367] divided the experimental and control groups into the use of a new cleansing agent and conventional cleansing agent, respectively. Specifically, this study did not verify the effectiveness of performing eyelid hygiene per se in MGD. Although it was an RCT, the strength of the evidence was considered equivalent to that of the three observational studies [368–370]. Moreover, all four studies included different methods of cleansing the eyelids (use/non-use of a cleansing agent, types of cleansing agent, number of eyelid hygiene performed per day, and whether the eyes were washed after cleansing the eyelids); hence, it cannot be ruled out that the difference in methods may have influenced the difference in results. Further, the risk of bias associated with COI cannot be ruled out when using specific cleansing agents.

SR Summary One RCT [367] and three clinical research studies [368–370] were selected to perform the SR. Of these, one observational study [370] used cotton balls moistened with water for eyelid hygiene, while the RCT [367] and two observational studies [368, 369] performed eyelid hygiene with commercially available cleansing agents.

In the RCT [367], one eye was cleaned with a cleansing agent containing tea tree oil, and the other eye was cleaned with a conventional cleansing agent. Comparison was made before and 3 months after the treatment. The strength of evidence of this study was comparable to the three observational studies [368–370], since the group which used the conventional cleansing agent was set as the control group. In two clinical studies [368, 369], cleansing agents were used to wipe the eyelids, and the results were compared before treatment and at 1 month [368] and 8 weeks after treatment [369]. In another clinical study [370], cotton balls moistened with water were used to wipe the eyelids, and the results were compared before and 6 weeks after treatment.

Subjective symptoms were assessed in all four studies. The RCT [367] and two clinical studies [368, 369] observed significant improvements after treatment by eyelid hygiene with a cleansing agent. Even the study that used water-moistened cotton balls [370] reports significant improvements.

Meibomian gland orifice/surrounding findings' were evaluated by all four studies. On using a cleansing agent, there was significant improvement in the following : plugging, capping, and foamy tear in the RCT [367], eyelid margin vascularity and plugging in one observational study [368], and meibomian gland obstruction in another observational study [369]. In the study using water-moistened cotton balls [370], no significant improvements were observed after treatment.

The RCT [367] and two observational studies [368, 369] evaluated the meibum grade. These studies indicate a significant improvement in expressibility [367, 369] and quality [367, 368] of meibum after treatment with a cleansing agent.

The RCT [367] and two observational studies [368, 370] assessed BUT. Among the studies in which cleansing agents were used, the RCT [367] and one clinical study [368] showed significant improvements after treatment. On using water-moistened cotton balls [4] a significant improvement in BUT was noted.

The RCT [367] and two clinical studies [368, 369] assessed ocular surface epithelial damage. On using cleansing agents, the RCT [367] and one observational study [369] show significant improvements after treatment; one study [368] shows no significant improvement.

Adverse events were evaluated in the RCT [367] and two observational studies [368, 369]. In the RCT [367], eye irritation was observed in 21 of 40 eyes (52.5%) on using a cleansing agent containing tea tree oil, and in 12 of 40 eyes (30%) using a conventional cleansing agent. No adverse events were observed in the other two studies [368, 369].

One observational study [368] evaluated meibography findings. However, findings before and after treatment were not compared. In 22 patients without atrophy of the meibomian gland, after treatment with the cleansing agent, meibography indicated significant improvements in the meibomian gland orifices/surrounding findings (eyelid margin vascularity), quality of meibum, and BUT. However, in six patients with atrophy of the meibomian gland on meibography, similar improvements were not evident. It was suggested that the presence or absence of atrophy of the meibomian gland may cause different outcomes to eyelid hygiene.

From the above, it is likely that eyelid hygiene with water-moistened cotton balls may improve subjective symptoms and BUT, and eyelid hygiene with cleansing agents may improve subjective symptoms, meibomian gland orifices/surrounding findings, meibum grade, BUT, and ocular surface epithelial damage. However, depending on the cleansing agent used, adverse events such as eye irritation, eye discomfort, and eye dryness may occur; although none of these adverse events are serious, caution is necessary.

CQ20 Is meibomian gland expression effective?

(Yukinobu Okajima and Yuichi Hori)

Recommendation MGX is effective in improving subjective symptoms and recommended as a treatment option for oMGD.

Strength of recommendation Marginally recommend "implementation"

Voting results: 1/12 (8%) strongly recommended "implementation" and 11/12 (92%) marginally recommended "implementation"

Strength of evidence for CQ C (weak): Limited confidence in estimated effect

Recommendation background The SR found the method of expression, treatment received before and after expression, and combination therapy with eye drops to be inconsistent among the studies. Three RCTs [205, 371, 372], three prospective studies [344, 373, 374], and one retrospective study [375] were selected for review. All studies focused on patients with oMGD. Meibum expression alone was effective in improving subjective symptoms evaluated by the OSDI and SPEED. However, the quality and quantity of meibum, BUT, Schirmer value, corneal staining score and other objective findings were not improved. Although no adverse events have been reported, it is concluded that the pain associated with MGX is taxing for the patient. MGX is not covered by JHI, but several types of forceps for meibum expression are sold in Japan. In clinical practice, these devices are used for both diagnosis and treatment.

SR Summary SR was performed on the effects of MGX alone on MGD patients. The most important outcome in judging the therapeutic effect was improvement of subjective symptoms such as OSDI and SPEED. In addition, the quality and quantity of the meibum, BUT, as an indicator of tear film stability, and corneal epithelial disorders were used as the outcomes in the examination findings. The occurrence of adverse events was also evaluated.

Although the mechanism of MGD improvement through meibum expression is unknown, Cui et al. [376] observed the meibomian gland orifices using anterior ocular segment optical coherence tomography. They report wider meibomian gland orifices in MGD than in normal eyes; these narrowed with meibum expression and became close to normal.

Literature search on the usefulness and efficacy of MGX alone identified three RCTs [205, 371, 372], two prospective studies [344, 373], one prospective study which compared eyes with and eyes without MGX subjected to IPL [374], and one retrospective study [375]. All studies focused on oMGD. No meta-analyses were available.

SR of these studies included evaluation of risk of bias, subjective symptoms (OSDI and SPEED), quality and quantity of the meibum, BUT, Schirmer value, corneal epithelial disorders, and adverse events. Regarding the risk of bias, the studies by Kaiserman et al. [371], Aketa et al. [205], Wang et al. [372], and Arita et al. [374, 375] had slightly high selection bias of randomization and assignment without masking, while studies by Han et al. [373] and Lee et al. [344] were randomized without assignment masking, and selection bias was high. The RCT by Kaiserman et al. [371] performed MGX with a cotton swab once a month and artificial tears were administered four times a day. When evaluated at 1 month and 2 months, improvement was observed in the primary endpoint of subjective symptoms (OSDI). However, quality and quantity of the meibum, BUT, Schirmer value, and corneal epithelial disorders did not improve. In addition, Aketa et al. [205] and Wang et al. [372] combined meibum expression with the standard MGD treatment methods. Aketa et al. [205] compared the inclusion and exclusion of MGX with the standard methods of hot eye mask and eyelid hygiene twice a day, 1.5% levofloxacin eye drops four times a day, 0.1% fluorometholone eye drops three times a day, 0.1% hyaluronic acid eye drops four times a day, and 100 mg oral minocycline twice a day. Both groups showed improvement in subjective symptoms, but when MGX was

included, improvement in other objective findings such as BUT was observed one month later. In addition, Wang et al. [372] studied the therapeutic effects due to the inclusion and exclusion of MGX exerted by tweezers/forceps in addition to the standard method of eyelid warming three times a day, eyelid hygiene, 0.3% tobramycin/0.1 dexamethasone combined eye drops once a day, and 0.1% hyaluronic acid eye drops four times a day. Both groups report improvement in subjective symptoms, but adding pressure using tweezers showed additional improvement in other objective findings such as BUT, corneal staining score, Schirmer value, quality of meibum, and secretion amount, 1 month later.

In the RCTs to date, there was no consistency in the methods used for expression, which included tweezers and cotton swabs. In addition, the severity of MGD evaluated in the RCTs was moderate to severe, indicating inconsistency. The concomitant medications, number of eye drops administered in a day, and observation period also differed. However, all RCTs observed improvements in the primary endpoint of subjective symptoms (OSDI and SPEED). Nonetheless, evaluation of the quality and quantity of meibum, BUT, Schirmer value, and corneal epithelial disorders showed that MGX alone was insufficient, and it was necessary to combine some other MGD treatment method. Furthermore, no serious adverse events were observed in any RCT.

The prospective study by Lee et al. [344] did not randomize the study sample, and the risk of bias was considered high. After mechanical compression once a week, twice a day eyelid hygiene and warming therapy, and 0.1% hyaluronic acid eye drops for 1-month, subjective symptoms and objective findings such as OSDI, BUT, staining score, and evaluation of quality and quantity of the meibum were significantly improved. However, the results of tear film examination with a tear interference imaging observation device reported no significant difference. There were also no serious adverse events.

Han et al. [373] performed hyperthermic massage for 5 minutes, meibum expression using cotton swab once a week, and administered artificial tears four times a day for 1 month for mild to moderate and severe MGD. In mild to moderate disease, meiboscore, OSDI, TBUT, meibum expression, and corneal staining score improved, but Schirmer value and meibum quality did not improve. Additionally, in severe cases, the meiboscore, OSDI, TBUT, and meibum expression improved, but no improvements in Schirmer values, meibum quality, and corneal staining score were observed. There were no serious adverse events.

