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REVIEW

Management Strategies for Evaporative Dry Eye Disease and Future Perspective

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ABSTRACT

Dry eye disease (DED) is a common disorder that remains challenging from a clinical perspective. Unstable or deficient tear film is a major factor contributing to DED and the inability to resolve the loss of tear film homeostasis that accompanies DED can result in a vicious circle of inflammation and treatment-refractory disease. Recently recognized as a multifactorial disease, the main etiological subtypes of DED are aqueous-deficient and evaporative which exist on a continuum, although evaporative dry eye (EDE) is the more frequent classification. Although attaining greater recognition in recent years, there is currently no consensus and no clear recommendation on how to manage EDE. Clarity on the early diagnosis and treatment of EDE may facilitate the avoidance of progression to chronic inflammation, permanent damage to the ocular surface, and treatment-refractory disease. The purpose of this review was to identify current best practice for management of EDE in order to help clinicians in providing accurate diagnosis and optimized treatment. We summarize recent literature considering the role of the lipid layer on tear film stability, the importance of its composition and of its dynamic behavior, and the link between its malfunction and the insurgence and maintenance of tear film-related diseases. We have provided an assessment of the best management of lipid-deficient EDE based upon an understanding of disease pathophysiology, while indicating the flow of current treatments and possible future evolution of treatment approaches. Lipid containing eye drops may be considered as a step closer to natural tears from artificial aqueous tears because they more closely mimic the aqueous and lipid layers and may be used in combination with other management approaches. As a next step, we recommend working with a wider expert group to develop full guidelines to enable patient-centered management of EDE.

KEY POINTS

- Dry eye is a multifactorial disease of variable presentation with the tendency to become a chronic disease for which it is essential to identify and treat the main pathogenic mechanisms involved and tailor the treatment to the individual patient.
- Early intervention is needed to prevent the vicious cycle of DED and may require a multifaceted management approach.
- EDE is not just a problem of MGD but can be the result of anything affecting blinking, mucin spreading, aqueous layer volume and content.
- Lipid-containing eye drops may provide significant relief of symptoms by improving the lipid layer and its spreading ability and, as such, are an appropriate component of the overall management of lipid-deficient EDE; natural lipid-containing eye drops should be the preferred treatment.

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Diagnosis; dry eye disease; evaporative dry eye; meibomian gland dysfunction; treatment

Introduction

Dry eye disease (DED) is among the most common ocular disorders affecting tens of millions of individuals worldwide with an estimated prevalence of 5% to 50% of the adult population, the wide range resulting from studies involving symptoms with or without signs.[1] Prevalence rates may even be higher in certain populations, affecting up to 75% of adults aged over 40 years, most often women.[1] The different clinical presentations of DED has led to some misunderstanding of the condition and the need for a consensus on a clinical definition, which was recently provided by a global panel of DED experts: "Dry eye is a multifactorial disease characterized by a persistently unstable and/or deficient tear film causing discomfort and/or visual impairment, accompanied by variable degrees of ocular surface epitheliopathy, inflammation and neurosensory abnormalities".[2] The loss of homeostasis of the tear film is accompanied by ocular symptoms of DED which may be transient and reversible and associated with subclinical inflammation; however, a reduced ability or inability to re-equilibrate the ocular surface with

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clinically evident inflammation and epithelial alterations identifies more severe disease states leading to chronic inflammation, persistent epithelial alterations, and frequent alterations in quality of vision.[3] If early disease remains untreated, DED may become an irreversible chronic inflammatory condition exacerbated by reduced aqueous tear flow, increased tear film evaporation, and repeated nerve stimulation, and these processes result in a self-perpetuating vicious circle of inflammation leading to treatment-refractory disease and permanent damage to the ocular surface.[4]

