OULUN AMMATTIKORKEAKOULU

Eliisa Loukkola

HOW TO ASSESS AND MANAGE MEIBOMIAN GLAND DYSFUNCTION INDUCED EVAPORATIVE DRY EYE PATIENT IN REGULAR OPTICAL STORE

Integrative literature review

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Eliisa Loukkola
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Oulu University of Applied Sciences

ABSTRACT

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Author: Eliisa Loukkola
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Background:
Meibomian gland dysfunction (MGD) is a prevalent eye condition, particularly among older adults, and is the leading cause of evaporative dry eye disease (EDED), the most common form of dry eye disease (DED). As Finland's population ages, the occurrence of MGD-induced EDED is likely to increase. Recently specialized dry eye clinics have been established in major Finnish cities. However, optometrists in general optical stores are often the first to encounter MGD-induced EDED patients. Thus, it is essential for them to know how to assess and manage this condition with basic equipment and recognize when to refer patients to specialists.

Purpose:
The purpose of the thesis is to describe by means of an integrative literature review how to assess and manage MGD-induced EDED among Finnish optometrists in general optical store. This thesis focuses only on non-medical treatments, because in Finland optometrists are not allowed to prescribe medications. Another aim is to increase optometrists' knowledge of MGD and provide a peek into new technology device treatment possibilities.

Methods:
The primary literature search for the integrative review was conducted by using PubMed, ScienceDirect Elsevier, and EBSCOhost, through the Academic Search Premier and CINAHL databases. The search was restricted to English-language publications from 2011-2024 with free full-text. This process yielded 829 records, which were then subjected to further exclusion criteria. The final selection of fourteen articles was illustrated using the PRISMA Flow chart by Covidence.

Results:
The results of this study enable Finnish optometrists to assess the clinical signs of MGD-induced EDED using regular optical store equipment and to manage the condition emphasizing early intervention with non-medical conventional treatments. It highlights the importance of referral and co-management with dry eye clinics and ophthalmologists.

Conclusions:
This thesis provides valuable insight into the assessment and management of MGD-induced EDED in regular optical stores. It emphasizes the importance of early detection, non-medical treatment approaches and the need for uniform guidelines.

Keywords: meibomian gland dysfunction, evaporative dry eye, MGD/evaporative dry eye assessment, MGD/evaporative dry eye management

CONTENTS

1 INTRODUCTION

Meibomian gland dysfunction (MGD) is a common eye problem encountered in general optical store practice. It can affect people of all ages but is more prevalent in older age. It's thought to be the leading cause of evaporative dry eye disease (EDED), which in turn is the biggest form of dry eye disease (DED). Because population in Finland is aging, MGD induced evaporative dry eye disease may become more prevalent.

MGD patients are mostly asymptomatic, but as the disease progresses symptoms like ocular dryness, foreign body sensation, burning, or photophobia can become serious and affect negatively to patients' quality of life (Chan et al., 2019). Therefore, it's important for optometrists to assess and manage MGD and raise awareness among patients about MGD even if it's asymptomatic.

Dry eye technology has taken huge development steps in recent years. Specialized dry eye clinics with advanced technology assessment and management equipment have been established around Finland biggest cities in last few years. Still usually the first eye professionals to encounter asymptomatic or slightly symptomatic MGD induced EDED patients are optometrists in basic eye examination in general optical store practice. That's why it's important to know how to assess and manage MGD-EDED with basic equipment and when to refer further to specialized dry eye clinics or to ophthalmologists.

There are no clinical guidelines for MGD nor to dry eye disease assessment and management in Finland (Duodecim, Suomen käypähoitosuositus). The only guideline available are Dry eye disease, Nordic guidelines 2016 and second edition 2022 created by Heegaard s. et all. They base their guidelines on TFOS International Dry eye workshops DEWS I (2007) and DEWS II (2017) and on international workshop on MGD (2011). The pamphlet gives very good information about DED assessment and management methods and is aimed at healthcare professionals dealing with Dry eye disease.

There is a clear need for uniform guidelines in Finland for assessing and managing of dry eye disease in general optical store. Dry eye disease is divided into two categories, aqueous deficiency dry eye (ADDE) and evaporative dry eye (EDE). ADDE is characterized by tear deficiency of the lacrimal glands, when watery components are not produced enough to the tear film, example in

Sjögrens syndrome. In evaporative dry eye disease (EDED) the problem is the decreased oil layer of tear film produced by meibomian glands. Because dry eye disease (DED) is an enormous topic, this thesis will concentrate on meibomian gland dysfunction induced evaporative dry eye disease (MGD-induced EDED), which is thought to be the more common form of DED (Cote, Zhang, et al., 2020).

The purpose of the thesis is to describe by means of an integrative literature review how to assess and manage meibomian gland dysfunction (MGD) induced evaporative dry eye disease among Finnish optometrists in general optical store. This thesis focuses only on non-medical treatments, because in Finland optometrists are not allowed to prescribe medications, only diagnostic medication use is allowed.

Another goal is to increase optometrists' knowledge and understanding of meibomian gland dysfunction and provide insights into advanced new technology device treatment possibilities for managing MGD-induced EDED.

2 DRY EYE DISEASE

Dry eye disease (DED) is commonly encountered in clinical practice, impacting from 5% to 50% of the population. Dry eye disease etiologies can be divided in two subgroups, aqueous deficient (ADDE) and evaporative dry eye disease (EDED) of which the later related to meibomian gland dysfunction (MGD) appears to be the most prevalent subtype (Craig, Nichols, et al., 2017).

The Tear film and ocular surface society (TFOS) have launched two international workshops on dry eye, TFOS DEWS I 2007 and TFOS DEWS II 2017, which again work as a blueprint for further studies.

The TFOS international dry eye workshop II definition for dry eye disease:

"Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles." (Craig et al., 2017).

3 THE MEIBOMIAN GLAND DYSFUNCTION

Meibomian gland dysfunction (MGD) is a prevalent chronic eye condition often seen in clinical practice and is a major cause of evaporative dry eye disease. A characteristic for MGD is that the quantity of meibomian gland secretion (meibum) is reduced and/or meibum quality is changed. These changes disrupt the tear film lipid layer stability which leads to evaporation of tears, tear hyperosmolarity, mechanical irritation and inflammation, leading to ocular surface damage and to evaporative dry eye disease (Sheppard & Nichols, 2023).

Many words have been used as synonyms for meibomian gland dysfunction (MGD), like meibomitis, meibomianitis, meibomian gland disease and posterior blepharitis. According to the international workshop of MGD, the meibomian gland dysfunction is the appropriate term to use, because it best characterizes the functional irregularities of the meibomian glands. Meibomitis and meibomianitis are subgroups of MGD, meaning conditions which specifically involve inflammation in the context of Meibomian Gland Dysfunction. Meibomian gland disease on the other hand means a wider spectrum of conditions affecting the meibomian glands, including neoplasia (abnormal growths) and congenital disorders. Posterior blepharitis is most often used as a synonym for MGD, but they are not interchangeable, cause posterior blepharitis refers to inflammatory conditions affecting the meibomian glands. MGD is a common cause of this inflammation, but just one potential contributing factor, often leading to posterior blepharitis but not exclusively causing it. (Nichols et al., 2011.)

Nevertheless, both resent blepharitis guidelines, Blepharitis Preferred Practice Pattern® (PPP) 2023 USA and Clinical Management Guidelines of Blepharitis (Lid margin disease) of The College of Optometrists in United Kingdom use meibomian gland dysfunction almost as a synonym for posterior blepharitis. Blepharitis PPP 2023 definition for the disease is, *"blepharitis is a chronic ocular inflammation that involves the eyelid margin primarily and is a common cause of chronic ocular irritation"*. They divide blepharitis into traditional clinical subcategories, as staphylococcal, seborrheic, meibomian gland dysfunction (MGD), or a combination thereof, but they also state that Meibomian gland dysfunction can also occur without inflammation. (Lin et al., 2024; College of Optometrists, 2024.) So the terminology stays complicated.

3.1 Definition, Prevalence and risk factors

Definition

Before year 2010 there was no global consensus of meibomian gland dysfunction definition, classification, diagnosis or therapy. The Tear Film and Ocular Surface Society (TFOS), a non-profit organization, brought together more than 50 international leading clinical and basic research experts around the world for an international workshop on MGD. It took more than two years to complete the workshop. (Nichols et al., 2011.) It can be considered as a very significant work, for example, The international workshop on meibomian gland dysfunction: Executive summary, have been cited for over thousand times according to google scholar.

The TFOS international workshop on meibomian gland dysfunction definition of MGD:

"Meibomian gland dysfunction (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." (Daniel Nelson et al., 2011).

Prevalence

According to Hassanzadeh et al.'s (2021) systematic review and meta-analysis, Meibomian Gland Dysfunction (MGD) is a relatively common condition, with an estimated prevalence of 35.8% globally. The study indicates that males are more likely to develop MGD compared to females and advancing age appear to increase the likelihood of experiencing MGD. Prevalence varied also between ethnicities being least common among African populations, with a prevalence of 21.2%, and Caucasian groups, at 29.5%. Conversely, the condition was found to be much more prevalent among Hispanic and Arab populations, with rates of 67.5% and 71.0%.

In Europe the prevalence of MGD without symptoms according to Viso et al. (2012) study is 21.9% and with symptoms 8.6%. Asymptomatic MGD gets more prevalent with age and in males and symptomatic MGD increased with age but wasn't linked to gender. Norwegian study by Badian et al. (2021) reported prevalence of MGD overall 93,8% among symptomatic patients visiting specialized dry eye clinic first time in Norway and found no difference between gender or age. These studies show a wide range of differences, which can be attributed to different methods of diagnosis,

the number of participants, the overall quality of the research, the ages of the subjects, and their ethnic backgrounds.

Risk factors

Meibomian Gland Dysfunction (MGD) is associated with several systemic, ophthalmic and medication-related risk factors. As we age, the likelihood of developing MGD increases. Hormonal imbalances, particularly a deficiency of androgens, can contribute to its onset. Medications like Isotretinoin also known as 13-cis-retinoic acid (used for acne), oral contraceptive therapy, postmenopausal hormone therapy, drugs for benign prostatic hyperplasia, antidepressants, and antihistamines, may contribute to MGD. Ophthalmic risk factors include anterior and posterior blepharitis, Demodex infestation, dry eye disease, incomplete blinking, wearing contact lenses and ocular surgeries. Systemic influences, such as rosacea, Stevens-Johnson syndrome, Sjögren's syndrome, cholesterol levels, psoriasis, atopy, hypertension, migraine headaches, thyroid disease and stem cell transplantation, play a role. Additionally, environmental factors like geographic location, temperature, humidity, and prolonged use of video display terminals impact MGD risk. (Schaumberg et al., 2011; Nichols et al., 2011; Wang et al., 2020.)

According to Tomioka et al. (2023) systematic review and meta-analysis there is a robust association between elevated cholesterol and triglyceride levels and the occurrence and severity of MGD. Their comparison between individuals with Meibomian Gland Dysfunction (MGD) and healthy controls showed higher total cholesterol (TC) and triglyceride (TG) levels to be more prevalent in MGD patients. Furthermore, MGD severity tends to be greater in individuals with dyslipidemia.

Another study by Tulsyan et al. (2021), involving 400 patients diagnosed with Meibomian Gland Dysfunction (MGD), elevated LDL cholesterol levels were associated with a 20% increased risk of moderate-severe MGD. However, other lipid parameters (total cholesterol, triglycerides, and HDL) did not show significant associations. The study also revealed that MGD severity tends to increase with age, particularly in patients aged 50 years and older. Hypertension was linked to a 36% higher risk of moderate-severe MGD, while diabetic patients faced an even more pronounced risk (57% higher). Additionally, post-menopausal women had a 53% elevated risk of MGD.

3.2 The anatomy and physiology of meibomian glands

Meibomian glands are holocrine sebaceus glands located at the posterior part of the eye lids within the tarsal plates. There are around 25-40 glands in the upper and about 20-30 in the lower eyelid. One single meibomian gland consists of clusters of secretory acini, ductules and the central duct. The anatomy of meibomian gland could be compared to a cluster of black currants, where the berries are represented as the acinus, the central stem as the central duct and the small stalks that connect the berries to the central stem as the ductules. The central ducts reform to excretory ducts near the lid margin, where they open anterior to mucocutaneus junction at lid margin epidermis and form meibomian gland orifices, by which the oily secretion called meibum produced by secretory acini cells called meibocytes enters the tear film forming the lipid layer (Knop et al., 2011). The driving force of meibum from meibomian glands to the tear film is the continuous secretion of acini and the muscle contraction of the orbicularis oculi muscle when blinking and the contraction of the Riolan's muscles around the excretory duct and among the acini a terminal part of the ductal system (Knop et al., 2011.)

3.3 Meibum importance to the tear film stability

Tear film is a crucial component of our eyes' health, which is traditionally divided into three distinct layers: mucin, aqueous and lipid layer. However, the TFOS DEWS II Tear Film subcommittee 2017 suggested that mixing occurs between the mucin and aqueous layers and preferred dividing the tear film in two layers, muco-aqueous and lipid layer.

The tear film lipid layer (TFLL) forms a thin barrier against watery tear evaporation and overspill. It lubricates the ocular surface and aids in the spreading of tears upon blinking and is significant for reducing surface tension and maintaining tear film stability. Tear film lipid layer is primarily composed of meibum which consists of two main types of lipids polar and nonpolar. Outermost nonpolar lipids (95%) create a hydrophobic barrier which helps prevent excessive tear evaporation and maintains tear volume. They consist of predominantly wax esters and cholesterol esters and a small number of triglycerides. Polar lipids (5%) adjacent to the aqueous-mucin layer have both hydrophilic and hydrophobic parts which include OAHFAs (O-acylated ω-hydroxy fatty acids), free cholesterol and phospholipids and they work as important surfactants reducing surface tension. (Willcox et al., 2017; Nagar et al., 2023.)

Meibum also forms a barrier against microorganisms and environmental factors maintaining the integrity of the tear film. Without sufficient meibum, tear film stability decreases, leading to dry eye symptoms, visual fluctuations and discomfort. (Willcox et al., 2017.)

3.4 Subcategories

Meibomian gland dysfunction is divided into two subcategories, *low-delivery* and *high-delivery state*. The *low-delivery state* is again divided into two subcategories, *hyposecretory and obstructive*. Hyposecretory MGD refers to a chronic abnormality of the meibomian glands where there is reduced meibum secretion without significant obstruction of the gland's terminal ducts. Obstructive form occurs when there is a blockage or obstruction in the terminal ducts of the meibomian glands and is further divided into subcategories cicatricial (scarring) and non-cicatricial form. Hyposecretory, obstructive (*low-delivery state)* and hypersecretory *(high-delivery state)* categories are all divided into main (primary) and contributing (secondary) causes. For example, mucus membrane pemphigoid contributes to obstructive cicatricial MGD as a secondary cause, while seborrheic dermatitis and acne rosacea are secondary causes of both obstructive non-cicatricial and hypersecretory MDG. (Nichols et al., 2011.)

3.5 Symptoms, signs and severity grading

Symptoms

Initially, meibomian gland dysfunction can be asymptomatic, meaning patients may not notice specific discomfort. However, as the disease progresses, it can lead to evaporative dry eye disease. Common symptoms of dry eye which don't specifically indicate a particular etiology include sensations like eye dryness, grittiness, or irritation, along with redness, burning sensations, and paradoxical tearing. Blurred vision and eyelid margin changes such as swelling or thickening may also occur. These symptoms can worsen throughout the day or in specific conditions, such as after prolonged screen time or exposure to wind or dry environments. (Tomlinson et al., 2011; Narang et al., 2023.)

Signs

Clinical key signs of Meibomian Gland Dysfunction (MGD) are changes in the quality and quantity of gland secretions (Nichols et al., 2011). Other signs include meibomian gland dropout, lid morphology changes like rounded, notched, or dimpled gland openings, anterior replacement of mucocutaneous junction, posterior replacement of MG orifices, visible small blood vessels (telangiectasia), hyperemia of the posterior lid margin, redness of conjunctiva, ridges of epithelial tissue between gland openings, formation of hard deposits within the glandular tissue, and potentially the development of chalazia. (Tomlinson et al., 2011).