In an article excerpt on the results of MGX alone, Arita et al. [374] report using the Arita method tweezer (Katena) eight times at 3-week intervals. Observations after 24 and 32 weeks showed no improvement in the SPEED score of subjective symptoms, plugging, meibum grade, NIBUT, BUT, LLT, eyelid vascularity, eyelid margin irregularity, meiboscore, angular conjunctival staining score, and Schirmer value. No serious adverse events were seen. Similarly, Arita et al. [375] showed improvement in the SPEED score of subjective symptoms, BUT, keratoconjunctival staining score, and meibum grade, but no improvement in LLT and Schirmer values on combining twice a day warming therapy meibocare with Arita method meibomian gland compression tweezer at 3-week intervals for 3 months. In addition, plugging showed improvement, but no improvement in vascularity was noted. It was reported that combined use of MGX and meibocare by tweezers improved mild and moderate MGD, but not on severe disease.

Based on the above, monotherapy of MGX for MGD improved subjective symptoms, but no improvements in other objective findings. Although there were no serious adverse events, the pain from compression should be considered a burden on the patients.

CQ21 Are diquafosol eye drops effective?

(Shima Fukuoka and Hiroaki Kato)

Recommendation The efficacy of DQS for MGD without dry eye is unknown. In cases of MGD with dry eye, DQS eye drops may improve subjective symptoms, meibomian gland orifice and surrounding findings, meibum grade, BUT, and ocular surface epithelial damage. Considering that in JHI does not cover DQS eye drops for MGD alone, we marginally recommend not to implement DQS eye drops for treating MGD.

Strength of recommendation Marginally recommend "not to be implemented"

Voting results: 1/4 (25%) marginally recommended "implementation" and 3/4 (75%) marginally recommended "not to be implemented". Eight members with COI were excluded from voting.

Strength of evidence C (weak): Limited confidence in estimate of effect

Recommendation background Systematic literature search on the effectiveness of DQS eye drops in MGD revealed one RCT [377] and three clinical studies [204, 378, 379]. From these, it was concluded that DQS eye drops may improve subjective symptoms, meibomian gland orifices and surrounding findings, meibum grade, BUT, and ocular surface epithelial damage in MGD with dry eye. However, the following three points are to be noted.

1. All of the studies included in this SR focused on MGD with dry eye. In epidemiological studies [6] of Japanese, the prevalence of MGD was 32.9% and of dry eye 33.4%, and the prevalence of MGD with dry eye was

12.9%. Therefore, the prevalence of MGD without dry eye is 20%, about 1.6 times that of cases of MGD with dry eye; therefore, new evidence is necessary regarding MGD without dry eye.

2. DQS eye drops improved subjective symptoms, BUT, and ocular surface epithelial damage, and their safety has already been reported in patients with dry eye [380, 381]. Considering the effectiveness of DQS eye drops for MGD, we should focus on the improvement in meibomian gland orifices and surrounding findings as well as the meibum grade, important objective findings in evaluating MGD. However, these two objective findings have only been examined in two observational studies with small sample sizes [204, 378]; therefore, it is necessary to accumulate further evidence.
3. DQS eye drops are used clinically as a therapeutic agent for dry eye only in Japan and neighbouring Asian countries. All the literature identified in this SR were from Japan. Since there were no studies from other countries, the possibility of ethnic differences in the effects of DQS remains unexplored.

In addition to the above three points, although DQS eye drops are covered by JHI for dry eye, their use for MGD alone is not approved, and the lack of insurance coverage should be considered.

SR Summary One RCT [377] and three clinical studies [204, 378, 379] were included in the SR. In all these studies, participants comprised patients with both MGD and dry eye. In the RCT [377], a single drop of DQS was administered to one eye, and a single drop of artificial tears to the other eye as a control. Time course of parameters, before and after eye drop administration, was measured noninvasively until 90 minutes later. DQS eye drops were administered six times a day for 3 months in one clinical study [204], and four times a day for ≥4 months (4–16 months) in another [378], and pre- and post-treatment comparisons were performed. Another clinical study [379] administered DQS eye drops for 2 months in patients with dry eye, who were then analyzed separately depending on the presence or absence of MGD, and the effect of DQS was compared pre- and post-treatment.

The RCT [377] shows significant improvement in subjective symptoms (ocular fatigue, dryness, itching, redness, and heavy sensation) up to 90 minutes after DQS administration compared with artificial tears. In the three clinical studies [204, 378, 379], DQS eye drops were continued for ≥2 months. One study [204] shows no significant improvements in subjective symptoms after treatment, another [378] shows a significant improvements after 4 months (4–16 months) of treatment, and another [379] shows a significant improvement 1 and 2 months after treatment.

Two clinical studies assessed the improvements in meibomian gland orifices and surrounding findings [204, 378]. One study [204] shows significant improvements in plugging and vascularity at 1, 2, and 3 months after treatment. However, no significant changes were observed in eyelid margin irregularity and displacement of MCJ. The other study [378] reports significant improvements in lid margin abnormality scores (summed scores of plugging, vascularity, eyelid margin irregularity, and displacement of MCJ) with observations regarding individual findings ≥4 months (4–16 months) after treatment.

Meibum grade was evaluated in two clinical studies [204, 378], both show a significant improvement in meibum grade after treatment (3 months [204] and 4–16 months [378]).

All four studies assessed BUT. In the RCT [377], NIBUT was significantly improved up to 90 minutes after DQS administration. In the clinical studies [204, 378, 379], BUT was significantly improved 1, 2, and 3 months after treatment [377], ≥4 months after treatment (4–16 months) [378], and 1 and 2 months after treatment [379].

The three clinical studies assessed ocular surface epithelial damage. Compared with before treatment, there was a significant improvement in scores 1, 2, and 3 months after treatment [204], ≥4 months after treatment (4–16 months) [378], and 1 and 2 months after treatment [379].

The RCT [377] evaluated tear film interference images. In cases where the tear film lipid layer interference pattern exhibited class 2 (evaporative dry eye pattern), a significant improvement was observed up to 90 minutes after the instillation of DQS compared to artificial tears.

The RCT [377] and one clinical study [204] assessed LLT. The RCT [377] reports a significant increase in LLT up to 60 minutes after the instillation of DQS compared to artificial tears. The clinical study [204] noted significantly increased LLT 20 minutes after DQS eye drop instillation.

Meibography findings are reported in two clinical studies [204, 378]. In one study [204], no significant changes were observed until 1 or 2 months of treatment, but a significant decrease in meiboscore was observed 3 months after treatment. In another study [378], a significant decrease in meiboscore and a significant increase in meibomian gland area were observed 4–16 months after treatment.

The RCT [377] and two clinical studies [204, 379] assessed adverse events. The RCT [377] showed no serious adverse events. One study [204] observed eye pain in 1 out of 14 cases (7.1%), and eye drops were discontinued. Another study [379] showed eye irritation, tearing, and discharge in 2 out of 32 cases (6.3%). No serious adverse events were observed in any of the reports [204, 379], and most of those observed were mild.

The above findings indicate that DQS eye drops may improve subjective symptoms, meibomian gland orifices and surrounding findings, meibum grade, BUT, and ocular

surface epithelial damage in patients with both MGD and dry eye.

CQ22 Are antimicrobial eye drops effective?

(Chika Shigeyasu and Masakazu Yamada)

Recommendation Only azithromycin eye drops had a high level of supportive evidence among the antimicrobial eye drops. Azithromycin eye drops in patients with MGD are effective in improving subjective symptoms, meibomian gland orifices and surrounding findings, and meibum grade. Although effective in prolonging BUT, the improvement is weak and has only a limited effect on keratoconjunctival epithelial disorders. Considering that adverse events are mild, although the frequency is relatively high; implementation is marginally recommended. Azithromycin eye drops are covered by JHI for eye disorders such as conjunctivitis, blepharitis, hordeolum, and dacryocystitis. If blepharitis is present with MGD, they will be covered by JHI.

Strength of recommendation Marginally recommend "implementation"

Voting results: 4/4 (100%) marginally recommended "implementation". Eight members with COI were excluded from voting.

Strength of evidence B (medium): Moderately confident in estimate of effect

Recommendation background Literature on the efficacy of antimicrobial eye drops for patients with MGD was systematically searched. This retrieved four RCTs [375, 382–384] and three observational studies [385–387] that report the effects of azithromycin eye drops. Among the types of antimicrobial eye drops, we conducted a search on azithromycin, a macrolide antimicrobial. No articles met the evidence level for other antimicrobial eye drops used in clinical settings, including new quinolones, cephem antibiotics, and other macrolides. The concentration of azithromycin eye drops used in each study varied; ranging from 1.0% [375, 382, 384, 386, 387] to 1.5% [383, 385] and some of the research was conducted outside Japan. The number of drops administered, and the duration of use also varied. In most studies, eyelid hygiene and artificial tear drop administration initiated before the study were continued during the study period. Along with studies in patients with MGD [375, 385, 386], SR was also performed with studies on diseases such as posterior and chronic blepharitis [382–384, 387], and a comprehensive judgment was made.

The most important therapeutic outcome in patients with MGD was the improvement in subjective symptoms. Outcomes considered among the examination findings were improvements in meibomian gland orifices and surrounding findings, prolongation of BUT (an indicator of tear stability), and reduction of keratoconjunctival epithelial disorders. Despite the occurrence of clinically important adverse events, these were relatively mild and secondary.

SR Summary Although treatment with azithromycin eye drops has been performed in patients with MGD, the overall therapeutic effect in Japan has not been evaluated. We conducted an SR on the effects of azithromycin eye drops in patients with MGD.