The heterogeneity of DED presentations and differences in the disease course remain challenging from a clinical perspective. While 10% of subjects will have aqueous-deficient DED, more than 80% have evaporative DED, or a combination of both.[5] DED can substantially affect vision and quality of life, as symptoms often impact on daily activities, including reading, writing, or working with a visual display monitor[5,6]. The economic impact of DED may be substantial, with an estimated annual average cost of $783 per patient, and at a $4 billion cost to the US economy accounted for by the high prevalence.[7]

Evaporative dry eye (EDE) can occur as a result of anything affecting the eyelid, e.g., meibomian gland dysfunction (MGD) and blink-abnormalities, or the ocular surface, e.g., mucin deficiency, reduced aqueous layer volume and content, contact lens wear.[8] While artificial tears have long been used in treatment of DED to supplement tears, lipid-containing eye drops have been developed more recently to closely mimic the combination of aqueous and lipid layers of the tear film.[9] Although EDE has become increasingly important in recent years, there is currently no consensus and no clear recommendation on how to manage the disorder. In this paper we review the current literature giving an assessment of the best management of lipid-deficient EDE based upon an understanding of the pathophysiology of disease. For a comprehensive review of medications and devices for treatment of all types of dry eye, the reader is directed to an earlier publication.[10]

Pathophysiology

The central mechanism of DED may be either evaporative tear loss or inadequate aqueous production, or a combination of both, which leads to hyperosmolarity, inflammation, and tissue damage.[11] Evaporation is an important feature in both forms of dry eye and tear water evaporation plays a major role in tear film thinning, instability and break-up.[12,13]. The tear film lipid layer (TFLL) acts as a barrier to water evaporation. Disruption of the lipid layer exposes the water/lipid interface directly to air which leads to high evaporation rates. Any variation in the regularity, spreading and thickness of the TFLL or in the water vapor barrier activity and in the physical properties of its composition can lead to elevated water evaporation.[13,14] In theory, the three processes of evaporation, tangential flow, and inward flow of tears across the surface of the cornea may collectively contribute to tear film thinning, break-up and dry spot formation (Figure 1).[15] However, while fluid flow into/out of the cornea is shown to have little influence on tear film break-up.[15] evaporation is demonstrated to be an important factor controlling tear-film thinning.[16]

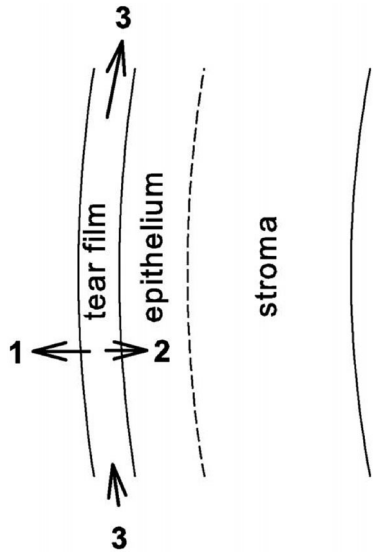

Figure 1. Three directions of tear flow that can cause tear film thinning. Arrow 1: flow across the outer tear surface, or evaporation; Arrow 2: flow into (or out of) the underlying epithelium; Arrow 3: flow into the plane of the tear film. If the outward flow (top arrow) is greater than the inward flow (bottom arrow) the tear film tends to thin. Republished with permission of the Association for Research in Vision & Ophthalmology from: Thinning rate of the precorneal and prelens tear films. Nichols JJ, et al. IOVS. 2005;46(7):2353-2361. ©2005, permission conveyed through Copyright Clearance Center, Inc.

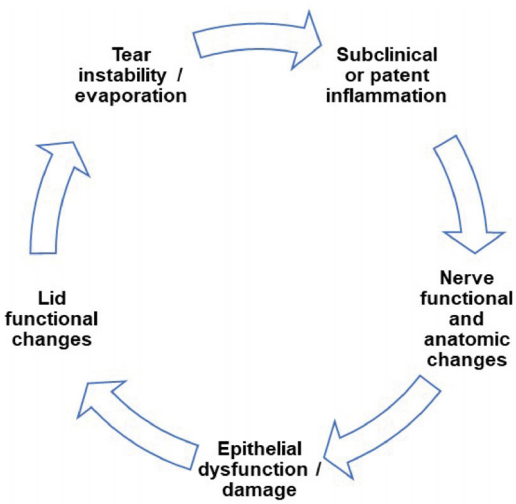

Figure 2. The five main pathogenic factors building the vicious circle in ocular surface diseases.