Severity grading

According to Geerling et al. (2011) severity grading of MGD is divided into four stages and additional plus disease when MGD co-exists together with other ocular surface disease:

1. Minimally altered expressibility and secretion quality, no symptoms, no corneal staining
2. Mildly altered expressibility and secretion quality, minimal to mild symptoms, none to limited corneal staining
3. Moderately altered expressibility and secretion quality, moderate symptoms, mild to moderate corneal staining, mainly peripheral
4. Severely altered expressibility and secretion quality, marked symptoms, marked corneal staining, central in addition

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

3.6 Assessment and differentiation

According to the International Workshop on Meibomian Gland Dysfunction, Report of the Diagnosis Subcommittee (2011), the assessment of MGD and MGD-induced evaporative dry eye should include several tests in a specific order to minimize unwanted effects between the tests.

First, they recommended gland expression with moderate digital pressure with finger or specific tool to the central part of the lower eye lid to find asymptomatic MGD by determining the meibomian gland functionality and ability to provide meibum. Expression is significant, cause meibum flow is not possible to observe from individual gland during blinking with slit lamp. If asymptomatic MGD

is diagnosed based on decreased or tenuous expressibility and poor quality of meibum, further ocular surface damage and dry eye tests are required at next visit.

Their recommendation for a two-step approach to the diagnosis of MGD is as follows:

Initially, differentiate normal patients from those with generic dry eye (either aqueous deficient or evaporative dry eye). In the second phase, distinguish MGD-induced evaporative dry eye from aqueous deficient dry eye. The following sequence of tests is suggested for use in a general clinic for diagnosing MGD-related disease in patients presenting with symptoms of ocular surface disease:

1. *Administration of a symptom questionnaire*
2. *Measurement of the blink rate and calculation the blink interval*
3. *Measurement of lower tear meniscus height*
4. *Measurement of tear osmolarity (if available)*
5. *Instillation of fluorescein and measurement of the tear film breakup time (TFBUT) and Ocular Protection Index (OPI)*
6. *Grading of corneal and conjunctival fluorescein staining*
7. *Schirmer test or alternate (phenol red thread test)*

Positive (abnormal) results in tests 1, 4, 5, and 6 provide partial evidence of the presence of a generic dry eye, without specifying whether it is aqueous-deficient or evaporative. Evidence of aqueous-deficient dry eye may be obtained by measuring tear flow or an assessment of aqueous volume on the basis of tear meniscus height or Schirmer test.

8. *If MGD has not been characterized (symptomatic/asymptomatic) at a previous visit, then it can be assessed at the end of this sequence as follows:*
    a. *Quantification of morphologic lid features*
    b. *Expression: quantification of meibum expressibility and quality*
    c. *Meibography: quantification of dropout.*

The results should be recorded by using the grading models assigned to each test which enables disease's progression evaluation during treatment. (Tomlinson et al., 2011.)

If infrared meibography systems are unavailable, ophthalmologists and optometrists can still identify abnormalities in the eyelid margin using slit-lamp microscopy. Notably, dimples at the lid margin can indicate gland dropout. According to Ha et al. (2021) research on the relationship between lid margin abnormalities and meibomian gland loss using infrared meibography revealed that out of 25 eyes with dimples, 21 (84%) showed either localized or complete loss of meibomian glands at the dimpled sites.

In addition to differentiation of meibomian gland dysfunction (MGD) from generic dry eye and aqueous deficiency dry eye, MGD shares also symptoms with various ocular surface disorders. Conditions such anterior blepharitis and demodex infestation can present with similar clinical features or as comorbidities, complicating the assessment process. Additionally, systemic diseases like Sjogren's syndrome and rosacea, as well as external factors such as contact lens use and allergic conjunctivitis, can mimic MGD symptoms. Misdiagnosis can lead to inappropriate treatment or delayed care. (Tomlinson et al., 2011; Wolffsohn et al., 2017.)

3.7 Management and a peek into new technology device treatments

Due to the chronic nature of the MGD, the primary aim in the management of MGD-induced DED is to restore the lipid layer of the tear film and reduce evaporation, which helps to alleviate ocular symptoms and signs. Managing Meibomian Gland Dysfunction (MGD) involves patient education and both at-home care methods, such as eyelid hygiene, warm compress, and artificial tear substitutes, as well as in-office treatments like manual gland expression, microblepharoexfoliation, thermal pulsation, intense pulsed light therapy and intraductal probing. (Sheppard & Nichols, 2023; Geerling et al., 2011.)

Eyelid hygiene with warm compress, massage and cleaning at-home are still the cornerstones of the meibomian gland dysfunction treatment. Artificial tear substitutes, ointments, lipid sprays/drops, and eyelid wipes/scrubs are often used. Environmental and dietary modifications like omega-3 intake should be also considered as first line treatment. In-office treatments which can be conducted with general optical store equipment are meibomian gland forceful expression and debridement scaling. If inflammation is present person should be referred to ophthalmologist to gain topical or systemic medication, cause in Finland, optometrists only have the allowance to prescribe diagnostic drugs. (Sabeti et al., 2020; Geerling et al., 2011.)

Numerous new technology device treatments have recently been introduced to the market in specialized dry eye clinics, which will be reviewed in this section, even though the analysis itself focuses on traditional, inexpensive treatments that can be easily implemented by patients or with general optical store equipment.

3.7.1 Eyelid hygiene

Lid hygiene is considered as the mainstay for treating MGD, involving warm compress and eyelid massage. Despite variations in technique and patient compliance, treatment is widely accepted among clinicians. Patients should be instructed in lid-warming and hygiene and encouraged to stay compliant with long-term symptom control. Regular follow-up exams are recommended to ensure adherence. Heat can be applied in various ways, such as using warm compresses like a hot wet towel or a heated rice or flaxseed bag, or with devices that emit infrared or hot air. Mechanical lid hygiene includes scrubbing, expressing, and cleaning the eyelashes and lid margins with various solutions and is often advised alongside lid warming for treating MGD. (Geerling et al., 2011.)

According to Borchman (2019) study, the optimal temperature for the eyelid heating is 40-41.5°C by which 90% lipid disorder is achieved. New study by G. Lee, (2024) compared three different warm compresses, hot towel, microwaveable eye mask, and self-heating eye mask. The review concluded that all three methods can reach 40°C and a single application, whether 5 minutes with hot towels or microwaveable eye masks, or 20 minutes with self-heating eye masks, improved tear quality immediately. Repeated applications relieved dry eye symptoms from MGD and improved meibomian gland health. Hot towels were effective but needed frequent reheating to maintain 40°C.

Review by Schjerven Magno et al. (2023) also emphasized the importance of reheating a wet towel every two minutes to maintain the optimal temperature, which they determined to be between 40°C and 47°C, "warm, but not painful." They advised testing the warmth against the inside of the wrist before applying it to the face. Subjective benefits can last for 6 months by supporting occasional retreatment according to Bilkhu et al. (2014).

3.7.2 Patient education, environmental and dietary modifications

Patient education, environmental, and dietary modifications play an important role in managing the MGD-induced EDED. Educating patients about the chronicity of the condition and the importance of consistent eyelid hygiene, including the use of warm compresses, massage, and cleaning, are essential in alleviating symptoms and preventing progression. Environmental modifications, such as using humidifiers in dry conditions and avoiding exposure to air conditioning or heating, help maintain adequate moisture levels in the eyes. Additionally, dietary changes, particularly increasing the intake of omega-3 fatty acids, may improve the quality of meibum. These modifications help patients to take control of their care, which might reduce the need for other treatments. (Rolando et al., 2018; Tong et al., 2021; Jones et al., 2017.)

3.7.3 Artificial tear substitutes, lipid-containing eye drops or ointments, liposomal sprays and Perfluorohexyloctane

Artificial tear substitutes and lubricants, commonly known as artificial tears (AT), play a significant role in treating MGD and aqueous-deficient dry eye (ADDE). While ADDE is not central to MGD, it often coexists with it, affecting many patients. Estimates suggest that 50% to 75% of MGD patients also experience reduced tear production. (Geerling et al., 2011.)

Artificial tears, not viscous, help by rinsing the ocular surface, diluting inflammatory molecules, and reducing pro-inflammatory stimuli. Key considerations in selecting ATs include preservative content, viscosity, and lipid supplementation. Preservative-free ATs are preferred for frequent use to avoid toxicity. Higher viscosity lubricants, such as gels and ointments, provide longer-lasting relief but may cause temporary blurring of vision and though are recommended at night before sleep. (Geerling et al., 2011; Jones et al., 2017.)

Lipid-containing eye drops or ointments and liposomal sprays are used to manage Meibomian Gland Dysfunction (MGD). Historically, these products cause vision to blur, but newer formulations are better accepted. Studies have shown that lipid supplements can improve symptoms and signs of MGD. Emulsion-based drops also demonstrated to rapidly reform the tear lipid film. Liposomal sprays have shown significant benefits in reducing lid margin inflammation and improving tear film stability in patients with evaporative dry eye. It has been confirmed that these sprays can increase

lipid layer thickness and non-invasive tear breakup time (NIBUT) in normal eyes. (Geerling et al., 2011; Jones et al., 2017.)

Perfluorohexyloctane (F6H8) is a water-free, physically and chemically inactive synthetic single-component lipid eyedrop. F6H8 has been approved as a medical device in Europe, Australia, and New Zealand. It has been on the market since 2015 and gained the FDA approval in the United States in 2023. (Ballesteros-Sánchez, De-Hita-Cantalejo, et al., 2023.)

The systematic review of six RCT-studies concluded that F6H8 enhanced DED signs and symptoms such as OSDI score, tear break up time (TBUT), tear lipid layer thickness (LLT) and total corneal fluorescein staining (tCFS). The study reported high patient satisfaction with minimal treatment emergent adverse events. They concluded that F6H8 appears to be an effective and safe treatment to recommend for dry eye patients and especially patients suffering from MGD. (Ballesteros-Sánchez, De-Hita-Cantalejo, et al., 2023.) In Finland Perfluorohexyloctane has been on the market by name Evo Tears since 2020.

3.7.4 Eyelid exfoliation treatment

Eyelid Exfoliation treatment is an in-office method used to exfoliate the accumulated biofilm debris, keratinized epithelia and MG obstructions from eyelid margins (Zhu et al., 2022). The treatment can be performed with mechanical eyelid debridement-scaling (LDS) when a stainless-steel golf spud (Hilco Wilson Ophthalmics) is used or with microblepharoexfoliation (MBE) the handheld BlephEx LLC instrument (Ballesteros-Sánchez, Gargallo-Martínez, et al., 2023).

The systematic review of Ballesteros-Sánchez A et al. (2023) concluded that eyelid exfoliation treatment yields better results compared to eyelid hygiene alone, with minimal reported complications and is therefore considered as a safe and effective treatment method for DED. They also found that LDS appears to be more effective than MBE in improving the expressibility of meibomian glands. Additionally, it leads to a reduction in microorganism load and lipase activity.

3.7.5 Meibomian gland expression

In-office meibomian gland expression (MGX) has been used for over 90 years. It involves pressing the eyelids together or using a rigid object on the inner lid while applying pressure on the outer surface. Significant pressure is often needed to release blocked meibum, but pain limits this despite using topical anesthetics. (Geerling et al., 2011.) Despite the discomfort, multiple studies have shown that manual meibomian gland expression is effective in treating meibomian gland dysfunction (MGD). It is advisable to perform this procedure monthly until the gland dysfunction is resolved. (Arita & Fukuoka, 2020.)

The first systematic review and meta-analysis show that MGX effectively reduces dry eye symptoms in MGD patients. However, there's not enough evidence to confirm its impact on dry eye signs and meibomian gland function. (Ballesteros-Sánchez, Sánchez-González, et al., 2023.)

3.7.6 Intraductal probing

Intraductal probing (Maskin Probe, Corza Medical) has been used since 2010, it involves mechanically opening of the meibomian gland central duct through orifices with 1mm-6mm length and 76 microns in diameter stainless-steel probes under local anesthesia and with aid of slit lamp microscope (Maskin & Alluri, 2019).

The first randomized, double-masked, sham-controlled clinical trial was Kheirkhah et al., (2020) which studied 42 refractory obstructive MG patients divided into three groups and compared intraductal probing on only upper lids with or without topical antibiotic/steroid and sham treatment. After four weeks symptoms were relieved in both intraductal probing groups, but not in sham group, but there were no significant changes in clinical signs. There were no adverse effects in the procedure.

A Magno et al. (2021) review of 14 studies concluded that existing research leaves the impact of meibomian gland probing (MGP) on subjective symptoms and objective signs measures uncertain. Some of the review studies reported positive outcomes with MGP, but these often-involved combined treatments. They stated that consequently, there is a critical need for robust clinical trials that are double-blinded, randomized, and placebo-controlled, with a sufficiently large sample size to yield reliable conclusions about this treatment approach.

3.7.7 Intense pulsed light (IPL)

Intense pulsed light (IPL) was first used for skin treatment, such as dermal vascular lesions, acne and facial rosacea. In 2002 Dr. Toyos noticed that his facial rosacea patients experienced also dry eye signs and symptoms relief after IPL treatment, and he developed the first devise targeted for MGD induced dry eye. In 2015 Toyos et al. 3-year retrospective study findings indicated that Intense Pulsed Light (IPL) shows potential as a treatment for evaporative Dry Eye Disease (DED) due to Meibomian Gland Dysfunction (MGD), and it has minimal side effects.

Since then, IPL has been used for MGD treatment and many studies have been published. Today there are over ten different IPL devises, of which M22; Lumenis, Israel/USA and E>Eye; E-SWIN, France are most common (Qin et al., 2023). The IPL system utilizes a xenon lamp to emit 500 - 1200 nm light to specifically target the sebaceous glands on the skin. Skin tone affects the intensity chosen for the treatment and darker skin types are at risk for depigmentation. Treatment is done with the aid of ultrasound gel to skin under the lower eye lid and both temples, also the upper eyelid can be treated with small spot size if there are upper eye lid symptoms. IPL should be repeated 3-4 times, within 2–6-week intervals to achieve better results, MGX is often combined to the treatment. (Qin et al., 2023.)

Mechanism of action is still unsure, but assumption is that it warms and liquefies meibum, decreases inflammatory cytokines via vessel thrombosis, reduces bacterial and parasitic growth and might enhance meibomian gland microstructure (Lam et al., n.d.). TOFS DEWS II, management and therapy report (2017) brought up three studies of which all concluded IPL to be safe and effective treatment, reducing symptoms and improving MG function and tear film quality.

PubMed search for intense pulse light and meibomian gave 95 results with free text, of which four were systematic reviews. Two studies were published in 2020; Liu et al., systematic review composed of four RCT studies (two combined IPL to MGX) main outcome measures were SPEED and NIBUT, they found no significant improvement on symptoms, but NIBUT showed significant improvement after IPL treatment follow-up duration ranging from 12 weeks to 9 months.

Another study of Cote et al. (2020) systematic review of three RCT studies (which were found to be same as in Liu et al. systematic review), studied effectiveness and safety of IPL treatment. They couldn’t determine the effectiveness, but they stated that two of the studies reported improvement

in TBUT. They were not able to make a meta-analysis of TBUT, NIBUT or SPEED because of substantial statistical heterogeneity. The safety of IPL remained also uncertain, because studies poorly reported adverse events.

The more resent systematic review of Demolin et al. (2023) which included 11 RCT concluded that IPL improves tear break up times (TBUT, NIBUT) but symptom relief (SPEED, OSDI) remained unclear. Another 2023 published meta-analysis and systematic review of 5 RCT studies, stated IPL to be effective treatment for MGD induced dry eye improving clinically significantly OSDI and TBUT. They also noted that IPL is safe treatment and even more effective when combined with other conventional techniques. (Qin et al., 2023.)

3.7.8 Thermal pulsation therapy

Thermal pulsation therapy is an in-office treatment where eyelids are warmed with an instrument with controlled heat and pulsation pressure against the lids or manual expression is produced to release obstructed meibum. There are many different treatment devices on the marked example LipiFlow system (TearScience, Inc, or Johnson & Johnson), MiBoFlo Thermoflo (Mibo Medical), TearCare (Sight Sciences, Inc) and Systane iLux thermal pulsation system (Alcon).