Four RCTs [375, 382–384] and three observational studies [385–387] identified improvements in subjective symptoms after using azithromycin eye drops. Four RCTs [375, 382–384] and three observational studies [385–387] report an improvement in meibomian gland orifices and surrounding findings on using azithromycin eye drops. Two RCTs [375, 382] demonstrate the efficacy of azithromycin eye drops in improving the meibum grade. Nonetheless, it should be noted that related literature is very limited. Two RCTs [375, 382] and three observational studies [385–387] show that azithromycin eye drops' administration improved BUT. Two RCTs [375, 382] and two observational studies [385, 387] indicate improvements in epithelial disorders. However, literature regarding the improvements in epithelial disorders after administering azithromycin eye drops is limited. Despite improvements being shown in all the above outcomes, there exists a risk of bias associated with COI and that may have had a significant impact on outcomes.

Two RCTs [382, 384] and two observational studies [385, 387] assessed adverse events. Although adverse events following azithromycin eye drops' administration were moderately frequent, we concluded that their severity was relatively mild.

Hence, azithromycin eye drops in MGD improves subjective symptoms, meibomian gland orifices and surrounding findings, as well as meibum grade. Although they prolong BUT, the change is insignificant; additionally, the eye drops have a limited effect on keratoconjunctival epithelial disorders. Although the frequency of adverse events is relatively high, they are mild. Therefore, implementation is marginally recommended.

Azithromycin eye drops are covered by JHI for the following eye diseases, conjunctivitis, blepharitis, hordeolum, and dacryocystitis. Hence, if the MGD involves blepharitis, JHI's coverage is available.

Azithromycin, a macrolide antimicrobial, inhibits lipase produced by bacteria in the eyelids by bacteriostatic action [388] and has an anti-inflammatory effect [389]. Additionally, it acts on epithelial cells of the meibomian gland and promotes lipid secretion [390, 391]. Due to the high viscosity, eye irritation and blurred vision are observed as adverse events; however, serious adverse events are unlikely.

CQ23 Are ophthalmic ointments (excluding corticosteroid-based ophthalmic ointment)/ oily eye drops effective?

(Takashi Itokawa and Eiki Goto)

Recommendation Ophthalmic ointments and lipid-containing eye drops reportedly improve the symptoms and findings in MGD (vascularity and plugging of meibomian gland orifice/surrounding findings, quality of meibum, BUT, and corneal epithelial disorders). However, only a few ophthalmic ointments and lipid-containing eye drops have been evaluated among the different types available. Therefore, no clear recommendation can be made.

Strength of recommendation Unable to make a clear recommendation.

Voting results: 1/4 (25%) marginally recommended "implementation", 1/4 (25%) marginally recommended "not to be implemented" and 2/4 (50%) were unable to decide. Eight members with COI were excluded from voting.

Strength of evidence D (very weak): Little confidence in estimate of effect

Recommendation background We systematically reviewed the efficacy of ophthalmic ointments and lipid-containing eye drops, other than corticosteroids, in MGD. Subjective symptoms, meibomian gland orifices/surrounding findings, quality of meibum, BUT, epithelial disorders, and adverse events were evaluated as outcomes.

Ophthalmic ointments were assessed in three studies: one on antimicrobials [392], one on immunosuppressants [393], and one on vitamin D3 [394]. RCT was only performed on immunosuppressants, and the studies on antimicrobials [392] and vitamin D3 [394] were prospective longitudinal studies without a control group. Therefore, the level of evidence is low. Among the antimicrobial ophthalmic ointments, ofloxacin ophthalmic ointment, containing both polar and non-polar lipids, improved the stability of the tear film and the eyelid margins and orifice findings [392]. Ofloxacin ophthalmic ointment is covered by JHI whenever the case involves blepharitis. Vitamin D3 reportedly suppresses keratinization and inflammation and is effective against keratinization of the meibomian gland orifices [394]. These ophthalmic ointments improved the subjective symptoms, meibomian gland orifice findings, quality of meibum, BUT, and epithelial disorders, with no adverse events [392, 394]. The efficacy of immunosuppressant ointments is also reported, but these are not covered by JHI for MGD; additionally, adverse events with complaints of burning sensation have been reported [393]. However, only one report each is available on these three types of ophthalmic ointments. Therefore, no clear recommendation can be made.

Six studies evaluated lipid-containing eye drops [395–400], and two among them were RCTs [395, 397]. Castor oil was used in one study [396], and lipid-containing eye drops sold overseas were used in five studies [395, 397–400]. These included polar lipids [395, 397, 399], perfluorohexyl octane [400], and mineral oil [398]. These eye drops have additional benefits other than physically increasing the lipid component. Castor oil has anti-inflammatory and antimicrobial effects [401, 402]. Lipid-containing eye drops available overseas contain polar lipids, thus improving tear film stability [403]. These lipid eye drops also improve subjective symptoms, meibomian gland orifice findings, meibum quality, epithelial disorders, and cause few adverse events [395–400]. Hence, lipid eye drops are effective in treating MGD. However, castor oil must be prepared and stored at low temperatures. Additionally, ready-to-use products are only sold overseas, and there is no JHI's coverage for their use in MGD. Since limited evidence is available on each type of lipid-containing eye drops, no clear recommendation can be made.

SR Summary All three studies on ophthalmic ointments [392–395] show improvements in subjective symptoms and meibomian gland orifice findings. Two studies [392, 393] show improvements in the quality of meibum, two studies [392, 394] show improvements in BUT (while one study does not show significant changes [393]), two studies [392, 394] show improvements in epithelial disorders, and one study reports adverse events [393]; the remaining two studies [392, 394] show no adverse events. Despite the presence of several types of ophthalmic ointments, only limited evidence is available.

All six studies [395–400] report improvements in subjective symptoms. Four studies [395–397, 400] that evaluated meibomian gland orifice findings show improvements. Two studies [399, 400] evaluated meibum quality and report an improvement. The four studies [395, 396, 399, 400] that assessed BUT show an improvement, and three out of four studies that assessed epithelial disorders [396, 399, 400] show improvements. Among five studies that evaluated adverse events, non-serious adverse events were noted in two [399, 400]. Since there were only a few reports on each type of lipid-containing eye drops, the evidence level was considered as D (very weak).

CQ24 Is topical corticosteroid administration (eye drops and ointments) effective?

(Yukinobu Okajima and Eiki Goto)

Recommendation Corticosteroid eye drops are used in combination with eyelid hygiene and warming therapy to improve the subjective symptoms, BUT, eyelid margin findings, and meibum quality in patients with MGD. However, there are few reports at high evidence level, and there is no JHI's coverage for corticosteroid eye drops for MGD. JHI's coverage is only available in case of concomitant blepharitis. Hence, topical corticosteroids are marginally recommended for treating MGD.

Strength of recommendation Marginally recommend "implementation"

Voting results: 4/4 (100%) marginally recommended "implementation". Eight members with COI were excluded from voting.

Strength of evidence C (weak): Limited confidence in estimate of effect

Recommendation background Two RCTs were identified on the topic [333, 404]. One RCT [333] that compared a group that used corticosteroid eye drops, eyelid warming, and eyelid hygiene with a group that used eyelid warming + eyelid hygiene; and another RCT [404] that compared a group that used corticosteroid and antibiotic eye drops along with eyelid hygiene with a group that used N-acetyl-cysteine eyedrop along with eyelid hygiene. No observational studies with a high level of evidence were found. Since no article evaluating the effects of corticosteroid ointments on MGD was found during the time period specified in our study, we only evaluated the studies on corticosteroid eye drops.

Outcomes evaluated included: (1) risk of bias, (2) primary endpoints of improvement in ocular findings by slit lamp microscopy and subjective symptoms, (3) improvement in bacterial tests and inflammatory markers as secondary endpoints, and (4) adverse events.

On using corticosteroid eye drops along with eyelid warming and eyelid hygiene, improvements in BUT, keratoconjunctival fluorescein staining, eyelid margin findings, and meibum quality were significantly greater compared with eyelid warming and eyelid hygiene without corticosteroid eye drops [333]. However, the corticosteroid eye drops used in this RCT were formulations that can not be prescribed in Japan. In the other RCT [404] that compared a group that used corticosteroid and antibiotic eye drops along with eyelid hygiene with a group that used N-acetyl-cysteine eyedrop along with eyelid hygiene, subjective symptoms, BUT, and Schirmer value significantly improved in the group that used corticosteroid and antibiotic eye drops along with eyelid hygiene after 1 month of treatment. However, the improvement rate of symptoms' score, BUT, and Schirmer value in the two groups was not significantly different. These results show the non-inferiority of corticosteroid and antibiotic eye drops to N-acetyl-cysteine in the treatment of MGD. The same group showed in another study [405] that N-acetyl-cysteine is effective in the treatment of MGD. Taken together, the results of this RCT [404] show that corticosteroid eyedrops are effective in the treatment of MGD.

As described above, corticosteroid eye drops have been shown to improve the subjective symptoms, BUT, eyelid margin findings, and meibum quality in MGD when used in combination with eyelid warming and eyelid hygiene. However, these are findings from two articles only. Furthermore, one of these studies used corticosteroids that cannot be prescribed in Japan, and the other study combined corticosteroid eye drops with antibiotics. In addition, corticosteroid eye drops are not covered by JHI for MGD, unless concomitant blepharitis is present. Based on the above, it is marginally recommended to administer corticosteroid eye drops for treating MGD.