Three pathogenic factors are always present in DED at different levels of expression: 1) tear film instability, 2) epithelial malfunction and damage, and 3) clinically evident inflammation. These factors can be exacerbated by two other pathogenic findings: lid margin changes and nerve damage (Figure 2).[17,18] Tear film instability is caused by changes in lipid layer function and in quantity, quality, and availability of tear fluid.[17] It is an important source of symptoms and a starting point for inflammation.

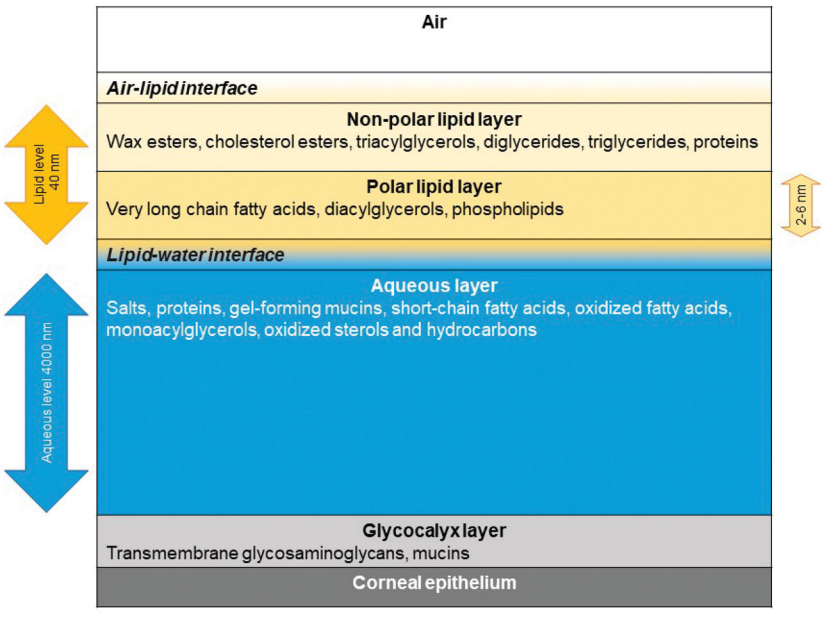

Figure 3. Model of the human tear film showing organization and components of the lipid and aqueous layers from the air surface to the corneal epithelium. Reproduced (translated) with permission from: Creuzot-Garcher C. II. Anatomy and regulation of the tear film. Figure 1–14. In: Report of the French Society of Ophthalmology 2015, Surface Oculaire (em-consulte.com) Copyright ©2015, Elsevier Masson SAS. All rights reserved.

Characteristics of the tear film lipid layer

The TFLL is composed primarily of an outer nonpolar lipid layer (wax esters, cholesterol esters, diesters, triglycerides, diglycerides, monoglycerides, free sterols, and free fatty acids) and inner polar layer (phospholipids and omega-hydroxy fatty acids) (Figure 3).[19–21] At the ocular surface, lipids of the TFLL prevent tear evaporation and are responsible for maintenance of ocular homeostasis, optimization of tear spreading patterns, direction of aqueous flow and prevention of film overflow during blinking.[9] In addition, the nonpolar lipids are supposed to be the main factor responsible for the control of tear water evaporation; they provide a clear optical surface, and present a barrier against foreign objects and organisms.[22] Polar lipids (phospholipids) are present in a relatively small concentration in the tear film, but they play a critical role in determining its surface properties and stability; decreasing the phospholipid/neutral lipid ratio decreases the stability of the lipid film.[23] Hence, as a treatment option, lipomimetic eyedrops containing phospholipids may be preferred to minimize the evaporative loss of tears from the ocular surface.[23] The polar tear lipids allow for an interface between the nonpolar lipid layer and the aqueous/mucin phase.[24] This interface may create structural stability by lowering surface tension of the aqueous tears, increasing viscoelasticity, and promoting proper segregation of the tear film molecules, thus allowing normal spreading of the tears and preventing ocular surface dewetting.[24] Patients lacking a visible lipid layer have a 4-fold higher rate of tear film evaporation than those with a continuous lipid layer, regardless of lipid layer thickness. Alterations in tear fluid flow or lipid composition or downregulation of tear proteins are found in most types of DED.[9]