The LipiFlow device heats the inner side of both upper and lower eyelid surfaces by using a large shell, like a scleral lens, which contains both warming 42.5°C and insulating components. The device is inserted comfortably in topical anesthesia, like a gonioscopy lens and additionally an inflatable silicone air bladder simultaneously makes motion for gland self-expression from the external side of the eye lid. (MGD Is Taking Heat, n.d.).

LipiFlow is the first 2011 FDA approved medical device for MGD treatment (Beining et al., 2022). It is the most studied thermal pulsation device and Pubmed search with search term LipiFlow AND meibomian, with no filters, gave 50 results. TFOS DEWS II Management and therapy report stated that single 12-minute LipiFlow treatment alleviates MGD symptoms and signs, and the positive effects can be sustained for even 3 years (Jones et al., 2017).

Meng et al., (2022) RCT study, which compared LipiFlow to a warm compress plus eyelid massage studied 100 eyes of 50 Chinese MGD subjects, they concluded that LipiFlow was a safe method and improved MGD symptoms and meibum secretion and these improvements lasted at least 3 months.

A Report by the American Academy of Ophthalmology, 'Thermal Pulsation in the Management of Meibomian Gland Dysfunction and Dry Eye' (Tao et al., 2023) which included 11 prospective research studies, concluded that a single 12-minute thermal pulsation LipiFlow treatment is safe and may alleviate subjective symptoms and objective signs of MGD compared with conventional methods (warm compress and eyelid hygiene) or no treatment among MGD and dry eye patients. Nine out of eleven of their included studies stated that LipiFlow was more effective than conventional methods. They were cautious of their statement, because four out of eight (quality level I) studies that they used were industry supported, and they noted that more high-quality studies are needed.

Two systematic studies, one systematic review and one systematic review and meta-analysis about LipiFlow, both concluded that more good quality research is needed to demonstrate the benefit of LipiFlow to other DED induced by MGD treatment methods (Hu et al., 2022; Pucker et al., 2024).

The MiBoFlo thermoflo treatment system is a manual in-office therapeutic device. Its purpose is to deliver consistent emissive heat of 42.2°C from thermoelectric pump to the outer skin of the eyelids. Ultrasound gel is used to facilitate a gentle lid massage by the practitioner at the same time.

Li et al. (2022) RCT study compared three 10-minute MiBoFlo treatments (each treatment spaced two weeks apart and followed by an eyelid compression) with Single 12-minute LipiFlow treatment, without any additional physical therapy among 108 eyes of 54 Chines subjects suffering from MGD. They concluded that MiBoFlo has the potential to enhance the management of MGD with no significant intergroup difference to LipiFlow by improving both symptoms (OSDI) and meibomian gland function (MGYLS and MGS), with the benefits lasting for at least two months. (GOMEZ et al., 2022) Retrospective before-and-after study of 102 dry eye clinic patients concluded that MiBoFlo treatment benefits can last even for 6 months.

TearCare warms eye lids for 12-minutes from the external side via four single-use skin adhesive, flexible SmartLid devices. Temperature can be modified between 41°C and 45°C and patient is allowed to blink during treatment and this will naturally squeeze out melted meibum. Right after the thermal cycle, the practitioner performs manual meibomian gland expression using topical anesthesia and expression forceps. This step ensures that any remaining gland obstructions are thoroughly cleared. (Badawi, 2018). TearCare is a 510k-exempt device listed by the FDA for MGD treatment 2021 (*Sight Sciences Receives FDA 510(k) Clearance of the TearCare® System for Treatment of Meibomian Gland Dysfunction (MGD), the Leading Cause of Dry Eye Disease - United States*, n.d.).

Badawi, 2018 pilot study of 24 participants divided into two groups compared a single TearCare treatment to conventional warm compress method of one's a day for 5 minutes. He concluded that TearCare is safe and effective for reducing signs and symptoms of DED even for 6 months. The Warm compress group indicated also a decrease in symptom questionnaires, but TearCare group fared statistically better.

Badawi extended the study in 2019 and TearCare group 12 participants were retreated 6 months after initial study, the results after 12-months showed further enhancement in the signs and symptoms of DED compared to initial baseline (Badawi, 2019). There was conflict of interest in Badawi studies because he is an employee of Sight Sciences.

Nine studies with search terms TearCare AND meibomian were found at Pubmed search and all except one review had conflict of interest to Sight Sciences. All those studies concluded TearCare to be a safe and effective treatment reducing signs and symptoms of DED.

The Systane iLux MGD Treatment System is a portable device, which consists of two main components: a single-use patient interface device made of bio-compatible medical grade silicone and a handheld battery-powered instrument. The disposable tip has inner and outer pads, the inner pad touches the palpebral conjunctiva, while the outer pad rests against the external eyelid. Temperature sensors continuously monitor the temperatures of the inner and outer eyelids, aiming to maintain a meibum melt temperature within the range of 38–42°C. If the temperatures on the inner or outer eyelids exceed 44°C or 45°C, the system automatically turns off the LEDs. Practitioners can adjust the pressure of the outer pad and monitor the meibum melting through the magnification lens of the device. (Beining et al., 2022.)

Tauber et al., (2020) compared Systane iLux and LipiFlow treatments among 142 patients divided in two equal groups and found no statistically significant differences between treatments, both enhanced MG function (MGS, TBUT) and OSDI scores after one week and four weeks' time and there were just few adverse effects, which were self-limited. This study was funded by Alcon research, LLC.

Schanzlin et al. (2022) study of 30 patients gave equal results on iLux treatment after one week and one month, improvement in MGS score, TBUT, SPEED and OSDI. A post-hoc analysis study of 12 months also reported similar results and concludes that iLux treatment effects can be sustained for even one year (Wesley et al., 2022).

4 THE PURPOSE AND OBJECTIVES OF THESIS

4.1 Purpose and objectives

The purpose of the thesis is to describe by means of an integrative literature review how to assess and manage meibomian gland dysfunction (MGD) induced evaporative dry eye disease among Finnish optometrists in general optical store. This thesis focuses only on non-medical treatments, because in Finland optometrists are not allowed to prescribe medications, only diagnostic medication use is allowed.

Another goal is to increase optometrists' knowledge and understanding of meibomian gland dysfunction and provide insights into advanced new technology device treatment possibilities for managing MGD-induced EDED.

4.2 The research questions

The research questions:

What MGD induced evaporative dry eye disease assessment methods should be preferred by optometrists in general optical store in Finland?

How should MGD induced evaporative dry eye disease be managed by optometrists in general optical store in Finland?

When to refer MGD induced evaporative dry eye patients to the specialized dry eye clinic or to the ophthalmologist?

5 IMPLEMENTATION OF THE THESIS

5.1 Integrative literature review as a research method

The thesis was conducted by one person, as an integrative literature review because it enables to provide a more comprehensive understanding of MGD-induced EDED assessment and management (Whittemore & Knafl, 2005). According to Toronto & Remington (2020) integrative review can include both experimental and nonexperimental research as well as theoretical and methodological literature. The primary objective of an integrative literature review is to enhance the understanding of a topic by synthesizing information from a variety of sources.

5.2 Criteria for the selection of studies

Inclusion criteria was, English language, free full-text, publication date not older than 2011, to search studies after international workshop of meibomian glands.

Exclusion criteria was studies before 2011, not in English language, not free full-text available, advanced new technology devices and/or medications used in assessment or management methods, animal studies, prescription medication needed studies or associated with specific disease.

5.3 Data search process and selection

A preliminary exploratory search was conducted in the PubMed database, which supports the search of biomedical and life sciences literature. The search clause used was “meibomian gland dysfunction” AND “evaporative dry eye” AND (assessment OR diagnosis OR examination OR monitoring OR evaluation) AND (management OR treatment OR care OR therapy). The inclusion criteria were set to English language, free full text, and publication date not older than 2011, aiming to find studies published after the International Workshop on Meibomian Glands. However, when combined with the terms “general practice” or “clinic,” the search yielded only one result, which was not suitable. As a result, these specific search terms were not used in primary search.

In May 2024, the primary search for relevant literature was conducted with the assistance of an information specialist from the Oulu University Library. Based on the research topic, the most appropriate and extensive databases were chosen following the guidance and recommendations provided by the information specialist.

The search was conducted by using three different databases according to information specialist recommendation: PubMed, Science direct Elsevier and EBSCOhost web source by using Academic Search Premiere and CINAHL databases.

Used search clauses

EBSCO -Academic Search Premier, CINAHL:
"evaporative dry eye*" OR "dry eye*" AND "meibomian glands" OR "meibomian gland dysfunction" OR "mg dysfunction" OR mgd AND "diagnostic techniques, ophthalmological" OR "ophthalmologic diagnostic technique*" OR "eye examination" OR "ophthalmic exam" OR monitoring OR evaluation OR therapeutics OR treatment OR care OR management OR "practice guideline" OR "practice pattern" OR "preferred practice pattern" OR ppp

PUBMED:
All Fields ("evaporative dry eye*" OR "dry eye*") AND ("meibomian glands" OR "meibomian gland dysfunction" OR "mg dysfunction" OR mgd) AND Title ("eye examination" OR "ophthalmic exam" OR monitoring OR evaluation OR therapeutics OR treatment OR care OR management OR "practice guideline" OR "practice pattern" OR "preferred practice pattern")

SCIENCE DIRECT ELSEVIER:
("diagnostic techniques, ophthalmological" OR "ophthalmologic diagnostic techniques" OR "eye examination" OR "ophthalmic exam" OR therapeutics OR treatment OR care OR management OR "practice guideline") AND ("evaporative dry eye" OR "dry eye") AND ("meibomian glands" OR "meibomian gland dysfunction" OR "mg dysfunction" OR mgd)

A total of 829 study articles were retrieved from three different databases and exported to the Covidence program for extraction. This included 380 articles from PubMed, 302 from ScienceDirect Elsevier, and 147 from EBSCOhost using the Academic Search Premier and CINAHL databases. The Covidence program removed 99 duplicates, and one duplicate was removed manually, leaving 729 studies for further extraction. The first extraction process involved screening the titles and abstracts of articles against the inclusion and exclusion criteria. Twenty-four articles that met the criteria were selected for the second phase. In the second phase, the full-texts of the selected articles were read and reviewed, and articles were again selected based on the inclusion and exclusion criteria, leaving 13 studies.

One hand-picked study was included in the integrative analysis. The TFOS DEWS II Diagnostic Methodology report was found during the primary search; therefore, the TFOS DEWS II Management and Therapy Report was also included. The total number of articles included was 14. All articles were peer reviewed. The number of retrieved, excluded, and included articles is reported in the PRISMA chart (Figure 1).

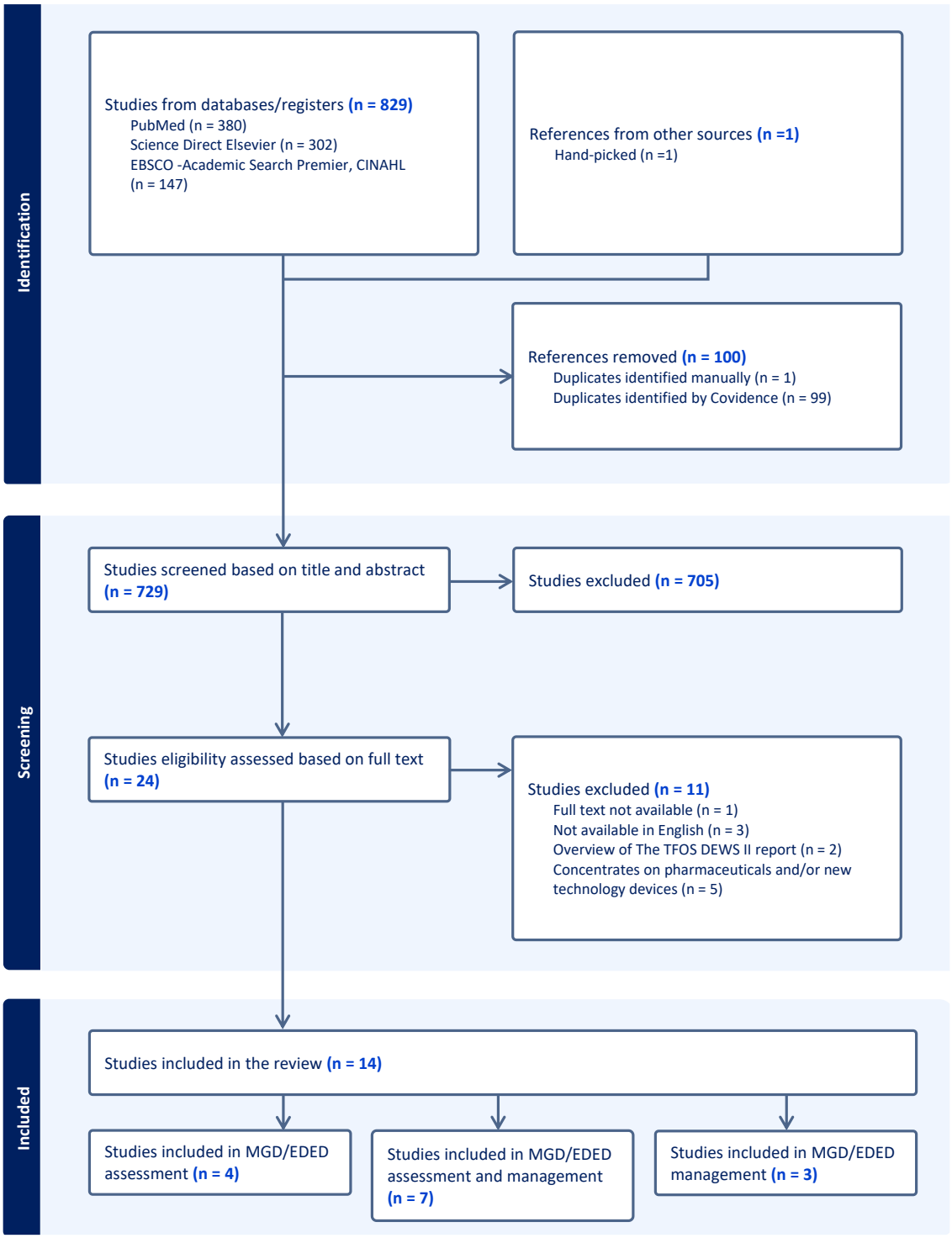

Figure 1. PRISMA flow chart from Covidence program, studies included in the review

5.4 Analysis of the data

Data analysis was conducted using mixed methods of research, inductive content analysis along with numerical analysis. The primary steps in content analysis are the preparation phase, the analysis/organization phase, and the reporting phase (Elo et al., 2022; Toronto & Remington, 2020). In the preparation phase, the data was read multiple times and thoroughly examined to develop a comprehensive understanding.

The analysis/organization phase of inductive content analysis consists of five steps: open coding, coding sheets, grouping, categorization, and abstraction (Toronto & Remington, 2020). During the analysis/organization phase, an inductive approach was employed to group the data. First, subheadings were collected in each article based on research questions and coding sheets were created. Coding sheets were then grouped, categorized and organized under broader headings and similar categories were combined. In the abstraction phase, from these headings, appropriate themes were developed to help explain the phenomenon in more detail and distinguish between the assessment of MGD-induced EDED that can be performed with general optical store equipment and the management of MGD-induced EDED that can be carried out in a general optical store or at home by the patient (Table 1 and 2).

In the reporting phase, each article (Tables 3-5) was read again several times to find answers to the research questions using created codes and themes. The answers were copied into a separate Word file for each study. These Word files were then printed out to make it easier to compare them. The text in printed Word files was then color-coded by theme to help with the comparison. The results are presented in textual form, with numerical insights and visualized using tables. Finally, in the discussion section, the findings are analyzed and compared to existing Blepharitis Preferred Practice Pattern® (2024) USA and Blepharitis (Lid Margin Disease) - College of Optometrists (2024) UK blepharitis guidelines, and Meibomian Gland Dysfunction Clinical Practice Guidelines (2023) Japan, where MGD is nowadays discussed.

6 RESULTS

Articles included in the review were mostly reviews plus one cross sectional study and one survey study. Articles were divided into assessment and management groups. The assessment group consists of eleven articles, of which four studies from Norway (Xiao et al., 2020), India (Singh et al., 2023), the United Kingdom (Cartes et al., 2023), and one international study (Wolffsohn et al., 2017) concerned mainly assessment, and seven study articles concerned both assessment and management. They were from Japan (Kojima et al., 2020), the USA (Milner et al., 2017), two from Italy (Rolando & Merayo-Lloves, 2022; Rolando et al., 2018), Singapore (Tong et al., 2021), India (Narang et al., 2023), and Europe (Geerling et al., 2017).