SR summary

1. Comparison of corticosteroid eye drops (0.5% loteprednol etabonate) and eyelid warming along with eyelid hygiene with eyelid warming, and eyelid hygiene without corticosteroid eye drops (RCT 1)

Lee et al. [333] compared the use of 0.5% loteprednol etabonate for 2 months with twice-daily eyelid warming with eyelid hygiene in 30 patients and twice-daily eyelid warming with eyelid hygiene alone in 30 patients. The participants had moderate to advanced MGD and were Koreans/Asians. The corticosteroid eye drops used in this study were Loteprednol (an ester of Loteprednol etabonate), a corticosteroid drug that has little tendency to increase intraocular pressure. At present, it cannot be prescribed in Japan.

1.1 Risk of bias

Although it is unclear whether this study was sufficiently randomized, randomization and allocation masking were performed, and the selection bias was likely low. This study had not received any funding from companies that produce therapeutic interventions.

1.2 Primary endpoints

These were evaluated at the beginning of treatment as well as at 1 month and 2 months. Significant improvements in BUT, fluorescein staining of cornea and conjunctiva, eyelid marginal findings, and meibum quality were observed in the group of corticosteroid eye drops with eyelid warming and eyelid hygiene compared to the group that received only eyelid warming and eyelid hygiene.

1.3 Secondary endpoints

Interleukin (IL) in tear fluid was measured. One month after the start of treatment, a decrease in IL-6, IL-8 and IL-1b was observed in the group that received corticosteroid eye drops along with eyelid warming and eyelid hygiene

while a decrease in IL-6 and IL-8 was observed in the group that received only eyelid warming and eyelid hygiene.

1.4 Adverse Events

There were no serious adverse events, and there was no significant difference in the increase in intraocular pressure between the two groups.

1.5 Summary

The effects of loteprednol etabonate eye drops and eyelid warming along with eyelid hygiene appeared after 1 month of treatment and were effective in moderate and severe MGD.

2. Comparison of corticosteroid and antibiotic eye drops (betamethasone 0.1%-sulfacetamide sodium 10%) and N-acetyl-cysteine eye drops (RCT 2)

Akyol-Salman et al. [404] compared the use of betamethasone 0.1%-sulfacetamide sodium 10% with eyelid hygiene (10 patients) and N-acetyl-cysteine with eyelid hygiene (10 patients) for treating MGD in Thai-Asians in one month.

2.1 Risk of bias

Although it remains unclear whether this study was sufficiently randomized, it is reported that randomization and allocation masking were performed, and the selection bias was likely low. This study did not receive any funding from companies that produce therapeutic interventions.

2.2 Primary endpoints

One month of topical therapy provided statistically significant improvements in BUT and Schirmer values as compared with the initial study visit in both groups ($P \leq 0.001$). Significant improvements for the symptoms of ocular burning, itching, and blurred vision were noted in both groups at 1 month as compared with 1 day. However, the improvement rates in symptoms' score were not significantly different between the two groups at 1 month after treatment. Moreover, there was no significant difference between the groups in the improvement rates of BUT ($P=0.232$) and Schirmer value ($P=0.202$) at 1 month after treatment. These results show the non-inferiority of corticosteroid and antibiotic eye drops to N-acetyl-cysteine in the treatment of MGD.

2.3 Secondary endpoints

No bacterial tests or inflammatory markers were evaluated.

2.4 Adverse Events

There were no serious adverse events and no increase in intraocular pressure was reported.

2.5 Summary

Because eyelid hygiene was performed in both groups, it is possible that the improvements in subjective symptoms and objective findings were due to eyelid hygiene. However, the same group showed in another study [405] that N-acetyl-cysteine is effective in the treatment of MGD. Because the current RCT [404] shows the non-inferiority of corticosteroid and antibiotic eye drops to N-acetyl-cysteine in the treatment of MGD, the results of this RCT [404] is thought to show that corticosteroid eyedrops are effective in the treatment of MGD.

From the above, corticosteroid eye drops were found effective in improving subjective symptoms and ocular findings in MGD in one RCT that combined corticosteroid eye drops and eyelid warming [333], and another RCT that combined corticosteroid and antibiotic eye drops with eyelid hygiene [404].

CQ25 Are cyclosporin A eye drops effective?

(Yuichi Kaji and Seika Den)

Recommendation CsA eye drops for MGD improve subjective symptoms, eyelid margin findings, and properties of the meibum to some extent, but the effect is limited. Considering that CsA eye drops are not an evidence-based treatment for MGD, and that they are not covered by JHI, it is marginally recommended not to use CsA eye drops for MGD.

Strength of recommendation Marginally recommend "not to be implemented"

Voting results: 4/4 (100%) marginally recommended "not to be implemented". Eight members with COI were excluded from voting.

Strength of evidence D (very weak): Little confidence in estimate of effects

Recommendation background Among the studies on CsA eye drops for MGD, three RCTs were identified [406–408]. Additionally, although not RCTs, we included two high-quality research reports [342, 409]. Few RCTs have evaluated the usefulness of CsA eye drops for MGD, and the outcome measures and test results that show improvements are not uniform. The CsA concentration used in all studies was 0.05%. These studies were supposedly conducted using CsA eye drops (Restasis®, Allergan) commercially available overseas. No side effects due to CsA eye drops were reported. However, there is no JHI's coverage for CsA eye drops for MGD. Since CsA eye drops provide limited effect on MGD, they cannot be considered evidence-based treatment. Therefore, we marginally recommend that the use of CsA eye drops not to be implemented.

SR Summary Cochrane, PubMed, and Ichushi-Web databases were searched for the terms meibomian gland and cyclosporin(e). Subsequently, we narrowed down the results using keywords including clinical trial(s), random, and selected three RCTs [406–408]. Furthermore, although not

RCTs, we included two high-quality research reports [342, 409].

Perry et al. [406] investigated the efficacy of 0.05% CsA eye drops in MGD by comparing their effect with artificial tears (12 eyes in the CsA group and 14 eyes in the artificial tear group). Injection and vascularity of the eyelid margin, and corneal epithelial damage improved significantly in the CsA group, but there was no difference in subjective symptoms or BUT. This study suggests that the anti-inflammatory effects of CsA were successful in reducing meibomian gland inflammation. However, due to the small number of parameters that showed improvement and small sample size, it is difficult to say that the study's findings can be considered solid evidence.

Schechter et al. [407] investigated the effectiveness of 0.05% CsA eye drops in ocular rosacea using artificial tears as a comparative control (21 eyes in the CsA group and 16 eyes in the artificial tear group). They defined ocular rosacea as vascularity of the eyelid margin and changes in the properties of meibum considered to be equivalent to MGD. Although this study reports improvement in Schirmer values, corneal epithelial damage, and subjective symptoms, there are some problems such as the fact that only Caucasian participants were included in the study.

Prabhasawat et al. [408] compared the efficacy of 0.05% CsA and artificial tears in MGD with BUT ≤ 8 seconds; better improvement in BUT was observed in the CsA group than in the artificial tears' group. The ease of expressing meibum was also improved in the CsA group, but only after 1 month of use. There was no difference in subjective symptoms, inflammatory findings at the eyelid margin, or keratoconjunctival epithelial damage. In this study, the inclusion criteria included meibum abnormalities, number of meibomian glands with abnormal expression of meibum, and inflammation of the eyelid margin and conjunctiva graded 0–3 for evaluation, rather than their presence or absence. In addition, the sample size was 36 eyes in the CsA group and 34 eyes in the artificial tears' group, which was higher than in other studies reviewed. This study had the highest level of evidence among the five studies listed in this SR. However, since the only significant finding was improved BUT, the effect of CsA eye drops in MGD seems weak. They suggest that the anti-inflammatory effect of CsA may have contributed to the improvement in BUT; however, if degeneration of the meibomian gland is involved in the pathology of MGD, the effect will be indirect. Additionally, it is possible that there was no significant difference in measured parameters other than BUT due to the administration of eyelid warming, eyelid hygiene with baby shampoo, and eyelid margin massage in both groups. These findings may suggest that the care of eyelid margins may be beneficial in improving MGD, rather than demonstrate the effectiveness of CsA.

Kim et al. [342] compared patients who were administered CsA and hyaluronic acid eye drops with patients who were administered hyaluronic acid eye drops alone, and report improvements in BUT, Schirmer value, eyelid margin vascularity, and subjective symptoms in the earlier group. However, the evidence levels of this study are low because the patients were not blinded regarding group allocation and the study was retrospective.

Rubin et al. [409] assigned 30 eyes with posterior blepharitis (inflammation of the posterior eyelid and vascularity of the meibomian gland orifice) to the CsA eye drops group (15 eyes) and the tobramycin and dexamethasone eye drops group (15 eyes), and compared the subjective symptoms, Schirmer value, BUT, and properties of meibomian gland secretions after 12 weeks. They demonstrate that the Schirmer value, BUT, eyelid health, and properties of meibomian gland secretion were improved to a greater extent in the CsA group compared with the tobramycin and dexamethasone eye drops group. Subjective symptoms such as blurred vision, foreign body sensation, and burning sensation were also improved. However, due to the small sample size, evidence cannot be considered substantial.

CQ26 Is oral *n*-3 fatty acid administration effective?

(Shima Fukuoka and Masatoshi Hirayama)

Recommendation In MGD, oral *n*-3 (omega-3) fatty acid administration may improve subjective symptoms, eyelid margin vascularity, and BUT. However, many uncertainties remain regarding suitable patients, dosage, content, and relationship with regular diet. In addition, it is necessary to take into account that in Japan, *n*-3 formulations are considered supplements and have no JHI's coverage. Based on the above, we marginally recommend oral *n*-3 fatty acid administration for MGD.