The constitution of the tear film depends on three elements: the secretion of tears, the correct spreading of tears on the ocular surface and their resorption, partly by the tear ducts and partly by evaporation on the ocular surface. Organization of the tear film is dynamic, and the tear film permanently modifies its characteristics in response to mechanical factors such as eyelid movements but also the amount of lipid and aqueous secretions, evaporation and drainage.[21] The tear film structure can be destabilized in different pathological conditions but also in the many situations of everyday life that are accompanied by a disruption of the balance between ocular surface and environment. The meibomian glands, found in the upper and lower eyelids, excrete lipids onto the ocular surface, lubricating the ocular surface during blinking and protecting against tear evaporation. Through dysfunction of the meibomian glands, reduced lipid secretion may contribute to tear film instability.[25] Regulation of lipid secretion from the meibomian gland occurs via neuronal, hormonal, and vascular influences. Moreover, meibomian gland function may be under direct neuronal (predominantly parasympathetic but also sympathetic and sensory sources) or indirect vascular (vasoactive intestinal polypeptide) influence to control lipid synthesis and/or excretion.[26,27]

Alteration of the lipid layer and role in ocular surface disease

Thickness of the lipid layer is an indicator of the presence of lipids but does not completely reflect their efficiency and is not a guarantee of their ability to hinder evaporation.[28] Thinning of the lipid layer on the tear film can be the result not just of the lack of lipids but of their inability to spread correctly into an effective elastic bilayer. The importance of quick and even distribution of an equilibrated lipid film is confirmed in studies by Goto *et al.* showing the presence of

delayed irregular spreading of lipids in the outer layer of the tear film in dry eye patients.[29]

Oxidative stress associated with direct contact with the environment, pollutants, and UV light exposure is a very potent and continuous stressor of the ocular surface and internal structures of the eye. The lipid-rich fraction of tears is particularly sensitive to oxidative damage that could alter tear film quality.[20,30] Oxidation inevitably changes the physical and chemical properties of lipids leading to rigidity in the lipid layer and restricting the ability of lipids to spread across the ocular surface.[14,31,32] Lipid peroxidation has been shown to perturb the bilayer structure and modify membrane properties such as membrane fluidity, permeability to different substances, and bilayer thickness.[31,32] The existence of a direct relationship between lipid peroxidation and membrane leakiness has been proposed. Furthermore, increased membrane permeability caused by oxidation of lipids and membrane proteins can disrupt ion gradients, therefore altering metabolic processes.[33]

The performance of the lipid layer is strongly influenced by the underlying aqueous tear fluid and the spread of the lipid layer could be related to the volume of tear liquid in the aqueous compartments in the tear film.[34] Some glycoproteins dissolved in the aqueous/mucin layer are fundamental for the lipid spreading. Impairment or malfunction of the lid-associated glands influences the quantity and quality of tear lipids and is a possible source of inflammation and infection. Additionally, the lipid layer spreads uniformly immediately after a blink in healthy eyes, while the distribution time of the lipid layer after a blink is significantly prolonged in patients with aqueous-deficient DED.[34] This is confirmed by the finding of a significant negative correlation between short lipid layer stabilizing time and the Schirmer test: the shorter time of spreading and stabilizing of the lipid layer correlates with the higher quantity of tear fluid available on the ocular surface.[35]