The management group consists of ten studies all together, the same seven articles concerning both assessment and management, plus three articles concerning mainly management, with one international (Jones et al., 2017) and two from the USA (Thode & Latkany, 2015; Matossian et al., 2022).

In the results section the textual results are summarized under assessment and management groups and visualized with tables 4 and 5. The studies included in the review are presented in Tables 1-3, which are divided into studies addressing assessment, management, and both assessment and management.

Table 1. Studies included in MGD/EDED assessment

Author, Year, Country	Article/ Publication	Study design	Main content/ conclusions/ results	Assessment/ management
Wolffsohn J, Arita R, Chalmers R et al./2017/ International	TFOS DEWS II Diagnostic Methodology report	Review	The report has determined, through scientific evidence and consensus, the most appropriate (efficacious) battery of tests to diagnose and monitor DED, as per the revised definition.	Assessment
Xiao J, Adil M, Chen X et al. /2019/ Norway	Functional and Morphological Evaluation of Meibomian Glands in the Assessment of Meibomian Gland Dysfunction Subtype and Severity	Cross-sectional study	Study concluded that patients with low-delivery MGD had worse dry eye parameters and ocular symptoms than those with high meibum delivery, indicating the pivotal role of meibum secretion in ocular surface health that should be targeted in MGD therapy.	Assessment
Singh S, Donthineni P, Srivastav S et al./2023/ India	Lacrimal and meibomian gland evaluation in dry eye disease: A minireview	Review	Review discusses the various techniques of evaluating the lacrimal and meibomian glands based on tests available in clinical practice.	Assessment
Cartes C, Segovia C, Calonge M et al./2023/ United Kingdom	International survey on dry eye diagnosis by experts	Survey	Survey offers updated and day-to-day diagnostic clinical practice by DED worldwide experts. The results highlight the importance of considering symptoms and clinical signs, especially those related to epithelial damage, tear film instability, and tear volume, without necessarily following strict criteria.	Assessment

Table 2. Studies included in MGD/EDED assessment and management

Author, Year, Country	Article/Publication	Study design	Main content/ conclusions/ results	Assessment/ management
Geerling G, Baudouin C, Aragona P et al. /2017/ Europe	Emerging strategies for the diagnosis and treatment of meibomian gland dysfunction: Proceedings of the OCEAN group meeting	Review	Review presents the results of discussions held by the OCEAN group in 2014 and aims to provide a practical guide to understanding and diagnosing MGD for the general ophthalmologist.	Assessment and management
Kojima T, Dogru M, Kawashima M et al./2020/ Japan	Advances in the diagnosis and treatment of dry eye	Review	Tear film-oriented diagnosis (TFOD) is a concept to clarify the cause of tear film instability by tear film, and tear film-oriented treatment (TFOT) is a concept to treat dry eye disease by replacing the lacking components of the tear film layer based on the TFOD.	Assessment and management
Milner M, Beckman K, Luchs J et al./2016/USA	Dysfunctional tear syndrome: Dry eye disease and associated tear film disorders - new strategies for diagnosis and treatment	Review	This review provides a practical and directed approach to the diagnosis and treatment of patients with Dysfunctional tear syndrome, emphasizing treatment that is tailored to the specific disease subtype as well as the severity of the condition	Assessment and management
Rolando M, Cantera E, Mencucci R et al./2017/ Italy	The correct diagnosis and therapeutic management of tear dysfunction: recommendations of the P.I.C.A.S.S.O. board	Review	Purpose, To describe a standard approach to manage tear dysfunction (TD), in order to obtain a clinically favourable outcome. Results, a multi-item flowchart for tear film dysfunction, with point-by-point explanatory guide, to better identify and manage the patient with this disorder is provided.	Assessment and management
Rolando M, Merayo-Lloves J/ 2022/ Italy	Management Strategies for Evaporative Dry Eye Disease and Future Perspective	Review	The purpose of the review is to identify the current best practice for management of EDE in order to help clinicians in providing accurate diagnosis and optimized treatment.	Assessment and management

Narang, Purvasha Donthineni, Pragnya Rao D'Souza, SharonBasu, Sayan/ 2023/ India	Evaporative dry eye disease due to meibomian gland dysfunction: Preferred practice pattern guidelines for diagnosis and treatment	Review	The review is specifically intended for general ophthalmologists to orient them toward helping them diagnose EDE, differentiate it from ADDE, and provide a simplified treatment approach including the adequate emphasis on prevention and patient counseling.	Assessment and management
Tong L, Lim L, Tan D et al./ 2021/ Singapore	Assessment and Management of Dry Eye Disease and Meibomian Gland Dysfunction: Providing a Singapore Framework	Review	The purpose of the article is to provide a framework for general ophthalmologists in Singapore to manage dry eye. They provide a guide to determine the most appropriate treatment (or combination of treatments) based on the severity and cause(s) of the disease, as well as the patient's needs and preferences.	Assessment and management

Table 3. Studies included in MGD/EDED management

Author, Year, Country	Article/Publication	Study design	Main content/ conclusions/ results	Assessment/ management
Jones L, Downie L, Korb D et al. /2017/ International	TFOS DEWS II Management and Therapy Report	Review	The report summarizes the management and therapeutic options for treating dry eye disease (DED).	Management
Thode A, Latkany R /2015/ USA	Current and Emerging Therapeutic Strategies for the Treatment of Meibomian Gland Dysfunction (MGD)	Review	While the standard method to treat MGD is simply warm compresses and baby shampoo, a more tailored approach to address the multiple aetiologies of the disease is suggested. Clinicians should offer patients a tailored treatment regimen according to clinical findings and patient preferences.	Management
Matossian C, Crowley M, Periman L et al./2022/ USA	Personalized Management of Dry Eye Disease: Beyond Artificial Tears	Review	Review describes artificial tears and the current knowledge in the personalized approach to the management of DED.	Management

6.1 Assessment

Dry eye assessment should rely on tests that are readily available in clinics to ensure broad acceptance and use among clinical practice (Wolffsohn et al., 2017).

Table 4, Themes and codes for assessment of MGD-induced EDED

	Themes	Codes
Assessment	**Patient history**	Symptoms, history, anamnesis, systemic medications, topical medications, risk factors of EDE due to MGD
	Preliminary assessments	Symptom questionnaires, external examination, skin, blinking abnormalities
	Primary assessments, slit-lamp examination	Refraction and BCVA, tests to rule out ADDE: tear volume assessment, direct examination of the lacrimal gland, inflammation of the ocular surface/ocular and/or conjunctival redness, damage to ocular surface/ocular surface staining, tear film stability/ fluorescein breakup time, fluorescein break-up patterns, eyelid margin morphology and meibum assessments
	Differential diagnoses and comorbidities	Anterior blepharitis and demodex, aqueous deficiency, concurrent allergic or contact lens–related conjunctivitis, ocular surface sensitivity

6.1.1 Patient history

Patient history should include medical history, ocular history (such as surgery, allergies, and contact lens wear), systemic and ocular medications (antiandrogens, medications for treating benign prostatic hyperplasia (BPH), hormone replacement therapy, glaucoma medications, antihistamines, antidepressants, and isotretinoin), identification of risk factors (age, female sex, hormonal changes, rosacea, seborrheic dermatitis, eyelid disease, contact lens use, eye make-up, refractive surgery, allergies, autoimmune diseases, BPH, smoking, alcohol consumption, prolonged VDT use, low humidity, wind/air-condition), chief complaints or current symptoms, and past or present therapy for dry eye disease. It is important to allocate sufficient time to the patient and listen carefully to their symptoms and discomfort, as this can provide initial insights into the dry eye subtype or aid in developing a differential diagnosis. (Milner et al., 2017; Rolando et al., 2018; Narang et al., 2023; Tong et al., 2021).

TFOS DEWS II Diagnostic Methodology Report provided eight triaging questions to use prior to diagnosis to differentiate and exclude conditions that can present similarly to DED. One of them is, Do the eyes itch, are swollen, crusty or have any discharge? The report stated that itching is usually associated with allergies while a mucopurulent discharge is associated with ocular infection. While Rolando & Merayo-Lloves (2022) stated that itching of the lid margin rather than the globe could be a differentiating factor of lipid-related evaporative dry eye. Additionally, the time when the symptoms were at their worst varied between these two studies. Lipid-related symptoms were reported to be worse in the morning, while general dry eye symptoms were worse in the evening.

6.1.2 Preliminary assessments

Symptom questionnaires

All analyzed studies recommended the use of symptom questionnaires, except for the study by Kojima et al. (2020), which focuses on tear film-oriented diagnosis. Among these studies, the Ocular Surface Disease Index (OSDI) was mentioned seven times, the Standard Patient Evaluation of Eye Dryness (SPEED) and DEQ-5 (5-Item Dry Eye Questionnaire) were each mentioned four times, and the Symptom Assessment in Dry Eye (SANDE) and McMonnies Questionnaire were both mentioned once. In the international survey on dry eye diagnosis by experts (Cartes et al., 2023), 96% of respondents utilized symptom questionnaires, with 71% using them always or frequently. The OSDI was the most used questionnaire (83%), followed by the DEQ-5 (30%).

The TFOS DEWS II Diagnostic Methodology Report (2017) comprehensively reviewed various validated symptom questionnaires and recommended the use of the OSDI or DEQ-5 at the initial stage of clinical examination of DED to quantify severity, monitor progression, and assess response to treatment. The report also highlighted that questionnaire validation is typically conducted using patient groups with Sjögren's syndrome versus non-Sjögren's syndrome ADDE and/or healthy controls, with minimal emphasis on EDED. Nevertheless, study by Xiao et al. (2020) found that hyposecretory MGD had the highest OSDI score, indicating that MG secretory activity could be a key factor in the development of ocular symptoms.

For the diagnosis of evaporative dry eye, Geerling et al. (2017) indicated that the SPEED questionnaire correlates more effectively with evaporative dry eye and noted the absence of a specific questionnaire designed for the assessment of MGD. Additionally, Rolando & Merayo-Lloves, (2022) preferred the McMonnies questionnaire due to its association with lipid-related issues. A Study of Narang et al. (2023) stated controversially that the questionnaire is not mandatory in routine clinical practice, but valuable for research.

External examination, skin and blinking abnormalities

It is recommended to perform an external examination while the patient is unaware of being observed, such as during the completion of a symptom questionnaire (Wolffsohn et al., 2017). Three analyzed studies advised observing clinical signs in the facial skin, such as rosacea, seborrheic dermatitis, or acne, which may indicate MGD (Narang et al., 2023; Tong et al., 2021; Milner et al., 2017). Eight analyzed studies emphasized the importance of observing the eyelids, noting incomplete closure and partial or incomplete blinks (Tong et al., 2021; Narang et al., 2023; Milner et al., 2017; Wolffsohn et al., 2017; Rolando & Merayo-Lloves, 2022; Xiao et al., 2020; Rolando et al., 2018; Geerling et al., 2017). The importance of complete blinking for meibomian gland function was highlighted in three studies, with incomplete blinking leading to increased evaporation and reduced meibum outflow (Xiao et al., 2020; Rolando & Merayo-Lloves, 2022; Wolffsohn et al., 2017). A study by Xiao et al. (2020) found that blink intervals were significantly reduced in all MGD subgroups compared to the control group, using a value of <10 seconds. Conversely, the TFOS DEWS II diagnostic methodology report stated that the normal blink rate is 10-15 blinks per minute, with a blink interval of 4-6 seconds.

6.1.3 Primary Assessment, slit-lamp examination

Visual function, best corrected visual acuity BCVA

Only four analyzed studies mentioned assessment of visual function or best corrected visual acuity (BCVA). Milner et al. (2017) recommended assessing conventional visual acuity (VA) and inquiring about the nature and frequency of fluctuating vision. A study by Kojima et al. (2020) also emphasized that despite good conventional BCVA the functional VA is reduced among DED patients. In the study by Cartes et al. (2023), it was found that 70% of experts in dry eye disease (DED) utilized visual function tests. The most frequently used test was the ETDRS scale (43%), followed by various functional visual acuity tests (26%) and the optical quality analysis system (13%). In contrast,

the TFOS DEWS II diagnostic methodology report did not recommend additional visual function tests until objective clinical measures of visual disturbance were widely available. Instead, they recommended evaluating visual disturbance subjectively using symptom questionnaires.

Tear film brake up time, osmolarity and fluorescein brake up pattern

All analyzed studies highlighted the importance of tear film break up time (TBUT) as a clinical test for tear film instability. TFOS DEWS II diagnostic methodology report recommended preferring non-invasive NITBUT but also approved fluorescein TBUT, which correlates well with NITBUT. However, if osmolarity measurement is used, TBUT should be done afterward due to its more invasive nature. Cartes et al. (2023) indicated that most DED experts (87%) evaluated tear stability using TBUT, while only 9% used NITBUT without TBUT. Additionally, TBUT was more important to European DED experts than to experts from North America, possibly due to the need for expensive additional devices.

The time when TBUT should be measured after fluorescein installation varies between studies, ranging from, after 2-3 blinks to 3 minutes. The amount of fluorescein used for TBUT also varied, but a minimal amount was recommended, with extra saline to shaken off or smaller area of fluorescein strip used (Singh et al., 2023; Wolffsohn et al., 2017). The test was recommended to replicate 2-3 times to provide more reliable results (Singh et al., 2023; Milner et al., 2017). A result under 10 sec result was considered a positive finding for DED in most of the studies (Milner et al., 2017; Wolffsohn et al., 2017; Singh et al., 2023; Geerling et al., 2017; Narang et al., 2023). Meanwhile, the Japanese Dry Eye Society and Asia Dry Eye society (JDES/ADES) consensus for DED diagnosis in 2016 was TBUT <5 seconds, which was used in three studies (Cartes et al., 2023; Tong et al., 2021; Xiao et al., 2020). Also Wolffsohn et al. (2017) mentioned to use value <5 sec when minimal or more controlled amounts fluorescein are used.

The capability of TBUT for MGD diagnosis varied. Narang et al. (2023) and Geerling et al. (2017) stated that TBUT test cannot be used for to differentiate between MGD/EDE and ADDE. In contrast, the reviews of Rolando & Merayo-Lloves, (2022), Kojima et al. (2020) and cross-sectional study by Xiao et al. (2020) indicated that a short TBUT value suggests poor lipid layer quality. The study by Xiao et al. (2020) showed that TBUT was significantly lower in all MGD subgroups compared to the control group. Additionally, they concluded that since TBUT is a test for tear film instability and low instability leads to increased tear film osmolarity, all MGD patients should have increased osmolarity. However, they found increased osmolarity values only in hyposecretory and obstructive MGD

groups, suggesting that reduced TBUT is a more prominent characteristic in evaporative DED with MGD than osmolarity. Osmolarity was also the least popular test among DED experts in a study by Cartes et al. (2023).

Studies by Tong et al. (2021) and Kojima et al. (2020) highlighted the significance of paying attention to the timing and pattern of fluorescein breakup occurrence. Tear film-oriented diagnosis is a new concept in DED diagnosis, which uses physical theory to assess abnormalities in the tear film. With this method, DED can be classified as aqueous deficient, increased evaporation, or low wettability type based on the breakup pattern. In the case of increased evaporation, random breaks will appear after the movement of fluorescein-stained aqueous tears is completed due to aqueous tear evaporation.

Ocular surface staining

All analyzed studies mentioned assessment of ocular surface staining for ocular surface damage. Six of the studies used both fluorescein and lissamine green dyes (Geerling et al., 2017; Kojima et al., 2020; Milner et al., 2017; Rolando et al., 2018; Narang et al., 2023; Wolffsohn et al., 2017). Cartes et al. (2023) conducted a survey study showing that all DED experts used ocular surface fluorescein staining, and 82% used lissamine green staining. Grading scales were used by 92% of the respondents, with 65% using the National institute scale and 34% using the ocular staining scale.

Six of analyzed studies highlighted the use of both fluorescein and lissamine green staining (Milner et al., 2017; Rolando et al., 2018; Narang et al., 2023; Wolffsohn et al., 2017; Cartes et al., 2023; Kojima et al., 2020). The studies by Rolando et al. (2018) and Milner et al. (2017) also recommended the use of yellow filter and Wolffsohn et al. (2017) recommended the use of a red filter with lissamine green to highlight the ocular surface damage.