Strength of recommendation Marginally recommend "implementation"

Voting results: 10/12 (83%) marginally recommended "implementation" and 2/12 (17%) marginally recommended "not to be implemented"

Strength of evidence C (weak): Little confidence in estimate of effect

Recommendation background A systematic literature search on the efficacy of oral *n*-3 fatty acid intake in patients with MGD retrieved six RCTs [410–415]. From these studies, it was concluded that oral *n*-3 fatty acid administration for MGD may improve subjective symptoms, eyelid margin vascularity, and BUT. However, the following three concerns are to be noted.

1. Among the studies included in this SR, four [410–413] included patients with MGD according to the diagnostic criteria of the international workshop on meibomian gland dysfunction, while two studies [410, 414] included patients with both MGD and dry eye, and one study [415] included patients with oMGD and chronic blepharitis. These differences in patient selection may have influenced the findings.
2. *N*-3 fatty acids are polyunsaturated fatty acids with the first double bond in the third carbon-carbon bond from the terminal methyl end of the carbon chain. EPA is produced from ALA, DPA is produced from EPA, and DHA is produced from DPA. Since different formulations were used in the RCTs, the amount of *n*-3 fatty acids contained in the formulations differed between these reports; it is necessary to further examine the optimal oral dosage and content of *n*-3 fatty acids. In addition to *n*-3 fatty acids, two studies have used formulations containing various vitamins [412, 413], and this may have affected the outcomes. In two studies [411, 413] there was continued administration of eyelid warming and in three studies [411, 413, 415] continued administation of eyelid hygiene and artificial tear instillation during the treatment period.
3. Only one RCT [415] included in this SR evaluated *n*-3 intake from a regular diet. Until now, two epidemiological investigations (not included in our SR) have been conducted on the effect of dietary intake of *n*-3 fatty acids on MGD [416, 417]; however, subjects were patients with MGD in general in one study [416], and patients with oMGD in the other [417]. In these epidemiological studies, the average daily intake of *n*-3 fatty acids in the MGD group was 1.87 g in the United States [416] and 2.5 g in Japan [417]. None of the studies included in this SR were conducted in Japan, and it is considered necessary to build further evidence on the effect of oral *n*-3 fatty acid administration in the Japanese population who consume relatively high *n*- 3 fatty acids in their daily diet.

In addition to the above three points, some *n*-3 fatty acid products are covered by JHI for treating hyperlipidemia, but not for MGD, for which they will be taken as a nutritional supplement.

SR Summary This SR included six RCTs [410–415]. *N*-3 fatty acid supplementation was 1.0–3.3 g/day in these RCTs [410–415]. In five RCTs [410–414], EPA and DHA were included in different ratios as *n*-3 fatty acids. In two studies [412, 413], vitamins A, C, and E were also included as antioxidants with DPA. In another study [415], ALA was included as *n*-3 fatty acids, along with *n*-6 (linoleic acid) and *n*-9 (oleic acid). The treatment period was 3 months in five studies [410–414] and 1 year in another study [415].

All six RCTs [410–415] assessed subjective symptoms. In the *n*-3 fatty acid group, OSDI improved significantly 3 months to 1 year after treatment in three studies [410, 411, 415], compared with the control group. In one RCT [413], OSDI improved significantly in both groups at 1 and 3 months after treatment compared with before, but there was no comparison between the two groups. In another study [412], health-related quality of life improved significantly after 3 months of treatment in the *n*-3 fatty acid group compared with the control group.

Two RCTs [413, 415] report improvement in meibomian gland orifices and surrounding findings. In both studies, there was a significant improvement in eyelid margin vascularity post-treatment (3 months [413] and 1 year after treatment [415], respectively) in the *n*-3 fatty acid group. In one study [415], the number of visible meibomian gland ducts on the upper and lower eyelids in both groups increased 1 year after treatment compared with pre-treatment condition, however, the percentage of meibomian gland orifice stenosis did not change. No RCTs assessed the improvements in plugging, eyelid margin irregularities, or displacement of MCJ.

Two RCTs [413, 415] assessed meibum grade. In one study [413], meibomian gland expressibility was improved in the *n*-3 fatty acid group compared with before and 1 and 3 months after treatment; however, there was no improvement in the control group. In another study [415], the sum of the character and color scores of meibum was improved in both groups compared with before treatment and 1 year after treatment; however, there was no significant difference between the two groups. The percentage of meibomian gland orifices without meibum expression did not change in both groups. When divided into two groups by the total score of meibum character and color, the proportion of eyes with good quality (healthy) meibum increased significantly in the *n*-3 fatty acid group, but not in the control group. Therefore, further investigation is necessary to verify whether oral *n*-3 administration is effective in improving meibum.

Five RCTs [410, 411, 413–415] evaluated BUT; all of them had studied BUT with fluorescein. In four studies [410, 411, 413, 414], BUT was significantly improved in the *n*-3 fatty acid group compared with the control group 1 month [413] or 3 months after treatment [410, 411, 413, 414]. In one study [415], BUT was significantly improved in both groups compared with before treatment and 1 year after treatment; but without any significant difference between the two groups.

Ocular surface epithelial damage was assessed in five RCTs [410, 411, 413–415]. In the *n*-3 fatty acid group compared with the control group, corneal epithelial damage improved significantly in two studies [410, 411], and corneal and conjunctival epithelial damage improved significantly in one study [414]. One study [411] showed improvement in conjunctival epithelial damage in both groups compared with before treatment, without any significant difference between the two groups. In

two studies [413, 415], corneal epithelial damage improved, and in one study [415], conjunctival epithelial damage did not improve compared with before treatment. Therefore, it was not possible to determine whether oral *n*-3 fatty acid administration was effective in improving ocular surface epithelial damage.

Biochemical tests were performed in two RCTs [410, 415]. After treatment with *n*-3 fatty acids, the *n*-3 (Omega 3) index (the percentage of EPA and DHA in fatty acids) in serum [410, 415] and red blood cells [410] increased significantly, and the *n*-6/ *n*-3 ratio in serum decreased significantly [415]; however, there was no change in the control group. There was no change in the composition of fatty acids such as *n*-3 and *n*-6 fatty acids in meibum [415]. In addition, in one study [410], the positive rate of matrix metalloprotease-9 in tears was significantly reduced after treatment in the *n*-3 fatty acid group compared with the control group.

Tear osmolality was significantly reduced in the *n*-3 fatty acid group compared with the control group 6 and 12 weeks after treatment in one RCT [410].

The international workshop on meibomian gland dysfunction classifies MGD stages into mild, moderate, and severe based on subjective symptoms, meibum quality, meibum expressibility, and eyelid margin signs [2]. There was one RCT that examined the MGD stage [410]; nonetheless, no significant improvement was noted in both groups.

Adverse events were noted in two RCTs [412, 413]. Two out of 64 patients (3.12%) had digestive upsets within 1 month after the start of oral administration, but they recovered immediately after discontinuation [413]. In the other study [412], two out of 64 patients (3.12%) discontinue oral administration after reporting fish-tasting regurgitation. No serious adverse events were observed in any of the studies.

From the above, it may be concluded that oral *n*-3 fatty acid administration in MGD may improve subjective symptoms, eyelid margin vascularity, and BUT.

CQ27 Is oral antimicrobial medication effective?

(Chika Shigeyasu and Masakazu Yamada)

Recommendation

1. **Oral macrolide (azithromycin)**

Azithromycin oral administration in patients with MGD is effective in improving subjective symptoms, meibomian gland orifices and surrounding findings. However, improvements in meibum grade remain unknown, and the effect of azithromycin on BUT prolongation and epithelial disorders is limited. Adverse events are infrequent but require attention. Although it is determined to be effective in MGD, considering that there is currently no JHI's coverage for its administration in ocular diseases, its implementation is marginally recommended.

2. **Oral tetracyclines (doxycycline, minocycline, and tetracycline)**

Doxycycline and minocycline are effective in improving subjective symptoms in patients with MGD; the effects of tetracycline are unknown. Although it is likely to be effective in improving meibomian gland orifice and surrounding findings, improvements in meibum grade remain unknown. BUT prolongation effects are limited for all three medications. Doxycycline and minocycline have limited effects on keratoconjunctival epithelial disorders; however, the effects of tetracycline remain unknown. Since adverse events occur on relatively long-term oral administration, it is determine they set cufoff values in gland drop out,d that they are frequent with oral doxycycline and require attention. It is concluded that the therapy is effective. In recent years, semi-synthetic tetracyclines (doxycycline and minocycline) have been used more frequently than natural ones. Adverse events are crucial because oral administration of tetracycline-based antimicrobials has a longer duration compared to oral azithromycin, and the safety is higher with oral azithromycin. Tetracycline antimicrobials are covered by JHI for eye diseases such as dacryocystitis and hordeolum, but not for MGD. Based on the above, we marginally recommend its implementation.