Improvements in the ability to characterize the biochemistry of the tear film may lead to the identification of new markers to diagnose and potentially treat DED. Tear film biomarkers are of increasing interest owing to their important role in the pathogenesis of ocular surface damage, and their potential role in better diagnosis and monitoring, as well as facilitating personalized treatment strategies.[36,37]

Epithelial malfunction caused by friction, adverse environmental factors, ocular surface irritation, and/or nerve impairment can lead to further injury. This plays a key role in the inflammatory reaction, initially involving innate immunological processes but after prolonged exposure leading to an adaptive reaction responsible for chronic disease.[17] Nerve function impairment and anatomical changes affect both epithelial viability and turnover in addition to tear film production and require further investigation.[17]

The role of the ocular surface microbiome in maintenance of the microenvironment homeostasis has been realized in recent years.[38,39] However, colonizing bacteria may also play a role in disease states. The commensal eye bacteria produce enzymes, like lipases, and toxins that can provoke cellular damage at the ocular surface, inducing an alteration of the lipid layer of the tear film with instability, ocular surface inflammation, and irritative symptoms. *Propionibacterium sp*., *Corynebacterium sp*. and *S. aureus* strains, from patients with chronic blepharitis produce lipolytic exoenzymes that can hydrolyze cholesterol esters and degrade lipids of the tear film[40–42]. This activity provokes symptoms similar to those occurring in dry eye, without an evident infective status. The exact role of bacteria in changing tear film lipids has yet to be fully resolved.

The lid margins are essential to maintain a healthy tear film and distribute it over the ocular surface to achieve an optimal refractive interface.[43] Lid margin changes, including thickening and rounding causing a reduced congruity with the eye bulb as well as the presence of eyelid notches can affect the shape and function of the menisci, such that tear film distribution and lipid layers spreading can be adversely affected.[17] To achieve an effective lipid layer, the nonpolar component, which retards water evaporation, is dependent on a properly structured polar phase, and this composite lipid layer must maintain integrity during a blink.[44,45] The central upper and lower lids overlap during spontaneous blinking, which prevents full lid margin apposition and provides the necessary space for tear film mixing. Incomplete blinks that may occur during some vision tasks, such as reading or while looking at a visual display screen, are thought to cause lipid layer deficiencies.[43] Lid deformity, e.g., due to swelling, influences tear film spreading by affecting lid apposition and dynamics. Drying of the ocular surface due to poor lid apposition or to lid deformity, leading to exposure or poor tear film resurfacing, are accepted causes of ocular surface drying, but they have received little formal study. Dry eye problems may also be caused by problems of lid congruity after plastic surgery of the lids.[46] Lid margin structures undergo some changes with increasing age, including increased lid margin thickness and increased laxity with or without ectropion, which may be directly responsible for poor tear film quality due to poor mixing of tear film components.[43]

Meibomian gland dysfunction (MGD) is reported to be the most common cause of EDE. MGD is characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion of meibum, which contributes to the lipid layer of the tear film.[8,19] Meibomian gland dropout, blockage and/or inflammation leads to stasis of the meibum inside the gland, and proliferation of bacteria and mites including *Staphylococcus* sp. and *Demodex folliculorum*. This ingrowth of bacteria enhances the production of lipid-degrading lipases and esterases that increase the viscosity and melting temperature of the meibum, reducing its secretion onto the surface of the tear film and thus completes the self-sustaining MGD circle.[25] It is the meibomian gland changes that connect the two vicious circles of MGD and DED. The absence of normal meibum reduces the lipid content of the tear film, allowing entry into the DED vicious circle, in which the lipid-deficient tear film promotes

increased tear evaporation, hyperosmolarity and inflammation.[25]