The study by Xiao et al., (2020) used Oxford Grading system, and Narang et al. (2023) also mentioned the Oxford system and the DEWS scheme (>5 corneal spots, >9 conjunctival spots or lid margin staining 2mm length and 25% width). On the other hand, Tong et al. (2021) recommended using digital imaging for documentation. They also highly recommended examining lid wiper epitheliopathy (LWE). Narang et al. (2023) and Geerling et al. (2017) stated that LWE is more commonly seen in MGD patients and according to Wolffsohn et al. (2017) combination of fluorescein

and repeated applications of lissamine green provides the most effective detection of LWE. Xiao et al. (2020) found that low-delivery MGD patients had worse ocular staining than the high-delivery group, but the studies by Geerling et al. (2017) and Singh et al. (2023) stated that ocular surface staining is not necessary diagnostic with MGD.

Tests to rule out ADDE, tear volume assessment and direct assessment of lacrimal gland

The Schirmer test without anesthesia was the most frequently mentioned tear volume test among the analyzed studies. Only two studies by Rolando et al. (2018) and Rolando & Merayo-Lloves, (2022) recommended assessing tear clearance instead. Also Cartes et al. (2023) survey found Schirmer test with (40%) or without (60%) anesthesia the most popular test for tear volume.

A Study by Xiao et al. (2020) found no significant difference between Schirmer test values among MGD subtypes, control group, nor among subgroups of MGD, which showed that tear production is sustained in MGD. Also study by Narang et al. (2023) stated Schirmer being normal in EDE and used to rule out ADDE. However, it was criticized for being invasive, variable, and insertion of the strip causing reflex tearing (Kojima et al., 2020; Wolffsohn et al., 2017). A study by Geerling et al. (2017) concluded that the Schirmer test cannot be regarded as a comprehensive diagnostic tool, because MGD and ADDE can coexist.

Secondly popular tear volume test was the tear meniscus height, which was performed by 78% of DED experts, according to a study by (Cartes et al. (2023). It was mentioned in seven analyzed studies (Narang et al., 2023; Kojima et al., 2020; Singh et al., 2023; Wolffsohn et al., 2017; Cartes et al., 2023; Tong et al., 2021; Milner et al., 2017). The cut of value of the test varied between studies, DEWS II diagnostic methodology report criteria were 0,2mm and a study of Milner et al. (2017) used 0,3mm. DEWS II also criticized the test for its poor repeatability between visits and its sensitivity to factors such as blink timing, measurement location, time of day, temperature, humidity, air speed, and effect of illumination.

Two studies by Wolffsohn et al. (2017) and Kojima et al. (2020) introduced a novel tear volume measurement tool, Strip Meniscometry. This instrument utilizes water-absorbing materials, rayon and pulp, to measure tear meniscus volume within 5 seconds, with a cutoff value of 4mm. Kojima et al. also suggested its potential for self-assessment, emphasizing the importance of precise contact with the tear meniscus.

The studies by Singh et al. (2023) and Narang et al. (2023) mentioned lacrimal gland evaluation which appears healthy (convex, smooth and pinkish) in normal and EDE patients, but shrinks, flattens, and shows whitish fibrotic areas or reddish color due to inflammation in ADDE. They also introduced the Direct Assessment of Tear Secretion (DATS) test, which reflects overall lacrimal gland activity and has demonstrated significant differences between MGD and Sjogren's syndrome ADDE. Singh et al. recommended using the DATS test over the Schirmer test.

Inflammation of ocular surface, ocular and/or conjunctival redness

The TFOS DEWS II diagnostic methodology report identifies conjunctival redness as the most prevalent clinical indicator of ocular surface inflammation, which can be readily observed using a standard slit-lamp examination. The report also highlights that inflammation is not exclusive to dry eye disease (DED) and may be present in other ocular or systemic conditions.

Similarly, study by Cartes et al. (2023) found that 81% of DED experts assess ocular surface inflammation, with conjunctival redness being the most frequently used indicator (66%), followed by the MMP-9 tear test (34%). Only a few other studies mentioned evaluating ocular surface inflammation without advanced devices. Milner et al. (2017) recommended documenting the presence and severity of inflammation during slit-lamp examinations and Rolando et al. (2018) advised observing ocular surface hyperemia in the interpalpebral area.

Eye lid margin anomalies, meibomian gland expression, meibum quality and quantity

All the reviewed studies recommended observing signs of meibomian gland dysfunction (MGD) such as lid margin anomalies, including telangiectasias, notching, hyperemia, thickening, changes in the mucocutaneous junction, collarettes, frothy secretions, keratinization, MG orifice obstruction, and swollen glands. According to study by Tong et al. (2021) hyperemia and edema of lid margin may suggest active disease and scalloping, notching and rounding of the lid margin indicates chronic, fibrotic MGD.

A study by Narang et al. (2023) used lid margin score, which grades eyelid margin anomalies by assigning one point for each; lid margin irregularity, vascular engorgement, and glandular orifice obstruction.

Eight studies recommended assessing meibum expression, the quantity and quality of meibum by applying firm digital pressure or with special device to provide standardized force to the eyelid (Cartes et al., 2023; Xiao et al., 2020; Narang et al., 2023; Wolffsohn et al., 2017; Tong et al., 2021; Geerling et al., 2017; Milner et al., 2017; Singh et al., 2023). Tong et al. (2021) recommended conducting meibum expression after other tests to prevent changes in baseline tear film measurements.

Meibum quality was graded from 8 central MGs in the lower eyelid as 0 (clear fluid), 1 (cloudy fluid), 2 (cloudy particulate) or 3 (toothpaste-like). Expressibility was graded from five central glands of lower eyelid, 0 (all glands expressible), 1 (3 to 4 glands expressible), 2 (1 to 2 glands expressible) or 3 (no glands expressible) (Narang et al., 2023; Xiao et al., 2020; Milner et al., 2017).

MG loss was examined with meibography in most of the studies. However, Rolando & Merayo-Lloves, (2022) noted that meibography is primarily useful for identifying extreme cases, such as normal or very severe conditions. Additionally, Tong et al. (2021) emphasized that meibography should not be used in isolation for diagnosing MGD but should be used alongside other clinical parameters. A study by Narang et al. (2023) used the meiboscore for MG loss, which was scaled as follows: 0 (no dropout), 1 (<1/3 total area dropout), 2 (1/3 – 2/3 total area dropout) or 3 (>2/3 total area dropout).

The TFOS DEWS II diagnostic methodology report indicated that the diagnostic significance of meibomian gland (MG) expressibility and duct appearance in dry eye disease (DED) remains unestablished. However, a study by Cartes et al. (2023) found that all DED experts conducted eyelid and meibum assessments, 90% evaluated MG expressibility and quality, primarily using digital pressure with a finger (78%), followed by the MG evaluator (19%) and chalazia clamp (13%). Additionally, 86% of DED experts utilized non-contact meibography.

6.1.4 **Differential diagnosis and comorbidities**

Differential diagnosis and comorbidities include a range of conditions, including allergic and infectious conjunctivitis, anterior blepharitis, demodex infestation, corneal and conjunctival abnormalities, keratitis, keratopathies, mucus fishing syndrome, lid-related diseases, contact lens-related

toxicity, chemical toxicity, corneal hyperalgesia, conjunctivochalasis, uveitis, episcleritis, rheumatological conditions, visual asthenopia, graft-versus-host disease, and psychological factors. (Milner et al., 2017; Wolffsohn et al., 2017; Tong et al., 2021).

Patient-reported symptoms help develop a differential diagnosis. For patients whose history indicates that the condition may not be primary dry eye disease (DED), a comprehensive differential diagnosis should be conducted using a slit-lamp biomicroscope. (Rolando et al., 2018; Wolffsohn et al., 2017).

The TFOS DEWS II Diagnostic Methodology report recommends examining the eyelid margin and eyelashes for signs of anterior blepharitis, such as redness, exanthema, sores, eschar, swelling, bullous formation, foamy discharge, and collarettes around the lashes. It also advises checking for demodex, indicated by cylindrical dandruff at the root of the eyelashes.

Additionally, the report suggests evaluating the palpebral conjunctiva for follicles, swelling, chalazion, or infectious hordeolum; the bulbar conjunctiva for redness and swelling; the cornea for ulcerations and possible trauma; and the anterior chamber for cells and flare, which indicate intraocular infection.

The report also highlights the importance of considering neuropathic pain rather than dry eye disease (DED) when chronic symptoms are present but minimal signs are observed, and these symptoms are refractory to treatment. The Cochet-Bonnet test can be used to evaluate ocular surface sensitivity in such cases.

A study by Tong et al. (2021) recommended examining everted lids, where large papillae suggest allergic conjunctivitis and petechiae or membranes indicating infective conjunctivitis. They also advised inspecting the eyelashes for signs of anterior blepharitis or demodex, and the palpebral conjunctiva for follicles or swelling.

For the conjunctiva, they recommended looking for copious discharge or chemosis indicative of conjunctivitis, sectorial redness for episcleritis, and prolapse for conjunctivochalasis. The bulbar conjunctiva should be checked for redness and swelling, and the cornea for ulcerations, infections, or foreign bodies.

Additionally, they suggested assessing proptosis and lid lag, which can indicate thyroid disease, and examining the red reflex for irregular pupils, which may suggest uveitis. The anterior chamber should be evaluated for intraocular inflammation, and visual acuity should be checked, noting that it should not be severely decreased and should improve with blinking. They also emphasized the importance of paying special attention to patients who are compliant but refractory to initial treatment.

A study by Geerling et al. (2017) emphasized the importance of distinguishing between meibomian gland dysfunction (MGD) without dermatitis and rosacea-associated MGD, as the latter tends to have a poorer prognosis.

6.2 Management

TFOS DEWS II Management and Therapy Report stated that *"there exists a significant role for conventional treatments in the management of MGD, including ocular lubricants, lid hygiene and warm compresses".*

All analyzed studies emphasized the importance of personalized management of dry eye disease (DED) based on disease severity, subtype, and coexistence of conditions. Matossian et al. (2022) noted that management strategies may vary depending on different environments and stages of a patient's life. The studies by Narang et al. (2023) and Geerling et al. (2017) underscored the significance of early treatment of meibomian gland dysfunction (MGD), primary aim being to increase the quality and the quantity of meibum, highlighting that managing MGD at the asymptomatic stage can potentially delay progression to symptomatic stages and reverse pathological changes. Thode & Latkany (2015) stated that clinicians should create treatment plans according to clinical findings and patient preferences.

Table 5, Themes and codes for management of MGD-induced EDED.

	Themes	Codes
Management	**Patient Education and dietary modifications**	Counseling and preventive Aspects, lifestyle intervention, local environmental considerations, omega-3 dietary supplementation, other dietary considerations, antioxidants
	Physical treatments	Treatments for lid abnormalities, eyelid hygiene, warm compresses, lid massage, forceful expression, debridement scaling
	Tear supplements, lubricants and conservation	Artificial tears and lubricants, lipid-based treatments, moisture chamber eyewear
	Follow-up and referral	Monitoring dry eye disease progression and management, compliance for management, recalcitrant cases, bacterial overionization, pharmacological treatments for meibomian gland dysfunction, quit ocular surface inflammation, systemic or topical medications

6.2.1 Patient education and dietary modifications

The studies by Narang et al. (2023), Rolando et al. (2018) and Tong et al. (2021) emphasize the need for extended patient counseling on the chronic nature of MGD-induced EDED. They stress the importance of setting realistic treatment goals, noting that while treatment is ongoing and may not show immediate results, proper management can significantly improve quality of life. Rolando et al. particularly underscores the importance of not underestimating the condition.

All analyzed studies except the study of Thode & Latkany, (2015) addressed lifestyle and environmental modifications as management options for DED. Implemented factors included lifestyle changes such as smoking cessation, reduced alcohol consumption, improved sleep quality, and increased blinking. Additionally, the impact of systemic or topical medications (e.g., prolonged use of antihistamines, diuretics, antidepressants), preservatives in topical medications like BAK, digital device use, and contact lens wear were considered. Environmental changes such as maintaining humidity, reducing wind exposure, and managing indoor heating and air-conditioning were also discussed.

A study by Kojima et al. (2020) highlighted exercise therapy as a significant lifestyle intervention, based on evidence of its effectiveness in treating depression. They also noted that the World Health Organization (WHO) has identified the sedentary lifestyle of desk workers as a health risk, comparable to smoking and obesity. Additionally, they referenced a study that found individuals in the

under 5 seconds TBUT group spent significantly more time seated daily compared to those in the over 5 seconds group.

All analyzed studies mentioned Omega fatty acid supplements as one treatment option for MGD patients. Seven of the studies mentioned the anti-inflammatory properties of omega-3 regulating the proinflammatory effects of omega-6, which reduces inflammation. (Milner et al., 2017; Rolando & Merayo-Lloves, 2022; Kojima et al., 2020; Thode & Latkany, 2015; Rolando et al., 2018; Narang et al., 2023; Jones et al., 2017).

The TFOS DEWS II Management and Therapy Report highlighted that the upper daily limit for omega-3 intake is 3000 mg, combining both food and supplements, as recommended by the U.S. Food and Drug Administration (FDA) and the National Health and Medical Research Council (NHMRC) of Australia. The report also noted that liver disease, atrial fibrillation, and bleeding disorders are contraindications for omega-3 supplementation, and there is a potential increased risk of prostate cancer. Additionally, the optimal dosage is still unresolved and requires further investigation (Jones et al., 2017; Milner et al., 2017; Thode & Latkany, 2015).

Other dietary modifications, The TFOS DEWS II Management and Therapy Report pointed out two studies, one on antioxidants and another on Aristotelia chilensis berry extract, both showing improvements in DED signs and/or symptoms. Kojima et al. (2020) also discussed studies on lactoferrin, probiotics, functional foods containing astaxanthin, all of which were effective in improving DED. They recommended consuming antioxidants from commonly available edible sources.

6.2.2 Physical treatments

All analyzed studies pointed out that the main purpose of treatment for meibomian gland dysfunction (MGD) is to reestablish the natural flow of meibum. Lid hygiene, in combination with warm compresses and lid massage, is the mains stay of the treatment of MGD.

Lid hygiene is an important aspect of MGD treatment. According to Jones et al. (2017) mild dilution of baby shampoo is the most widely accepted lid scrub for lid hygiene, typically applied with a cotton bud. However, there are no universally accepted guidelines for lid cleaning.

The studies by Kojima et al. (2020), Jones et al. (2017) and Thode & Latkany (2015) noted that while baby shampoo is considered effective for lid hygiene, it may act as a strong irritant. Additionally, Thode & Latkany (2015) cautioned that the use of tear-free baby shampoo for lid hygiene may even cause allergic reactions, particularly the ingredient cocamidopropyl betaine (CAPB), which could exacerbate symptoms. Preferably, premedicated products such as lid scrubs, solutions, wipes, or foams are recommended, as they can also aid in the mechanical expression of meibum (Jones et al. 2017; Thode & Latkany, 2015). A study by Kojima et al. (2020) underscored that lid hygiene should be consistently practiced at all stages of MGD, not just in the early phases, but also as the disease progresses.

Demodex mites, while not currently evidenced to be directly connected to MGD-associated dry eye disease (DED), might still contribute to the pathology of MGD, highlighting the need for proper lid hygiene (Jones et al., 2017; Kojima et al., 2020; Geerling et al., 2017). According to a study by Thode & Latkany (2015), Demodex mites are found in a significant number of cases: 90% of patients with anterior blepharitis, 60% with MGD, and 90% with mixed blepharitis.

Demodex mites can be treated with tea tree oil (Tong et al., 2021; Geerling et al., 2017). A diluted solution of tea tree oil at 50% was recommended by Milner et al. (2017), but Jones et al. (2017) preferred pre-formulated wipes equivalent to 25% whole tea tree oil, which are less toxic to the ocular surface compared to stronger concentrations. Tea tree oil contains terpinen-4-ol, which is an effective ingredient for killing Demodex due to its antimicrobial and anti-inflammatory properties. For mild symptoms, it's used once daily and for moderate to severe symptoms, it's used twice daily, allowing the solution to dry on the surface. The typical treatment duration is around two months, after which it can be adjusted based on the patient's response (Thode & Latkany, 2015).