Strength of recommendation

1. Oral macrolides (azithromycin); Marginally recommend "implementation"
2. Orla tetracyclines (doxycycline and minocycline); Marginally recommend "implementation"

Voting results: 12/12 (100%) marginally recommended "implementation"

Strength of evidence

1. Oral macrolides (azithromycin); B (medium): Moderately confident in estimated effect
2. Oral tetracyclines (doxycycline and minocycline); C (weak): Little confidence in estimated effect

Recommendation background Literature on the efficacy of oral antimicrobials for patients with MGD was systematically searched. This retrieved 12 interventional studies [182, 356, 418–427], including 10 RCTs [182, 356, 418–420, 422, 423, 425–427] and four observational studies [428–431]. Among the different types of oral antimicrobials, studies on azithromycin (macrolide antibiotic), and doxycycline, minocycline, and tetracycline (tetracycline antibiotics) were

searched. Articles on clarithromycin (a macrolide antibiotic which may be used in clinical practice) that met the evidence level were not found. Only one article about tetracycline was available, so it was excluded from the assessments of the strength of recommendation and for the strength of evidence. Additionally, based on concomitant diseases in MGD considered in each study [418–420, 422, 423, 425, 427, 429], SR was also performed for rosacea [182, 424, 428, 431], posterior blepharitis [356, 421, 426], and meibomitis [430] regarding which literature search was performed, and comprehensive assessment was done.

The most important outcome for therapeutic effects in patients with MGD was improvements in subjective symptoms. Outcomes considered in the laboratory findings were improvements in meibomian gland orifices and surrounding findings, prolongation of BUT, an indicator of tear film stability, and reduction in keratoconjunctival epithelial disorders. The occurrence of adverse events was observed relatively frequently with oral doxycycline, and there were many digestive symptoms crucial to the evaluation. Although the oral administration of tetracycline-based antimicrobials has JHI's coverage for eye diseases such as dacryocystitis and hordeolu, there is no JHI's coverage for MGD or for oral administration of macrolide-based antimicrobials. Administration is contraindicated in cases of renal damage, liver damage, infants, children, and during pregnancy.

SR Summary

1. Oral macrolide

1) Azithromycin

Oral azithromycin has been administered for treating MGD. However, the overall therapeutic effect in Japan has not been evaluated. In this study, we conducted a SR of the effects of azithromycin in patients with MGD.

Five interventional studies [418, 419, 421, 422, 426] and one observational study [428] assessed the improvement of subjective symptoms. Oral azithromycin administration was as effective as azithromycin eye drops for improving subjective symptoms in MGD, posterior blepharitis, and ocular rosacea.

Four interventional studies [419, 421, 422, 426] and one observational study [428] report improvements in meibomian gland orifices and surrounding findings after administering oral azithromycin in patients with MGD, posterior blepharitis, and ocular rosacea.

There was no study with a high level of evidence that evaluated meibum grade following oral azithromycin administration. Hence, the effects of oral azithromycin on meibum grade are unknown.

Five interventional studies [418, 419, 421, 422, 426] and one observational study [428] assessed improvements in BUT. Only limited effect was identified for oral azithromycin for improving BUT in patients with MGD, posterior blepharitis, and ocular rosacea.

Five interventional studies [418, 419, 421, 422, 426] and one observational study [428] assessed epithelial disorders on administering oral azithromycin. Improvement in epithelial disorders was noted in some patients with MGD [419, 422] as well as in posterior blepharitis [426]; nonetheless, the overall effect was limited.

Two RCTs that report on adverse events were identified [419, 422]. Adverse events associated with oral azithromycin were seen less frequently in patients with MGD and were judged to be mild in severity.

From the above, oral azithromycin administration in MGD is effective in improving subjective symptoms, meibomian gland orifices and surrounding findings. Improvement in meibum grade is unknown and limited effect is present on BUT prolongation and keratoconjunctival epithelial disorders. Adverse events are infrequent but require attention.

Azithromycin, a macrolide-based antimicrobial agent, acts bacteriostatically, inhibits bacterial lipase [388], and has an anti-inflammatory effect [389]. It reportedly acts on epithelial cells of the meibomian gland and promotes lipid secretion [390, 391]. As with azithromycin eye drops, oral administration is effective. Compared with other oral antimicrobial medications, there are few side effects due to the short duration of oral administration (cardiovascular symptoms are reported and care is needed when prescribing to patients with cardiovascular disorders), and higher benefit than cost is noted. Although it is judged to be effective in MGD, there is currently no JHI's coverage for ocular diseases.

2. Oral tetracyclines

1) Doxycycline

In MGD, treatment using oral doxycycline has been performed in various countries, but the overall therapeutic effect in Japan has not been evaluated. In this study, we conducted an SR of the effects of doxycycline oral administration in patients with MGD.

Seven interventional studies [356, 419, 420, 422, 424, 425, 427] and one observational study [431] had assessed subjective symptoms and found doxycycline oral administration to be as effective as azithromycin eye drops in patients with MGD, posterior blepharitis, and ocular rosacea.

Six interventional studies [356, 419, 420, 422, 424, 425] and one observational study [431] evaluated improvements in meibomian gland orifices and surrounding findings. Doxycycline oral administration was as effective as azithromycin oral administration with respect to meibomian gland orifice and surrounding findings in patients with MGD, posterior blepharitis, and ocular rosacea.

The effects on meibum grade remains unclear as it was not possible to find articles with a high level of evidence.

BUT prolongation effect was reviewed using six interventional studies [419, 420, 422, 424, 425, 427] and one observational study [431]. In half of the patients with MGD [425, 427], it is reported to be effective for ocular rosacea [424, 431]; overall, the effect of doxycycline oral administration on BUT was limited.

Six interventional studies [356, 419, 420, 422, 424, 425] that assessed epithelial disorders were reviewed. doxycycline oral administration improved epithelial disorders in patients with MGD, posterior blepharitis, and ocular rosacea.

Seven interventional studies that report adverse events were reviewed [356, 419, 420, 422, 424, 425, 427]. Adverse events associated with oral doxycycline were relatively frequent in patients with MGD, posterior blepharitis, and ocular rosacea, and required caution.

Based on the above, doxycycline oral administration in MGD improves subjective symptoms and meibomian gland orificef and surrounding findings. The effects on meibum grade remains unclear and BUT prolongation is limited. It is effective on keratoconjunctival epithelial disorders. Overall, it is concluded to be therapeutically effective. Adverse events are relatively frequent and require caution.

In addition to bacteriostatic action, tetracycline-based antimicrobials have an inhibitory effect on lipases produced by bacteria, especially by suppressing cytokines and matrix metalloproteinases [96, 432]. Doxycycline, unlike minocycline, is known to be a highly fat-soluble tetracycline s and has good translocation to the eyelids and eye tissue; it is reported effective even at low doses [433]. However, since the administration period is longer than azithromycin, it is necessary to be cautious of adverse events, and the safety and benefit-cost ratio of azithromycin are judged to be comparatively higher. Doxycycline is covered by JHI for eyelid abscess, dacryocystitis, hordeolum, and keratitis in the ophthalmology field, but not for MGD. Based on the above, we marginally recommend its implementation.

2) Minocycline

Although oral minocycline has been administered in MGD, the overall therapeutic effect in Japan has not been evaluated. We conducted an SR of the effects of minocycline oral administration in patients with MGD.

An RCT [423] showed that minocycline oral administration was likely to be effective in improving subjective symptoms in MGD. Nonetheless, few reports have a high level of evidence.

One RCT [423] and two observational studies [429, 430] assessed improvements in meibomian gland orifices and surrounding findings and report that minocycline oral administration can improve meibomian gland orifices and surrounding findings in patients with MGD and meibomitis.

There were no articles with a high level of evidence that evaluated meibum grade following minocycline oral administration. Therefore, the effect of minocycline oral administration on meibum grade is unclear.

One RCT [423] and one observational study [429] found that minocycline oral administration was effective in prolonging BUT in patients with MGD.

One RCT and two observational studies [429, 430] demonstrate that minocycline oral administration does not improve keratoconjunctival epithelial disorders in patients with MGD and meibomitis.

Adverse events are reported in one RCT [423]. Low frequency digestive symptoms, similar to other antimicrobial oral medications are reported. These require caution.

From the above, minocycline oral administration in MGD is likely to be effective in improving subjective symptoms and meibomian gland orifices and surrounding findings. Effect on meibum grade is unclear. Additionally, it may prolong BUT. Limited improvement in keratoconjunctival epithelial disorders can be expected; however, therapeutic effectiveness has been concluded. Although the frequency of adverse events is low, caution should be exercised. Therefore, its implementation is marginally recommended.

Minocycline, a tetracycline antimicrobial agent, acts bacteriostatically, has an inhibitory effect on lipase produced by bacteria in the eyelids, and an anti-inflammatory effect [96]. Minocycline is known to be highly fat-soluble among the tetracyclines, has good translocation to eyelid and eye tissue, and been reported to be effective even at low doses [433].

Due to adverse effects, it is necessary to refrain from use in infants, pregnant/breastfeeding women, patients with liver and kidney diseases. JHI's coverage is available for dacryocystitis and hordeolum, but not for MGD. Based on the above, we marginally recommend its implementation.

3) Tetracycline

Tetracycline has conventionally been administered to patients with MGD overseas. In Japan, the overall therapeutic effect has not been evaluated. We systematically reviewed the effects of tetracycline oral administration in patients with MGD.

In recent years, no study with a high level of evidence has evaluated subjective symptoms following tetracycline oral administration. Therefore, the effect of tetracycline oral administration on subjective symptoms is unknown.

One RCT [182] reports improvements in meibomian gland orifices and surrounding findings after tetracycline oral administration. The same study reports that in rosacea, tetracycline oral administration may prolong BUT. However, in recent years, azithromycin oral administration has become

mainstream. There are few studies with a high level of evidence on the topic.

The effects of tetracycline oral administration on meibum grade and epithelial disorders, and the adverse events related to tetracycline oral administration in MGD are unclear because of the lack of high-level evidence.