Management

Diagnosis

A recent publication from a dry eye Experts Board defines a three-step method for accurate diagnosis of DED as: 1) administration of a patient symptoms questionnaire, 2) observation of the ocular surface at the slit lamp to study the tear film and staining of the ocular surface to identify epithelial damage and lid conditions, and 3) testing for tear clearance and corneal sensitivity.[47] While multiple questionnaires exist for the diagnosis of DED, assessment of treatment, and impact of DED on quality of life.[6,48] the Symptom Assessment in Dry Eye (SANDE) questionnaire, which comprises only two questions that the patient answers on a 100 mm horizontal visual analog scale to quantify the patient-reported symptoms of ocular dryness and/or irritation, may be preferred to quantify the severity, frequency and change in symptoms over time, e.g., for repeat comfort assessment.[49] The SANDE questionnaire is rapid, inexpensive, reliable, easy to perform and easy for the patient to complete; it does not depend on language as the patient's responses are recorded on a visual scale. In a direct comparison, the SANDE questionnaire performed well against the 12-item symptom-frequency based Ocular Surface Disease Index (OSDI) questionnaire.[50] The OSDI measures frequency of symptoms, environmental triggers and vision related quality of life, and is widely used in DED clinical trials.[51] The OSDI and Dry Eye Questionnaire 5-question survey (DEQ-5) are recommended by the TFOS DEWS II committee as symptom screening tools for DED diagnosis.[52] DEQ-5 is a shortened version of the DEQ which includes questions about the severity and frequency of ocular discomfort and dryness and can discriminate between DED diagnoses.[53] It is important to differentiate lipid-related symptoms from other causes so that the appropriate tear substitute may be prescribed. For example, the patient may describe itching which may indicate allergic disease; however, by determining the location of the itching at the lid margin rather than the ocular bulb this would identify lipid-related problems. A questionnaire that probes the time of day that the symptoms are most burdensome, such as the McMonnies questionnaire for dry eye classification, may help to distinguish symptoms that are more frequent in the morning and associated with lipid-related problems.[54]

Several technology-related tests have been developed to help the clinician to identify lipid-layer problems, these include interferometry.[55] meibography.[56] dynamic interference lipid pattern (DLIP) test.[57] and the meibomian gland expressor.[58] While seemingly attractive, some, such as meibography, need expensive instruments and are only useful to detect extreme cases, i.e., normal and very severe meibomian dysfunction, leaving uncertainty in the intermediate presentations. A morphologic test (such as infrared meibography) which allows observation of meibomian gland structure should be combined with a function test (e.g., meibomian gland expression or DLIP test) to obtain a useful evaluation of lipid layer performance. Tear break-up time (TBUT), the interval of time that elapses between a complete blink and the first break in the tear film, is frequently used to test tear film stability and is a good marker of lipid layer efficiency with short TBUT indicative of poor lipid layer quality.[52] Interferometry is also used to assess the stability of the tear film in a non-invasive manner and can also be used to measure the thickness of the lipid layer (TearScience®, LipiView®) which may be indicative of meibomian gland dysfunction.[52,59] Interferometry of the normal eye provides repeatable pictures after blinking, while in the dry eye shape changes occur because the lipid layer cannot spread efficiently. Dynamic interferometry may be evaluated with several devices, including commercial devices and the slit lamp, and should be used more often. A shorthand approach to diagnosing lipid-deficient EDE through symptoms, signs and diagnostic tests is outlined in Table 1. Signs and symptoms indicative of lipid-deficient EDE include worse symptoms in the morning, inflammation of the meibomian gland or lid margin, and insufficient or partial blinking. Additional diagnostic criteria identified through tests include altered TBUT, interferometry, and random or no exposition areas as identified through examination of the staining pattern of the ocular surface.

Table 1. Diagnostic criteria to identify lipid-deficient evaporative dry eye disease.