Warm compresses were a common recommendation in the analyzed studies for the treatment of meibomian gland dysfunction (MGD). However, there was variability in the suggested temperature, duration, and frequency of their application. Tong et al. (2021) stated that the optimal temperature should be over 40°C and applied for 8-10 minutes per day. Jones et al. (2017) also recommended temperatures of over 40°C, but not over 45°C, which patients' pain response will prevent. Geerling et al. (2017) recommended applying a hot compress for 5 minutes in the morning and evening. Kojima et al. (2020) also recommended twice-daily self-treatment for patients. Rolando et al. (2018) suggested a temperature range of 40-45°C using a warm wet compress or an eyelid warming device such as Blephasteam. Also, Tong et al. (2021) mentioned eyelid warming device, USB- device.

Thode & Latkany (2015) referred to different clinical handbooks, which suggest that warm compresses should be applied for 5-15 minutes, repeated up to four times a day. They also stated that improvements are best achieved with dry warming devices, for example microwaveable masks. Interestingly, they also discussed that when allergies present as comorbidity of MGD, would cold compresses be a better treatment option.

Jones et al. (2017) referred to several studies: one found improvement in Meibomian Gland (MG) and tear film function after 2-4 weeks of treatment; another showed therapeutic benefit after 12 weeks; and a third, which lasted for 2 weeks with treatment twice a day, reported benefits that lasted for up to 6 months, with occasional retreatment providing greater comfort. They also introduced a study where infrared warm compresses were used for 5 minutes twice a day for 2 weeks, which also improved symptoms and signs.

Eye lid massage for MGD was recommended in seven analyzed studies (Thode & Latkany, 2015; Milner et al., 2017; Rolando & Merayo-Lloves, 2022; Matossian et al., 2022; Geerling et al., 2017; Narang et al., 2023; Jones et al., 2017). However, Jones et al. (2017) advised against eyelid massage when the cornea is heated to 36-39.4°C, as it may cause corneal deformation and blurred vision. They emphasized the importance of patient education on the proper technique for lid massage to avoid these complications.

In-office manual expression is an effective treatment, according to Kojima et al. (2020) and Matossian et al. (2022) studies, particularly when used in conjunction with warm compresses and lid hygiene. A study by Narang et al. (2023) recommended the use of atraumatic specialized expressor forceps for manual expression in-office. Tong et al. (2021) suggested that therapeutic expression, exfoliation, and debridement can serve as additional treatments for MGD. Also, Milner et al. (2017) emphasized the role of in-office cleaning and debridement of the lid margin as a beneficial procedure.

Thode & Latkany (2015) referenced a study by Korb and Greiner, which found that manual expression combined with heat is effective. This study involved a six-month treatment program where in-office MG expression was performed once every six weeks, alongside daily warm compresses and lid hygiene with baby shampoo as part of patient self-care.

The study by indicated that after any meibomian gland targeted treatment for MGD, such as thermal vectored pulsation, intense pulsed light (IPL), or probing, it's essential for patients to continue with lid hygiene and warm compresses to prevent gland blockage. They also noted that combining topical anti-inflammatory therapy with lid hygiene and warm compresses can enhance treatment outcomes. Additionally, Tong et al. (2021) reported that there is no degree of gland drop-out that would prevent the benefits of treatment for MGD, implying that the loss of meibomian glands is not a contraindication for treatment.

6.2.3 Tear supplements, lubricants and tear conservation

All the ten analyzed studies mentioned artificial tear (AT) supplements as a treatment for DED. A study by Narang et al. (2023) stated that while artificial tears are not the primary treatment for MGD, they can help manage the symptoms by stabilizing and supplementing the tear film, which is a common factor in EDE and other ocular surface diseases. Also, the study by Matossian et al. (2022), Rolando & Merayo-Lloves, (2022) and Jones et al. (2017) pointed out that ATs does not address the underlying cause of DED.

Matossian et al. (2022) emphasized that the effectiveness of ATs depends on the product type and usage frequency, as patients tend to use fewer drops when instructed to use as needed compared to a strict frequency recommendation. Additionally, they mentioned that environmental changes in patients' daily activities may require customization of AT instillation frequency. A study by Tong et al. (2021) recommended 4 to 6 installations of preservative-free eye drops per day for the management of mild DED and Thode & Latkany, (2015) up to eight times per day based on different clinical handbooks. Rolando et al. (2018) highlighted the significance of using artificial tears not just for symptom relief but also for their role in modifying the pathological stage of ocular surface diseases. Eight of analyzed studies recommended the use of preservative-free tear supplements and lubricants to avoid possible toxicity effects (Narang et al. (2023); Jones et al. (2017); Matossian et al. (2022); Tong et al. (2021); Geerling et al., (2017); Milner et al., (2017); Rolando & Merayo-Lloves, (2022); Rolando et al., 2018).

More viscous artificial tears, such as ointments and gels, were advised for use before sleeping due to their longer retention time on the eye surface and their tendency to cause blurred vision (Tong et al., 2021; Matossian et al., 2022; Milner et al., 2017; Narang et al., 2023; Rolando & Merayo-Lloves, 2022; Jones et al., 2017).

The use of emollients, lipid-based eye drops, and sprays was recommended for the treatment of Meibomian Gland Dysfunction (MGD) and EDE to stabilize the tear film lipid layer, restore tear film stability, and reduce evaporation, thereby improving both symptoms and signs of the condition (Narang et al., 2023; Geerling et al., 2017; Jones et al., 2017; Rolando & Merayo-Lloves, 2022; Milner et al., 2017; Matossian et al., 2022; Tong et al., 2021). Geerling et al. (2017) stated that novel preservative-free perfluorohexyloctaine (F6H8) enhances significantly symptoms and signs of MGD/EDE.

A study by Rolando & Merayo-Lloves, (2022) stated that lipid-based eye drops are proven to be more effective than water-based eye drops in reducing tear film osmolarity and enhancing tear film stability in patients with mild to moderate Evaporative Dry Eye (EDE).

The studies by Geerling et al. (2017), Tong et al. (2021), Matossian et al. (2022), Milner et al. (2017) Jones et al. (2017) and Rolando et al. (2018) further emphasized the role of artificial tears, not gels in diluting inflammatory cytokines and other irritants, which can help reduce tear film osmolarity and downregulate inflammation. This dilution effect may be sufficient to cleanse the ocular surface in the early stages of DED.

Sodium hyaluronate is the most used artificial tear (AT) in Japan, according to Kojima et al. (2020). The studies by Rolando & Merayo-Lloves, (2022) and Rolando et al. (2018) have identified tear supplements containing Sodium hyaluronate (HA) as the current gold standard, significantly improving tear film stability and ocular surface damage. Additionally, the studies by Kojima et al. (2020) and Jones et al. (2017) has highlighted the good wound healing properties of HA. Furthermore, a study by Tong et al. (2021) has emphasized the effectiveness of hypotonic HA in reducing inflammation. The studies by Rolando & Merayo-Lloves, (2022) and Rolando et al. (2018) also highlighted trehalose for its epithelial protecting properties, improving signs and symptoms in mild to severe DED.

Tear conservation with moisture chamber spectacles/goggles were recognized as a beneficial intervention for evaporative dry eye to slow evaporation of tears (Kojima et al. (2020); Tong et al. (2021); Jones et al. (2017). The use of the punctal plugs in treating EDE were found to remain controversial and are not recommended for EDE Jones et al. (2017).

6.2.4 Follow-up and referral

The studies of Narang et al. (2023), Milner et al., (2017), Tong et al. (2021) and Matossian et al. (2022) highly recommended follow-up visits for successful management of MGD/DED. They recommend periodic reassessment of patient understanding of the disease and adherence to treatment to prevent dissatisfaction. Additionally, due to the frequent variation between patient-reported symptoms and clinical signs, ongoing monitoring and adjustment of the treatment plan is crucial, as disease characteristics may change over time.

Jones et al. (2017) stated a follow-up frequency of 1 to 3 months, while Matossian et al. (2022) recommended that the frequency should be tailored based on the severity of the condition, the treatment used, and the patient's response to the treatment. The study by Milner et al. pointed out that poor patient compliance with follow-up visits leads to challenges in treating DED.

Seven analyzed studies mentioned patient compliance problems to the treatment (Tong et al., 2021; Narang et al., 2023; Matossian et al., 2022; Geerling et al., 2017; Thode & Latkany, 2015; Milner et al., 2017; Jones et al., 2017). A study by Tong et al. highlighted that compliance with treatment is crucial for sustaining therapeutic benefits. They also pointed out the need to show patients any improvements in clinical measure scores, when their symptoms are not improving.

All analyzed studies indicated that medical therapy is indicated when there is evident inflammation. Studies by Milner et al. (2017) and Thode & Latkany, (2015) noted that if conventional treatments do not significantly improve symptoms, alternative therapies, including antibiotics, are necessary. The studies by Jones et al., (2017), Tong et al. (2021), Narang et al. (2023) and Rolando & Merayo-Lloves, (2022) emphasized that moderate to severe cases may require additional or more intensive treatments. Tong et al. (2021) identified persistent epithelial defects, corneal filaments, conjunctivalization, and deep vascularization as indicators of more severe DED.

Narang et al. (2023) noted that in recalcitrant cases, the presence of eyelash loss, nodular masses, cicatricial changes, localized crusting, and scaling of the dermis could indicate carcinoma or immune-mediated disease. They recommend that moderate to severe cases with pain, those unresponsive to treatment, or cases involving visual loss, orbital involvement, or systemic disease should be promptly referred to a specialist ophthalmologist.

7 DISCUSSION

Conducting the review turned out to be very difficult due to the overlapping of many conditions, aqueous deficiency dry eye overlapping evaporative dry eye, which often also coexists. Meibomian gland dysfunction (MGD) overlapping posterior blepharitis and can also coexist with anterior blepharitis. Additionally, demodex is commonly associated with MGD, thus differential diagnosis is difficult as mentioned also in Japanese MGD guideline 2023.

MGD has nowadays been classified under posterior blepharitis guidelines, rather than dry eye guidelines in both the Blepharitis Preferred Practice Pattern® (PPP) 2023 USA (Lin et al., 2024) and the Clinical Management Guidelines, Blepharitis (Lid Margin Disease) - College of Optometrists UK (*Blepharitis (Lid Margin Disease) - College of Optometrists*, 2024). Both use MGD and posterior blepharitis almost synonymously and the Clinical Management Guidelines, Blepharitis (Lid Margin Disease) - College of Optometrists UK states that posterior blepharitis is the leading cause of evaporative dry eye. Only one Japanese guideline specifically concerning about MGD was found (Amano et al., 2023). USA PPP 2023 stated that MGD can occur without inflammation, and in this case the term posterior blepharitis is incorrect.

The MGD patients being mostly asymptomatic highlights the importance of assessment of lid margin changes, in general eye examination, including telangiectasias, notching, hyperemia, thickening, changes in the mucocutaneous junction, collarettes, frothy secretions, keratinization and expression and quality of the meibum.

Assessment of lid margin changes were an important diagnostic tool for MGD among analyzed studies, which were in conjunction witch Blepharitis Preferred Practice Pattern® 2023, Japanese Meibomian Gland Dysfunction Clinical Practice Guidelines 2023 and the college of optometrists Blepharitis Clinical Management Guidelines. Hyperemia and edema of lid margin may mark active disease and scalloping, notching and rounding of the lid margin indicate chronic, fibrotic MGD.

Expression of meibum is recommended to be performed after other tests, to prevent changes in baseline tear film measurements, but according to the International Workshop on Meibomian Gland Dysfunction, Report of the Diagnosis Subcommittee (2011), it could be done during a general eye

examination. And, if the quality or quantity of meibum is found to be decreased, more accurate tests for MGD-induced EDED can be conducted during the next visit.

When MGD progresses to EDED symptoms will appear. There is no evidence of specific symptoms to differentiate MGD from other ocular surface disorders. Time of the day when symptoms occur may help to distinguish between MGD and aqueous dry eye disease (ADED), in MGD symptoms are worse in the morning and in ADED in the evening. Also, itching of the lid margin may be a symptom for MGD.

Risk factors of MGD according to Japanese guideline are age, male gender, postmenopausal women, Asian ethnicity, rural residence, extended time with VDT, smoking, use of SCL, ocular surgery and glaucoma eye drops. Also, rosacea, diabetes, dyslipidemia, hypertension, and hyperthyroidism are risk factors. These are mostly in line with analyzed studies, though analyzed studies included also dry eye risk factors. Only difference is the gender women gender being stronger risk factor among analyzed studies.

Almost all the analyzed studies recommend using symptom questionnaires, of which OSDI being mostly used. For lipid-based conditions, McMonnies and SPEED questionnaires were recommended. Controversially none of the guidelines mentioned questionnaires, but symptoms were included in patient history. Also, the study of Narang et al. (2023) stated that questionnaires would not be mandatory in clinical practice. On the other hand, questionnaires can be useful in follow-up when the treatment effectiveness can be compared, and the blinking habits and skin of the patient can be observed while filling out the questionnaire.

There is no single test to diagnose MGD-induced EDED, slit-lamp examination may include tear volume assessment or direct examination of the lacrimal gland, Inflammation/redness of the ocular surface, ocular surface staining, tear film stability (Fluorescein breakup time (BUT), Fluorescein break-up patterns) and eyelid margin morphology and meibum assessments.

Both tear volume tests, Schirmer test and tear meniscus height are thought to have poor repeatability during visits and cannot be used for comprehensive tests because MGD and ADDE often coexist. An interesting novel test, Strip meniscometry to measure tear volume in 5 seconds, was found when conducting analysis, which could be used also for self-assessment and may enhance

compliance to MGD treatment aiming to reduce evaporation. Another interesting test found was direct assessment of tear secretion (DATS).

Examining tear film stability, fluorescein BUT were mostly used among survey study among dry eye experts, though TFOS DEWS II recommended NITBUT. Japanese guideline 2023 stated that BUT cannot be specifically used for MGD diagnosis, but the study by Xiao et al. (2020) found BUT to be more prominent characteristic in MGD-EDED compared to osmolarity, which again TFOS DEWS II highlights. Additionally, Japanese guideline did not recommend NITBUT for MGD diagnosis, because cut-off value has not been specified, but pointed out that fluorescein break up pattern (BUP) may be used as an auxiliary test for the diagnosis of MGD, when random breaks will appear. Also, Blepharitis Preferred Practice Pattern® 2023 listed BUP as one slit-lamp test.

Ocular surface staining with fluorescein and lissamine green dye or with combination was recommended among all analyzed studies. Additionally, the use of yellow filter was recommended to use with fluorescein and a red filter with lissamine green to highlight the ocular surface damage. Also, guidelines recommend staining, Blepharitis Preferred Practice Pattern® 2023 stated that inferior and superior punctate epithelial erosions are clinical features of MGD, and the college of optometrists Blepharitis Clinical Management Guidelines again stated punctate epithelial erosion over lower third of cornea being the clinical features of posterior blepharitis (most often caused by MGD). Additionally, lid wiper epitheliopathy (LWE) is a more prominent sign for MGD and should be noted, combination of fluorescein and repeated applications of lissamine green provides the most effective detection of LWE.

The main purpose of meibomian gland dysfunction (MGD) management is to reestablish the natural flow of meibum, it is important to start even if there are no symptoms, because it may delay pathological changes and turning into symptomatic disease.

The treatment plan should be created according to clinical findings and patient references. Here if patients are frustrated to do warm compress/lid hygiene treatment at home they should be educated on advanced treatment options. Though better results are gained when combining home regimen and medical and/or advanced new technology treatments in moderate and severe cases. Therefore, conventional treatment has a significant role in managing MGD.

Patients should be educated about the chronic nature of MGD-EDED and the need for ongoing treatment, according to analysis and guidelines. Additionally, counseling patients to minimize lifestyle and environmental risk factors, maintain good hydration, blinking and considering an omega-3 rich diet or supplementation is recommended. An interesting insight was the potential benefit of exercise on dry eye. Moreover, prolonged use of visual display terminals (VDTs) can lead to a sedentary lifestyle, which the WHO has highlighted as being as dangerous as obesity and smoking.