From the above, we conclude that effects following tetracycline oral administration on subjective symptoms such as meibum grade, and keratoconjunctival epithelial disorders in MGD are unknown. It is likely to improve meibomian gland orifices and surrounding findings and prolong BUT. Related adverse events are unclear. Therefore, it is unlikely to have any therapeutic benefits. There are few reports with a high level of evidence, and in recent years, semi-synthetic tetracyclines (doxycycline and minocycline) or macrolides (azithromycin) have become more commonly used than natural tetracyclines. Since only one article was available regarding the use of tetracycline in MGD, it was excluded from the assessment of strength of recommendation and strength of evidence.

CQ28 Is intense pulsed light effective?

(Reiko Arita and Naoyuki Morishige)

Recommendation IPL therapy in MGD effectively improves subjective symptoms, meibomian gland orifices and lid margin abnormalities, meibum grade, BUT, and corneal epithelial disorders. Adverse events are infrequent, mild, and reversible. Therefore, it is strongly recommended to be implemented. In Japan, IPL therapy is not approved for MGD (approved for MGD in the United States, South Korea, China, and Taiwan) as of November 2022, and there is no JHI's coverage. From this point of view, we will limit our current level of recommendation.

Strength of recommendation Marginally recommend "implementation"

Voting results: 8/8 (100%) marginally recommended "implementation". Four members with COI were excluded from voting.

Strength of evidence A (strong): Strongly confident in estimate of effect

Recommendation background IPL was originally a phototherapy used in cosmetic dermatology, but it has been proved effective in MGD in recent years [434]. Subsequently, a multi-center collaborative study on the safety and efficacy of IPL therapy for refractory MGD was published in Japan [435], and at the same time the efficacy of IPL therapy in MGD has been reported internationally. We searched the Cochrane, PubMed, and Ichushi-Web databases using the keywords meibomian gland dysfunction, evaporative dry eye, blepharitis, and IPL; studies that were not RCTs were excluded. In total, seven RCTs [374, 436–441] were included. Only one study evaluated all outcomes [374]. The results of the seven RCTs are as follows:

1. Subjective symptoms: assessed in five studies [374, 434, 438, 440, 441]; improvement shown in four studies [374, 434, 440, 441], no change in one study [438].
2. Meibomian gland orifices and lid margin abnormalities (plugging, vascularity, eyelid margin irregularity, and displacement of MCJ): assessed in two studies; improvement shown in both studies [374, 440].
3. Meibum grade: assessed in five studies; improvement shown in these studies [374, 437–439, 441].
4. BUT: assessed in four studies; improvement shown in these studies [374, 438, 439, 441].
5. Corneal or keratoconjunctival epithelial disorders: assessed in four studies [374, 437, 438, 441]; improvement shown in three studies [374, 437, 441], unchanged in one study [438]).
6. Adverse events: reported in one study [438]

The SR showed that only one study reports an adverse event [438], which was temporary and reversible. Since improvement in subjective symptoms, the main outcome considered in MGD treatment, can be expected by implementing IPL, the recommendation level of IPL is not reduced. There is still no international consensus or enforcement guidelines on how to implement IPL, specifically, on the frequency and number of applications. All the seven RCTs reviewed performed IPL therapy on the lower eyelids only [374, 436–441]. Four studies included meibum expression after IPL [374, 437–439]. The number of IPL applications varied among three times [436, 437, 439, 441], five times [440], and eight times [374]. Frequency was every 3 weeks [374], every 4 weeks [437–439], and on days 1, 15, and 45 [436, 441]. The follow-up period after IPL therapy was up to 6 months [441], 8 months [374], and 9 months [439]; however, there are no studies yet on the period until recurrence or response.

Focusing on costs, IPL has been approved for MGD overseas, but it has not yet been approved for MGD in Japan as of November 2022, and is not covered by JHI. Therefore, IPL is conducted at a cost of approximately 5,000 to 15,000 yen/treatment without insurance. Although the level of evidence is high, due to the above reasons, we decided to marginally recommend its implementation.

SR summary Although treatment with IPL has been performed in patients with MGD, the overall therapeutic effect has not been evaluated in Japan. Therefore, we conducted an SR of the effects of IPL therapy in patients with MGD.

Among the five RCTs [374, 434, 438, 441] that assessed subjective symptoms, four studies report improvements [374, 434, 440, 441], while no change is reported in one study [438]. Therefore, IPL therapy can be considered effective in improving subjective symptoms in MGD.

Two RCTs [374, 440] demonstrate that IPL therapy was effective in improving meibomian gland orifices and lid margin abnormalities. It should be noted that the number of studies is small.

Five RCTs [374, 437–439, 441] report that IPL was very effective in improving meibum grade.

Improvements in BUT are reported in four RCTs [374, 438, 439, 441], and improvements in NIBUT are reported in two RCTs [374, 436]. Therefore, IPL therapy is considered effective in improving BUT.

Corneal or keratoconjunctival epithelial disorders were evaluated in four RCTs [374, 437, 438, 441]. Of these, three showed improvements [374, 437, 441], while one showed no change [438]. Hence. IPL treatment may be considered effective in improving keratoconjunctival epithelial disorders.

Three RCTs [374, 436, 440] evaluated lipid layer grade by tear interference imaging observation device, and the improvement in LLT as an outcome indicating effectiveness.

Tear meniscus height [436], tear evaporation rates [436], meiboscore by meibography [374, 441], osmotic pressure [441] are examples of outcomes that did not show significant differences before and after treatment.

Pain, heat sensation, and partial eyelash loss were seen in only one RCT [438]. Hence, we conclude that the frequency of adverse events in IPL therapy is low, reversible, and mild.

An RCT reports some mechanisms induced byIPL to be the basis for the efficacy this treatment generates in MGD [437]. Inflammatory cytokines (IL-6, IL-17, and PG-E) in the lacrimal fluid were significantly reduced after IPL therapy [437]. In addition, liquefaction of the meibum due to the rise in temperature in the deep part of the skin was also considered to be a mechanism of that effect [442]. From the safety standpoint, based on the use of IPL in cosmetic dermatology for several decades, adverse events to the eyelid skin are unlikely to occur. However, long-term safety of ocular tissues, such as the lens and retina, has not been confirmed; this is one matter to study in the future.

Depending on the treatment method, there are some differences in the recommended protocol (treatment duration, frequency, and energy), mostly based on the model of the device used. In addition, four RCTs [374, 437–439] performed meibum expression during the treatment period. Nonetheless, there are no reports yet on the differences in the results with and without meibum expression. In the future, it will be necessary to establish an internationally standardized protocol.

Based on the above, IPL therapy in MGD is effective in improving subjective symptoms, meibomian gland orifices and lid margin abnormalities, meibum grade, BUT, and keratoconjunctival epithelial disorders. Since adverse events are infrequent, mild, and reversible, its implementation is strongly recommended on an evidence basis. However, since IPL is not approved for MGD in Japan and is not covered by JHI, the expense needs to be borne by the patient.

CQ29 Is thermal pulsation therapy effective?

(Takashi Itokawa and Yuichi Hori)

Recommendation Thermal pulsation therapy improves subjective symptoms and certain objective findings (meibomian gland orifice and surrounding findings, quality of meibum, and BUT) in patients with MGD. However, its implementation is only marginally recommended considering that there is currently no JHI's coverage.

Strength of recommendation Marginally recommend "implementation"

Voting results: 6/6 (100%) marginally recommended "implementation". Six members with COI were excluded from voting.

Strength of evidence B (medium): Moderately confident in estimate of effect

Recommendation background Eight RCTs have evaluated thermal pulsation therapy (LipiFlow®) [335, 336, 343, 357, 420, 443–445], and comparisons were made with eyelid warming in five studies, pre-cataract surgery in one study [444], oral administration of antimicrobials in one study [420], and integrin antagonist (lifitegrast®) in one study [445]. The study in which LipiFlow® was used before cataract surgery included not only patients with MGD but also healthy individuals [444]. In all the studies LipiFlow® was used once, with a treatment time of 12 minutes. Subjective symptoms were improved in four of the eight studies [335, 336, 343, 444]. Plugging showed a significant improvement in two out of four studies [343, 444]. The quality of meibum showed an improvement in three out of five studies [335, 343, 444]. BUT was improved in two out of seven studies [343, 444]. Corneal epithelial disorders were improved in one out of five studies [444]. Adverse events were examined in six studies [335, 343, 357, 420, 443, 445]; two reported no adverse events [357, 445], and four reported mild adverse events [335, 343, 420, 443]. There was no uniformity in the severity of MGD and the setting of treatment in the control groups in the RCTs; therefore, evidence level was set as B (medium).

In Japan, LipiFlow® was approved as a medical device in 2019. As of 2021, LipiFlow® is not covered by JHI. Based on the above, thermal pulsation therapy is marginally recommended.

SR Summary SR was performed concerning the efficacy of thermal pulsation therapy (LipiFlow®) as a treatment for MGD, and the outcomes included subjective symptoms, meibomian gland orifices and surrounding findings, quality of meibum, BUT, keratoconjunctival epithelial disorders, and adverse events.

Eight RCTs using LipiFlow® were identified. The breakdown of the control group included five studies with eyelid warming [335, 336, 343, 357, 443], one study with pre-cataract surgery [444], one study with oral antimicrobials [420], and one study with integrin antagonist eye drops [445].