Physical treatments include eyelid hygiene, warm compresses and lid massage as at home treatments which are the mains stay of the treatment of MGD. Also, in the college of optometrist's Dry eye Clinical Management Guidelines, recommended to treat first MGD as predisposing factor of DED.

In office treatments which can be conducted with basic optical store equipment are forceful meibomian gland expression (MGX) when just anesthetic eye drops, and Q-tip are needed and debridement scaling which can be done example with disposable lid stick. Japanese guideline also recommended MGX treatment to improve subjective symptoms, though it may be painful for patient. For lid hygiene, premedicated products such as lid scrubs, solutions, wipes, or foams are recommended, as they can also aid in the mechanical expression of meibum. And if demodex coexists tea tree oil extract wipes are recommended.

The temperature and time for warm compress treatment varied a lot among analyzed studies. The college of optometrists, Blepharitis Clinical Management Guidelines stated that *dry warm compresses* should be preferred in posterior blepharitis and applied twice daily for not less than 5 minutes at 40°C in combination with vertical lid massage. Also, Blepharitis Preferred Practice Pattern® 2023 recommended the use of warm compresses and eye lid massage ones or twice daily but recommended warning patients to avoid using too hot compresses and glaucoma patients to avoid massage. Japanese guideline of MGD also strongly recommended warm compress treatment and moderately eyelid hygiene. The compliance for treatment can be enhanced with discussion with patients on how to fit warm compress, massage and lid hygiene into everyday routines.

Because ADDE often coexists with MGD-EDED preservative free tear supplements, lubricants and tear conservation with moisturizing goggles are also recommended treatment, though they do not address the underlying cause. Artificial tears can downgrade inflammation by diluting inflammatory

cytokines, which may be enough, and prescribed medication may not be needed. Also, lipid-based tear supplements were found to dilute tear film debris and reduce osmolarity.

Trial and error are common when finding suitable artificial tears and lubricants. It is suitable to recommend intervals for installation of artificial tears and lubricants, for better patient compliance. Lipid-based tear supplements are recommended for MGD-EDED and novel topical perfluorohexyloctane (marketing in Finland by name Evotears), approved by FDA in 2023 was stated to prevent tear evaporation and improve symptoms and corneal staining in patients with dry eye disease after 8 weeks according to analysis and Blepharitis Preferred Practice Pattern® 2023.

Follow-up visits are important for monitoring MGD-EDED progression and adjusting the treatment and frequency being 1-3 months depending on severity and/or treatment. Blepharitis Preferred Practice Pattern® 2023 stated that patients with mild blepharitis could be advised to return if their symptoms worsen. It's also important to encourage the patient to keep compliant with treatment and show any improvements in clinical measurements when symptoms are not improving.

Optometrists should practice within their areas of expertise and, if necessary, seek guidance from or refer patients to ophthalmologists. They should also stay updated on the least advancements in dry eye technology and co-operate with dry eye clinics. In recalcitrant cases, when conventional treatments fail, referral to specialized dry eye clinics or ophthalmologists is needed, regarding the severity. In severe MGD-EDED cases when inflammation exists, the conjunctival redness is the most prevalent marker, referring to ophthalmologists is needed. Special care should be taken if there is pain, lash loss or cicatricial changes, because of the possibility of carcinoma or immune mediated diseases.

The absence of clinical guidelines for MGD and dry eye disease in Finland is an important gap that should be addressed. The thesis calls for the development of uniform guidelines to ensure consistent and effective management of MGD-induced EDED across all optical stores in Finland. These guidelines should include standardized assessment methods, treatment recommendations, and referral criteria to specialized dry eye clinics or ophthalmologists when necessary.

The topic of further study could include written instructions for patients on how to conduct lid hygiene, warm compress and massage to gain best management results.

7.1 Reliability and Ethics of the thesis

This integrative review was conducted by a single researcher, which may reduce reliability. Another factor that may reduce reliability is the lack of formal quality appraisal and study designs being mostly reviews. A structured approach was employed throughout the review process, which included clearly defined inclusion and exclusion criteria, search strategies developed with the help of a library information specialist, consistent data extraction methods, and a transparent analysis process. Detailed documentation of each step in the review process was maintained, including records of search strategies, data sources, and the reasons for including or excluding studies. This careful documentation enhances the reproducibility of the review.

8 CONCLUSIONS

This thesis provides valuable insight into the assessment and management of MGD-induced EDED in regular optical stores. It emphasizes the importance of early detection, non-medical treatment approaches and the need for uniform guidelines.

Early detection and management of meibomian gland dysfunction induced evaporative dry eye disease is important preventing the progression of symptoms and improving patients' quality of life. The thesis highlights that many patients are asymptomatic in the early stages, making it essential for optometrists to be alert and proactive in their assessments in general eye exams.

Regular eye examinations and patient education about the chronicity of the MGD-induced EDED and the importance of on-going self-treatment, with non-medical conventional lid hygiene, warm compress, massage, artificial tear substitutes and dietary, lifestyle and environmental modifications can play a significant role in managing this condition effectively.

While new advanced assessment and treatment devices are available and have been proven effective and safe for diagnosis, it is essential to understand conventional methods. These treatment options remain crucial as they form the foundation for all advanced treatments. This is like dental care, where regular brushing, flossing, and mouthwash use are necessary, along with routine dental visits for tartar removal and oral health checks. Optometrists have a responsibility to educate patients about meibomian glands and their significance in maintaining ocular health.

Developing and implementing standardized guidelines for the assessment and management of MGD-induced EDED is important for consistent and effective care.

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REFERENCES

Amano, S., Shimazaki, J., Yokoi, N., Hori, Y., Arita, R., Obata, H., Kawashima, M., Koh, S., Suzuki, T., Suzuki, T., Yamaguchi, M., Yamada, M., Itokawa, T., Iwashita, H., Usui, T., Uchino, M., Oya, F., Okajima, Y., Kaido, M., … Soma, T. (2023). Meibomian Gland Dysfunction Clinical Practice Guidelines. In *Japanese Journal of Ophthalmology* (Vol. 67, Issue 4, pp. 448–539). Springer. https://doi.org/10.1007/s10384-023-00995-8

Arita, R., & Fukuoka, S. (2020). Non-pharmaceutical treatment options for meibomian gland dysfunction. In *Clinical and Experimental Optometry* (Vol. 103, Issue 6, pp. 742–755). Blackwell Publishing Ltd. https://doi.org/10.1111/cxo.13035

Badawi, D. (2018). A novel system, TearCare®, for the treatment of the signs and symptoms of dry eye disease. *Clinical Ophthalmology*, *12*, 683–694. https://doi.org/10.2147/OPTH.S160403

Badawi, D. (2019). TearCare® system extension study: Evaluation of the safety, effectiveness, and durability through 12 months of a second TearCare® treatment on subjects with dry eye disease. *Clinical Ophthalmology*, *13*, 189–198. https://doi.org/10.2147/OPTH.S191588

Badian, R. A., Utheim, T. P., Chen, X., Utheim, Ø. A., Ræder, S., Ystenæs, A. E., Aakre, B. M., & Sundling, V. (2021). Meibomian gland dysfunction is highly prevalent among first-time visitors at a Norwegian dry eye specialist clinic. *Scientific Reports*, *11*(1). https://doi.org/10.1038/s41598-021-02738-6

Ballesteros-Sánchez, A., De-Hita-Cantalejo, C., Sánchez-González, M. C., Jansone-Langine, Z., de Sotomayor, M. A., Culig, J., & Sánchez-González, J. M. (2023). Perfluorohexyloctane in dry eye disease: A systematic review of its efficacy and safety as a novel therapeutic agent. In *Ocular Surface* (Vol. 30, pp. 254–262). Elsevier Inc. https://doi.org/10.1016/j.jtos.2023.10.001

Ballesteros-Sánchez, A., Gargallo-Martínez, B., Gutiérrez-Ortega, R., & Sánchez-González, J. M. (2023). Eyelid Exfoliation Treatment Efficacy and Safety in Dry Eye Disease, Blepharitis, and Contact Lens Discomfort Patients: A Systematic Review. In *Asia-Pacific Journal of Ophthalmology* (Vol. 12, Issue 3, pp. 315–325). Lippincott Williams and Wilkins. https://doi.org/10.1097/APO.0000000000000607

Ballesteros-Sánchez, A., Sánchez-González, J. M., Carmen Sánchez-González, M., Rocha-de-Lossada, C., & Gargallo- Martínez, B. (2023). Efficacy of meibomian gland expression combined with Home-Based therapy in the management of dry eye Disease: A systematic review

and Meta-Analysis. In *Contact Lens and Anterior Eye*. Elsevier B.V. https://doi.org/10.1016/j.clae.2023.102107

Beining, M. W., Magnø, M. S., Moschowits, E., Olafsson, J., Vehof, J., Dartt, D. A., & Utheim, T. P. (2022). In-office thermal systems for the treatment of dry eye disease. In *Survey of Ophthalmology* (Vol. 67, Issue 5, pp. 1405–1418). Elsevier Inc. https://doi.org/10.1016/j.survophthal.2022.02.007

Bilkhu, P. S., Naroo, S. A., & Wolffsohn, J. S. (2014). Randomised masked clinical trial of the MGDRx eyebag for the treatment of meibomian gland dysfunction-related evaporative dry eye. *British Journal of Ophthalmology*, *98*(12), 1707–1711. https://doi.org/10.1136/bjophthalmol-2014-305220

Blepharitis (Lid Margin Disease) - College of Optometrists. (2024, June 10). © College of Optometrists, Version 18. https://www.college-optometrists.org/clinical-guidance/clinical-management-guidelines/blepharitis_lidmargindisease

Borchman, D. (2019). *The optimum temperature for the heat therapy for meibomian gland dysfunction*. https://doi.org/10.1016/j.jtos.2019.02.005

Cartes, C., Segovia, C., Calonge, M., & Figueiredo, F. C. (2023). International survey on dry eye diagnosis by experts. *Heliyon*, *9*(6). https://doi.org/10.1016/j.heliyon.2023.e16995

Chan, T. C. Y., Chow, S. S. W., Wan, K. H. N., & Yuen, H. K. L. (2019). Update on the association between dry eye disease and meibomian gland dysfunction. In *Hong Kong Medical Journal* (Vol. 25, Issue 1, pp. 38–47). Hong Kong Academy of Medicine Press. https://doi.org/10.12809/hkmj187331

Cote, S., Ac, Z., Ahmadzai V, Li, M. A., Oppedisano J, Nair K, Busija L, & Le, D. (2020). *Cochrane Library Cochrane Database of Systematic Reviews Intense pulsed light (IPL) therapy for the treatment of meibomian gland dysfunction (Review)*. https://doi.org/10.1002/14651858.CD013559

Cote, S., Zhang, A. C., Ahmadzai, V., Maleken, A., Li, C., Oppedisano, J., Nair, K., Busija, L., & Downie, L. E. (2020). Intense pulsed light (IPL) therapy for the treatment of meibomian gland dysfunction. *The Cochrane Database of Systematic Reviews*, *2020*(3). https://doi.org/10.1002/14651858.CD013559

Craig, J. P., Nelson, J. D., Azar, D. T., Belmonte, C., Bron, A. J., Chauhan, S. K., de Paiva, C. S., Gomes, J. A. P., Hammitt, K. M., Jones, L., Nichols, J. J., Nichols, K. K., Novack, G. D., Stapleton, F. J., Willcox, M. D. P., Wolffsohn, J. S., & Sullivan, D. A. (2017). TFOS DEWS II Report Executive Summary. In *Ocular Surface* (Vol. 15, Issue 4, pp. 802–812). Elsevier Inc. https://doi.org/10.1016/j.jtos.2017.08.003

Craig, J. P., Nichols, K. K., Akpek, E. K., Caffery, B., Dua, H. S., Joo, C. K., Liu, Z., Nelson, J. D., Nichols, J. J., Tsubota, K., & Stapleton, F. (2017). TFOS DEWS II Definition and Classification Report. In *Ocular Surface* (Vol. 15, Issue 3, pp. 276–283). Elsevier Inc. https://doi.org/10.1016/j.jtos.2017.05.008

Daniel Nelson, J., Shimazaki, J., Benitez-del-Castillo, J. M., Craig, J., McCulley, J. P., Den, S., & Foulks, G. N. (2011). The international workshop on meibomian gland dysfunction: Report of the definition and classification subcommittee. *Investigative Ophthalmology and Visual Science*, *52*(4), 1930–1937. https://doi.org/10.1167/iovs.10-6997b

Demolin, L., Es-Safi, M., Soyfoo, M. S., & Motulsky, E. (2023). Intense Pulsed Light Therapy in the Treatment of Dry Eye Diseases: A Systematic Review and Meta-Analysis. *Journal of Clinical Medicine*, *12*(8). https://doi.org/10.3390/JCM12083039

Elo, S., Kajula, O., Tohmola, A., & Kääriäinen, M. (2022). Laadullisen sisällönanalyysin vaiheet ja eteneminen. *HOITOTIEDE 2022, 34 (4)*, 215–225. https://journal.fi/hoitotiede/article/view/128987/78028

Geerling, G., Baudouin, C., Aragona, P., Rolando, M., Boboridis, K. G., Benítez-del-Castillo, J. M., Akova, Y. A., Merayo-Lloves, J., Labetoulle, M., Steinhoff, M., & Messmer, E. M. (2017). Emerging strategies for the diagnosis and treatment of meibomian gland dysfunction: Proceedings of the OCEAN group meeting. *Ocular Surface*, *15*(2), 179–192. https://doi.org/10.1016/j.jtos.2017.01.006

Geerling, G., Tauber, J., Baudouin, C., Goto, E., Matsumoto, Y., O'Brien, T., Rolando, M., Tsubota, K., & Nichols, K. K. (2011). The international workshop on meibomian gland dysfunction: Report of the subcommittee on management and treatment of meibomian gland dysfunction. *Investigative Ophthalmology and Visual Science*, *52*(4), 2050–2064. https://doi.org/10.1167/iovs.10-6997g

GOMEZ, M. L., AFSHARI, N. A., GONZALEZ, D. D., & CHENG, L. (2022). Effect of Thermoelectric Warming Therapy for the Treatment of Meibomian Gland Dysfunction. *American Journal of Ophthalmology*, *242*, 181–188. https://doi.org/10.1016/j.ajo.2022.06.013

Ha, M., Kim, J. S., Hong, S. Y., Chang, D. J., Whang, W. J., Na, K. S., Kim, E. C., Kim, H. S., & Hwang, H. S. (2021). Relationship between eyelid margin irregularity and meibomian gland dropout. *Ocular Surface*, *19*, 31–37. https://doi.org/10.1016/j.jtos.2020.11.007

Hu, J., Zhu, S., & Liu, X. (2022). Efficacy and safety of a vectored thermal pulsation system (Lipiflow®) in the treatment of meibomian gland dysfunction: a systematic review and meta-analysis. *Graefe's Archive for Clinical and Experimental Ophthalmology*, *260*(1), 25–39. https://doi.org/10.1007/s00417-021-05363-1

Jones, L., Downie, L. E., Korb, D., Benitez-del-Castillo, J. M., Dana, R., Deng, S. X., Dong, P. N., Geerling, G., Hida, R. Y., Liu, Y., Seo, K. Y., Tauber, J., Wakamatsu, T. H., Xu, J., Wolffsohn, J. S., & Craig, J. P. (2017). TFOS DEWS II Management and Therapy Report. *The Ocular Surface*, *15*(3), 575–628. https://doi.org/10.1016/J.JTOS.2017.05.006

Kheirkhah, A., Kobashi, H., Girgis, J., Jamali, A., Ciolino, J. B., & Hamrah, P. (2020). A randomized, sham-controlled trial of intraductal meibomian gland probing with or without topical antibiotic/steroid for obstructive meibomian gland dysfunction. *The Ocular Surface*, *18*(4), 852–856. https://doi.org/10.1016/J.JTOS.2020.08.008

Knop, E., Knop, N., Millar, T., Obata, H., & Sullivan, D. A. (2011). The international workshop on meibomian gland dysfunction: Report of the subcommittee on anatomy, physiology, and pathophysiology of the meibomian gland. *Investigative Ophthalmology and Visual Science*, *52*(4), 1938–1978. https://doi.org/10.1167/iovs.10-6997c

Kojima, T., Dogru, M., Kawashima, M., Nakamura, S., & Tsubota, K. (2020). Advances in the diagnosis and treatment of dry eye. In *Progress in Retinal and Eye Research* (Vol. 78). Elsevier Ltd. https://doi.org/10.1016/j.preteyeres.2020.100842

Lam, P. Y., Co Shih, K., Fong, P. Y., Chung, T., Chan, Y., Lap, A., Ng, K., Jhanji, V., & Tong, L. (n.d.). *A Review on Evidence-Based Treatments for Meibomian Gland Dysfunction Running Short Title: Treatment of Meibomian Gland Dysfunction*.

Lee, G. (2024). Evidence-Based Strategies for Warm Compress Therapy in Meibomian Gland Dysfunction. *Ophthalmology and Therapy*. https://doi.org/10.1007/s40123-024-00988-x

Li, S., Yang, K., Wang, J., Li, S., Zhu, L., Feng, J., Tian, L., & Jie, Y. (2022). Effect of a Novel Thermostatic Device on Meibomian Gland Dysfunction: A Randomized Controlled Trial in Chinese Patients. *Ophthalmology and Therapy*, *11*(1), 261–270. https://doi.org/10.1007/s40123-021-00431-5

Lin, A., Ahmad, S., Amescua, G., Cheung, A. Y., Choi, D. S., Jhanji, V., Mian, S. I., Rhee, M. K., Viriya, E. T., Mah, F. S., & Varu, D. M. (2024). Blepharitis Preferred Practice Pattern®. *Ophthalmology*, *131*(4), P50–P86. https://doi.org/10.1016/j.ophtha.2023.12.036

Liu, S., Tang, S., Dong, H., & Huang, X. (2020). Intense pulsed light for the treatment of Meibomian gland dysfunction: A systematic review and meta-analysis. *Experimental and Therapeutic Medicine*, *20*(2), 1815–1821. https://doi.org/10.3892/ETM.2020.8838

Magno, M., Moschowits, E., Arita, R., Vehof, J., & Utheim, T. P. (2021). Intraductal meibomian gland probing and its efficacy in the treatment of meibomian gland dysfunction. In *Survey of Ophthalmology* (Vol. 66, Issue 4, pp. 612–622). Elsevier Inc. https://doi.org/10.1016/j.survophthal.2020.11.005

Maskin, S. L., & Alluri, S. (2019). Intraductal meibomian gland probing: Background, patient selection, procedure, and perspectives. In *Clinical Ophthalmology* (Vol. 13, pp. 1203–1223). Dove Medical Press Ltd. https://doi.org/10.2147/OPTH.S183174

Matossian, C., Crowley, M., Periman, L., & Sorkin, S. (2022). Personalized Management of Dry Eye Disease: Beyond Artificial Tears. In *Clinical Ophthalmology* (Vol. 16, pp. 3911–3918). Dove Medical Press Ltd. https://doi.org/10.2147/OPTH.S384819

Meng, Z., Chu, X., Zhang, C., Liu, H., Yang, R., Huang, Y., & Zhao, S. (2022). *Efficacy and Safety Evaluation of a Single Thermal Pulsation System Treatment (LipiFlow®) on Meibomian Gland Dysfunction: A Randomized Controlled Clinical Trial*. https://doi.org/10.21203/rs.3.rs-1889630/v1

MGD is Taking Heat. (n.d.). Retrieved April 1, 2024, from https://www.reviewofoptometry.com/article/mgd-is-taking-heat

Milner, M. S., Beckman, K. A., Luchs, J. I., Allen, Q. B., Awdeh, R. M., Berdahl, J., Boland, T. S., Buznego, C., Gira, J. P., Goldberg, D. F., Goldman, D., Goyal, R. K., Jackson, M. A., Katz, J., Kim, T., Majmudar, P. A., Malhotra, R. P., McDonald, M. B., Rajpal, R. K., … Yeu, E. (2017). Dysfunctional tear syndrome: Dry eye disease and associated tear film disorders - new strategies for diagnosis and treatment. In *Current Opinion in Ophthalmology* (Vol. 28, Issue 1, pp. 1–48). Lippincott Williams and Wilkins. https://doi.org/10.1097/ICU.0000000000000355

Nagar, S., Ajouz, L., Nichols, K. K., Kumar, S., Zhao, C., Naidoo, K. K., Robinson, M. R., & Borchman, D. (2023). Relationship Between Human Meibum Lipid Composition and the Severity of Meibomian Gland Dysfunction: A Spectroscopic Analysis. *Investigative Ophthalmology and Visual Science*, *64*(10). https://doi.org/10.1167/iovs.64.10.22

Narang, P., Donthineni, P. R., D'Souza, S., & Basu, S. (2023). Evaporative dry eye disease due to meibomian gland dysfunction: Preferred practice pattern guidelines for diagnosis and treatment. *Indian Journal of Ophthalmology*, *71*(4), 1348–1356. https://doi.org/10.4103/IJO.IJO_2841_22

Nichols, K. K., Foulks, G. N., Bron, A. J., Glasgow, B. J., Dogru, M., Tsubota, K., Lemp, M. A., & Sullivan, D. A. (2011). The international workshop on meibomian gland dysfunction: Executive summary. *Investigative Ophthalmology and Visual Science*, *52*(4), 1922–1929. https://doi.org/10.1167/iovs.10-6997a

Pucker, A. D., Yim, T. W., Rueff, E., Ngo, W., Tichenor, A. A., & Conto, J. E. (2024). LipiFlow for the treatment of dry eye disease. *Cochrane Database of Systematic Reviews*, *2024*(2). https://doi.org/10.1002/14651858.CD015448.pub2

Qin, G., Chen, J., Li, L., Zhang, Q., Xu, L., Yu, S., He, W., He, X., & Pazo, E. E. (2023). Efficacy of intense pulsed light therapy on signs and symptoms of dry eye disease: A meta-analysis and systematic review. *Indian Journal of Ophthalmology*, *71*(4), 1316. https://doi.org/10.4103/IJO.IJO_2987_22

Rolando, M., Cantera, E., Mencucci, R., Rubino, P., & Aragona, P. (2018). The correct diagnosis and therapeutic management of tear dysfunction: recommendations of the P.I.C.A.S.S.O. board. In *International Ophthalmology* (Vol. 38, Issue 2, pp. 875–895). Springer Netherlands. https://doi.org/10.1007/s10792-017-0524-4

Rolando, M., & Merayo-Lloves, J. (2022a). Management Strategies for Evaporative Dry Eye Disease and Future Perspective. In *Current Eye Research* (Vol. 47, Issue 6, pp. 813–823). Taylor and Francis Ltd. https://doi.org/10.1080/02713683.2022.2039205

Rolando, M., & Merayo-Lloves, J. (2022b). Management Strategies for Evaporative Dry Eye Disease and Future Perspective. In *Current Eye Research* (Vol. 47, Issue 6, pp. 813–823). Taylor and Francis Ltd. https://doi.org/10.1080/02713683.2022.2039205

Sabeti, S., Kheirkhah, A., Yin, J., & Dana, R. (2020). Management of meibomian gland dysfunction: a review. In *Survey of Ophthalmology* (Vol. 65, Issue 2, pp. 205–217). Elsevier USA. https://doi.org/10.1016/j.survophthal.2019.08.007

Schanzlin, D., Owen, J. P., Klein, S., Yeh, T. N., Merchea, M. M., & Bullimore, M. A. (2022). Efficacy of the Systane iLux Thermal Pulsation System for the Treatment of Meibomian Gland Dysfunction After 1 Week and 1 Month: A Prospective Study. *Eye & Contact Lens*, *48*(4), 155. https://doi.org/10.1097/ICL.0000000000000847

Schaumberg, D. A., Nichols, J. J., Papas, E. B., Tong, L., Uchino, M., & Nichols, K. K. (2011). The international workshop on meibomian gland dysfunction: Report of the subcommittee on the epidemiology of, and associated risk factors for, MGD. *Investigative Ophthalmology and Visual Science*, *52*(4), 1994–2005. https://doi.org/10.1167/iovs.10-6997e

Schjerven Magno, M., Olafsson, J., Beining, M., Moschowits, E., Lagali, N., Wolffsohn, J. S., Craig, J. P., Vehof, J., Dartt, D. A., & Utheim, T. P. (2023). Hot towels: The bedrock of Meibomian gland dysfunction treatment – A review. *Contact Lens and Anterior Eye*, *46*(2), 101775. https://doi.org/10.1016/J.CLAE.2022.101775

Sheppard, J. D., & Nichols, K. K. (2023). Dry Eye Disease Associated with Meibomian Gland Dysfunction: Focus on Tear Film Characteristics and the Therapeutic Landscape. In *Ophthalmology and Therapy*. Adis. https://doi.org/10.1007/s40123-023-00669-1

Sight Sciences Receives FDA 510(k) Clearance of the TearCare® System for Treatment of Meibomian Gland Dysfunction (MGD), the Leading Cause of Dry Eye Disease - United States.

(n.d.). Retrieved April 21, 2024, from https://www.sightsciences.com/us/sight-sciences-receives-fda-510k-clearance-of-the-tearcare-system-for-treatment-of-meibomian-gland-dysfunction-mgd-the-leading-cause-of-dry-eye-disease/

Singh, S., Donthineni, P. R., Srivastav, S., Jacobi, C., Basu, S., & Paulsen, F. (2023). Lacrimal and meibomian gland evaluation in dry eye disease: A mini.review. In *Indian Journal of Ophthalmology* (Vol. 71, Issue 4, pp. 1090–1098). Wolters Kluwer Medknow Publications. https://doi.org/10.4103/IJO.IJO_2622_22

Tao, J. P., Shen, J. F., Aakalu, V. K., Foster, J. A., Freitag, S. K., McCulley, T. J., Vagefi, M. R., Kim, S. J., & Wladis, E. J. (2023). Thermal Pulsation in the Management of Meibomian Gland Dysfunction and Dry Eye: A Report by the American Academy of Ophthalmology. *Ophthalmology*, *130*(12), 1336–1341. https://doi.org/10.1016/j.ophtha.2023.07.009

Tauber, J., Owen, J., Bloomenstein, M., Hovanesian, J., & Bullimore, M. A. (2020). Comparison of the iLUX and the lipiflow for the treatment of meibomian gland dysfunction and symptoms: A randomized clinical trial. *Clinical Ophthalmology*, *14*, 405–418. https://doi.org/10.2147/OPTH.S234008

Thode, A. R., & Latkany, R. A. (2015). Current and Emerging Therapeutic Strategies for the Treatment of Meibomian Gland Dysfunction (MGD). *Drugs*, *75*(11), 1177–1185. https://doi.org/10.1007/s40265-015-0432-8

Tomioka, Y., Kitazawa, K., Yamashita, Y., Numa, K., Inomata, T., Hughes, J. W. B., Soda, R., Nakamura, M., Suzuki, T., Yokoi, N., & Sotozono, C. (2023). Dyslipidemia Exacerbates Meibomian Gland Dysfunction: A Systematic Review and Meta-Analysis. *Journal of Clinical Medicine*, *12*(6), 12. https://doi.org/10.3390/JCM12062131

Tomlinson, A., Bron, A. J., Korb, D. R., Amano, S., Paugh, J. R., Ian Pearce, E., Yee, R., Yokoi, N., Arita, R., & Dogru, M. (2011). The international workshop on meibomian gland dysfunction: Report of the diagnosis subcommittee. *Investigative Ophthalmology and Visual Science*, *52*(4), 2006–2049. https://doi.org/10.1167/iovs.10-6997f

Tong, L., Lim, L., Tan, D., Heng, W. J., Lim, J., Chan, C., Arundhati, A., & Tan, A. (2021). Assessment and Management of Dry Eye Disease and Meibomian Gland Dysfunction: Providing a Singapore Framework. In *Asia-Pacific Journal of Ophthalmology* (Vol. 10, Issue 6, pp. 530–541). Lippincott Williams and Wilkins. https://doi.org/10.1097/APO.0000000000000417

Toronto, C. E., & Remington, R. (2020). *A Step-by-Step Guide to Conducting an Integrative Review*. Springer. https://doi.org/10.1007/978-3-030-37504-1

Toyos, R., McGill, W., & Briscoe, D. (2015). Intense Pulsed Light Treatment for Dry Eye Disease Due to Meibomian Gland Dysfunction; A 3-Year Retrospective Study. *Photomedicine and Laser Surgery*, *33*(1), 41. https://doi.org/10.1089/PHO.2014.3819

Tulsyan, N., Gupta, N., & Agrawal, N. (2021). Risk Factors Associated with Meibomian Gland Dysfunction: A Hospital Based Study. *Nepalese Journal of Ophthalmology*, *13*(1), 59–64. https://doi.org/10.3126/nepjoph.v13i1.30605

Viso, E., Rodríguez-Ares, M. T., Abelenda, D., Oubiña, B., & Gude, F. (2012). Prevalence of Asymptomatic and Symptomatic Meibomian Gland Dysfunction in the General Population of Spain. *Investigative Ophthalmology & Visual Science*, *53*(6), 2601–2606. https://doi.org/10.1167/IOVS.11-9228

Wang, M. T. M., Vidal-Rohr, M., Muntz, A., Diprose, W. K., Ormonde, S. E., Wolffsohn, J. S., & Craig, J. P. (2020). *Systemic risk factors of dry eye disease subtypes: A New Zealand cross-sectional study*. https://doi.org/10.1016/j.jtos.2020.04.003

Wesley, G., Bickle, K., Downing, J., Fisher, B., Greene, B., Heinrich, C., Kading, D., Kannarr, S., Miller, J., Modi, S., Ludwick, D., Tauber, J., Yeh, T. N., & Srinivasan, S. (2022). Systane iLux Thermal Pulsation System in the Treatment of Meibomian Gland Dysfunction: A Post-Hoc Analysis of a 12-Month, Randomized, Multicenter Study. *Clinical Ophthalmology*, *16*, 3631–3640. https://doi.org/10.2147/OPTH.S379484

Whittemore, R., & Knafl, K. (2005). The integrative review: Updated methodology. In *Journal of Advanced Nursing* (Vol. 52, Issue 5, pp. 546–553). https://doi.org/10.1111/j.1365-2648.2005.03621.x

Willcox, M. D. P., Argüeso, P., Georgiev, G. A., Holopainen, J. M., Laurie, G. W., Millar, T. J., Papas, E. B., Rolland, J. P., Schmidt, T. A., Stahl, U., Suarez, T., Subbaraman, L. N., Uçakhan, O., & Jones, L. (2017). TFOS DEWS II Tear Film Report. In *Ocular Surface* (Vol. 15, Issue 3, pp. 366–403). Elsevier Inc. https://doi.org/10.1016/j.jtos.2017.03.006

Wolffsohn, J. S. c, Arita, R., Chalmers, R., Djalilian, A., Dogru, M., Dumbleton, K., Gupta, P. K., Karpecki, P., Lazreg, S., Pult, H., Sullivan, B. D., Tomlinson, A., Tong, L., Villani, E., Yoon, K. C., Jones, L., & Craig, J. P. (2017). TFOS DEWS II Diagnostic Methodology report. *The Ocular Surface*, *15*(3), 539–574. https://doi.org/10.1016/J.JTOS.2017.05.001

Xiao, J., Adil, M. Y., Chen, X., Utheim, Ø. A., Ræder, S., Tønseth, K. A., Lagali, N. S., Dartt, D. A., & Utheim, T. P. (2020a). Functional and Morphological Evaluation of Meibomian Glands in the Assessment of Meibomian Gland Dysfunction Subtype and Severity. *American Journal of Ophthalmology*, *209*, 160–167. https://doi.org/10.1016/j.ajo.2019.09.005

Xiao, J., Adil, M. Y., Chen, X., Utheim, Ø. A., Ræder, S., Tønseth, K. A., Lagali, N. S., Dartt, D. A., & Utheim, T. P. (2020b). Functional and Morphological Evaluation of Meibomian Glands in the Assessment of Meibomian Gland Dysfunction Subtype and Severity. *American Journal of Ophthalmology*, *209*, 160–167. https://doi.org/10.1016/j.ajo.2019.09.005

Zhu, D., Gupta, R. R., Stein, R. L., Quintero, J., Morcos, M. M., Link, T. J., & Perry, H. D. (2022). *Randomized Prospective Evaluation of Microblepharoexfoliation BlephEx as Adjunctive Therapy in the Treatment of Chalazia*. www.corneajrnl.com