One of the five studies that compared with eyelid warming [443] had performed eyelid warming and eyelid hygiene on the eye with LipiFlow®, another had performed eyelid hygiene only [357]. For the control groups, four studies had performed eyelid warming and eyelid hygiene [335, 336, 357, 443] and one had performed eyelid warming alone [343]. In all five studies, after LipiFlow®, subjective symptoms showed significant improvement. Significant improvement in the control group was observed in three studies [335, 336, 343] in the control group. Plugging was assessed in three studies [336, 343, 357], which significantly improved compared after LipiFlow ®. Comparison with the eyelid warming group was done in two studies [336, 343], and a significant improvement was observed in the LipiFlow® group in one study [343]. Meibum quality improved significantly after LipiFlow® in three [335, 343, 357] out of four studies [335, 343, 357, 443] that assessed it. Of the four studies that compared with eyelid warming [335, 343, 357, 443], two [335, 343] show significant improvements with LipiFlow ®. Of the four studies that evaluated BUT [336, 343, 357, 443], three [343, 357, 443] show significant improvements after LipiFlow®. There was a significant improvement in the LipiFlow® group in one [343] of the three studies [336, 343, 357] that compared with eyelid warming. There was no significant difference between the two groups in keratoconjunctival epithelial disorders.

One report studied of LipiFlow® before cataract treatment [444], and the LipiFlow® treatment group showed significant improvements in subjective symptoms, plugging, quality of meibum, BUT, and corneal epithelial disorders. In a report with oral administration of antimicrobial agents in the control group, only subjective symptoms were significantly improved in the LipiFlow ® group [420]. One study reports [445] that the subjective symptoms and eyelid vascularity were significantly improved in the integrin antagonist eye drops group.

Adverse events were studied in six of the six RCTs [335, 343, 357, 420, 443, 445]. There were no adverse events in two studies [357, 445]. Discomfort immediately after LipiFlow® was the major issue in the remaining four studies [335, 343, 420, 443]. No serious events were noted.

LipiFlow® is proposed as an option for treating MGD to significantly improve subjective symptoms and other objective findings compared with conventional treatment. Furthermore, studies indicate that the method is more suitable in cases with mild changes in meibum quality, morphology of meibomian glands, and short duration of illness [335, 357, 375, 444]. It is possible that the therapeutic benefits of LipiFlow® will be increased based on proper case selection.

CQ30 Is probing effective?

(Yuichi Kaji and Seika Den)

Recommendation Although intraductal meibomian gland probing for oMGD improves subjective symptoms, it is a rare and invasive treatment for improving obstruction of the meibomian gland orifices, meibum grade, BUT, and keratoconjunctival epithelial disorders. Therefore, it is marginally not recommended for implementation.

Strength of recommendation Marginally recommend "not to be implemented"

Voting results: 12/12 (100%) marginally recommended "not to be implemented"

Strength of evidence D (very weak): Little confidence in estimate of effect

Recommendation background Literature search using the keywords meibomian gland dysfunction, probe, and probing was performed in Cochrane, PubMed, and Ichushi-Web databases. RCTs were screened using clinical trial(s) and random as keywords. Only two reports were identified [446, 447]. Both employed regimens that combined intraductal probing with other treatment methods. Studies comparing the effects of the presence and absence of probing alone could not be found in our search. Although probing is reported as useful in improving subjective symptoms in both reports, no research is available to provide any substantial evidence. In addition, there was little improvement in meibomian gland orifice findings, eyelid margin findings, meibum grade, BUT, and keratoconjunctival epithelial disorders. It was concluded that the treatment itself should not be recommended because it is invasive, requires repetitions, and does not have JHI's coverage. Similar results were seen in high-quality research reports of non-RCTs [448–450].

SR Summary Other than two retrieved RCTs [447], we examined three high-quality research studies [448–450] though they were not RCTs. Participants in all studies had oMGD.

The probing of the meibomian gland is a treatment using a device aimed at opening obstructed orifices of the meibomian glands. The method was first reported by Maskin in 2010 [451]. This treatment is said to improve the tear lipid layer and subjective symptoms; however, most related studies were retrospective and uncontrolled, including the one by Maskin [451]. Two controlled studies were by Kheirkhah et al. [446] and Huang et al. [447]. Both employed regimens that combine other treatment methods with probing; studies that compare the presence and absence of probing exclusively could not be found in our research.

Kheirkhah et al. [446] divided the participants into: (1) a group that used antibiotics and corticosteroid-containing ophthalmic ointment after probing, (2) a group that used a lubricant ointment containing dextran or the like after probing, and (3) a group that used a lubricant ointment without probing. When the changes in subjective symptoms, BUT, keratoconjunctival epithelial disorder, eyelid margin vascularity, and meibum expression were compared in each group before and 1 month after probing, it was concluded that both groups 1 and 2 that underwent probing showed significant improvements in subjective symptoms. Nonetheless, there were no changes in BUT and other findings. Since the degree of improvement was higher in group 1 in this report, the anti-inflammatory effect of corticosteroids after probing may have had an influence. Therefore, the effect of probing alone remains unclear.

Huang et al. [447] performed a comparison of subjective symptoms, BUT, corneal epithelial disorders, meibum expression, and eyelid findings before and after treatment in three groups: the IPL group, probing group, and IPL with probing group. It is reported that the group that underwent both IPL and probing had a higher degree of improvement in subjective symptoms, BUT, properties of meibum, and eyelid margin vascularity than IPL or probing alone. The other groups also reported improvement in all endpoints following treatment. However, the study was not an RCT that focused solely on probing. In addition, since it is believed that not only the amount of tear lipids is involved in the pathology of MGD, but also the inflammation of the meibomian gland and intraductal bacterial lipase activity, probing alone is considered to have limited efficacy.

Ma et al. [448] compared a group that used probing and 0.1% fluorometholone eye drops with a group that used 0.1% fluorometholone eye drops alone. The group that utilized probing showed improvements in the properties of meibum, inflammatory findings at the eyelid margin, and BUT. However, improvements in the findings were also observed with 0.1% fluorometholone eye drops alone. The effects of probing alone were not evaluated.

Incekalan et al. [449] compared a group that received conventional MGD treatment (eyelid warming, massage, eyelid hygiene, artificial tear drops, antibiotic eye drops, and oral omega-3 and azithromycin) with a group that received probing in addition to these conventional treatments. The group that received probing showed improvements in BUT, Schirmer value, meibum expression, and meibum quality when compared to the baseline. However, there was no significant difference in the improvement ratio of each parameter between the conventional treatment group and the conventional treatment plus probing group. Hence, there is a limit to determining the effect of probing alone.

Sik Sarman et al. [450] performed probing in patients with MGD and report improvements in subjective symptoms, BUT, and eyelid inflammation. However, the diagnostic criteria for MGD are unclear, and the comparison was with pre-treatment conditions, without a control group. Furthermore, since antibiotics, corticosteroids, and artificial tears were administered after probing, there were limitations in determining the therapeutic effect of probing alone.

Bleeding from the eyelid and meibomian gland orifices may occur during probing. No special treatment was required to stop the bleeding in any of the studies and no post-treatment complications are mentioned.

Chapter 5

Initiatives after Publication

Post publication organizational structure

Committees	Mode of action after publication
Guideline Supervisory Board	Disseminate and utilize the guidelines. Check for publication of new evidence.
Guidelines Preparation Team	Disseminate and utilize the guidelines. Check for publication of new evidence.
Systematic Review Team	Disseminate and utilize the guidelines. Check for publication of new evidence.

Adoption

Steps	Course of action
Creation of a summary version	Creation of a summary version is under consideration.
Media applications	Published in the Journal of Japanese Ophthalmological Society and the Japanese Journal of Ophthalmology. Post on the websites of the Japanese Ophthalmological Society, the Japan Cornea Society, and the Japan Dry Eye Society.

Steps	Course of action
Promotion of the use of the clinical practice guideline	Promote the adoption and use in daily practice through applicable societies and research associations (Japanese Ophthalmological Society, Japan Cornea Society, and Japan Dry Eye Society)

Effectiveness evaluation

Methods	Specific measure
Investigate its use through related societies and research societies (Japanese Ophthalmological Society, Japan Cornea Society, and Japan Dry Eye Society)	Questionnaires

Revisions

Aspects	Policy
Period	Revision planned in five years. As well as periodic revisions whenever important evidence emerges.
Method	Decisions to be made based on the current practice guidelines.
Organizational structure	Reorganize the guideline supervisory board, guideline secretariat, guideline preparation team, and systematic review team.

Funds for guideline preparation

Financed by a research fund of the Japan Cornea Society and a research and awareness activities fund of the Dry Eye Research Society.

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Declarations

Conflict of interest S. Amano, Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events (Senju, Novartis, Santen, ZEISS, Luminus, Otsuka), Other financial or non-financial interests (M's Science, Sciones Health Clinical, MIC Medial, IDD); J. Shimazaki, Consulting fees (Santen, QD Laser, IDD), Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events (Santen, Otsuka, Senju), Participation on a Data Safety Monitoring Board or Advisory Board (Santen); N. Yokoi, Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events (Santen, Senju, Lumenis), Patents planned, issued or pending (Kowa, Rexxam); Y. Hori, Grants or contracts (Santen, Senju, Alcon, Novoxel, KOWA), Consulting fees (Lumenis, Santen, Senju, Kao), Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events (Santen, Senju, Otsuka, Lumenis, Menicon, Johnson & Johnson); R. Arita, Consulting fees (Lumenis, Alcon, TOPCON, Santen, ROHTO), Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events (Lumenis, Senju, Santen, TOMEY, ROHTO, AMO), Support for attending meetings and/or travel (Santen), Patents planned, issued or pending (Non-contact meibography, Eye mask containing menthol, Image analysis of meibography, Vitamin D application for meibomian gland dysfunction).

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