Signs & symptoms
Symptoms worse in the morning
Inflammation of the meibomian gland / lid margin
Insufficient / partial blinking
Alteration in diagnostic tests
Tear film break-up time (TBUT)
Interferometry (slit lamp, LipiView®, TearScope®)
Staining pattern: random / no exposition areas

It is of critical importance that the diagnostic approach determines the relevance of each of the pathogenic factors in the patient's clinical presentation such that an effective, long-lasting, and personalized treatment can be administered and modified if necessary. As a multifactorial disease with multiform presentation and course, discerning the different involvement of each component of the ocular surface structure is essential to identify the best treatment approach tailored to the individual needs of the patient. A simple flowchart developed by an Experts Board provides guidance on achieving the right diagnosis and appropriate treatment based upon identification of the etiological factors involved (Figure 4).[47]

Treatment

Treatment of DED should be aimed at re-establishing and maintaining the ocular surface system homeostasis that was disrupted due to the vicious circle of the disease. All factors present which contribute to and maintain the vicious circle of the disease must be considered and potentially treated simultaneously (Figure 4). A management algorithm for patient-centered treatment based upon the predominant pathophysiology and severity of symptoms, while indicating

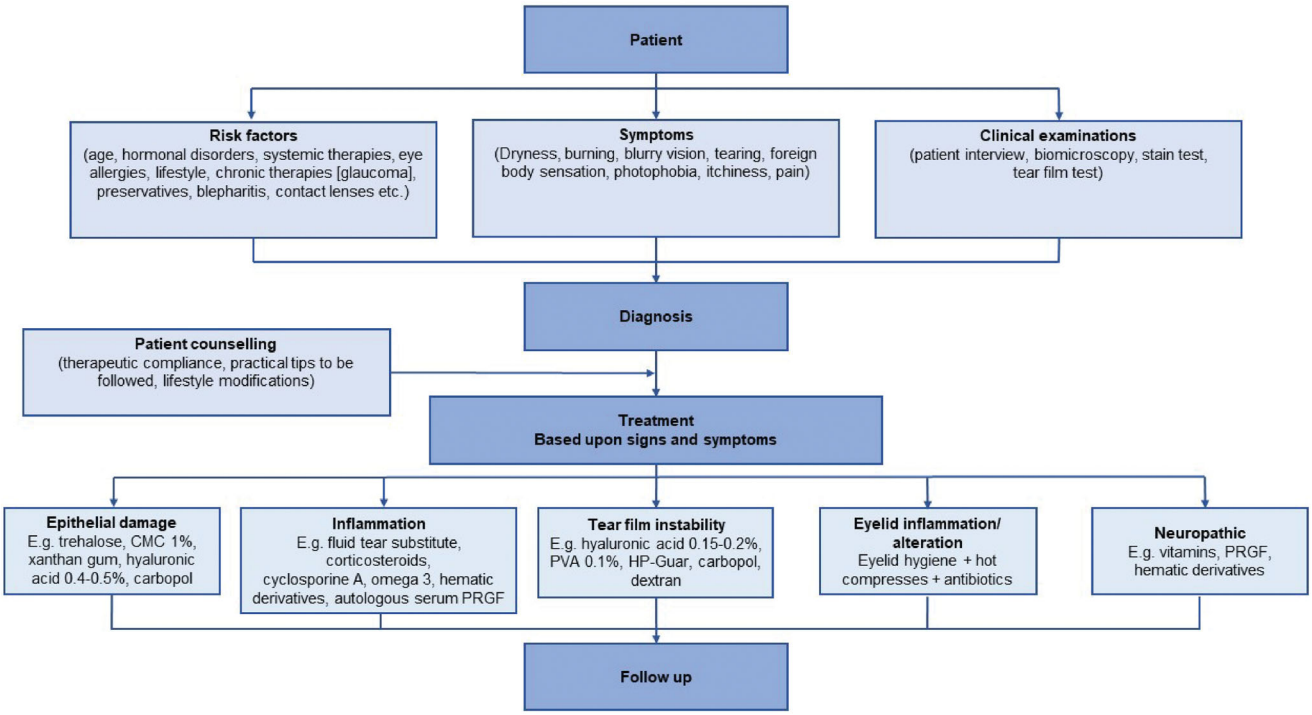

Figure 4. Multi-item flowchart to define the diagnosis and appropriate treatment of patients with dry eye disease. CMC: carboxymethylcellulose; Hp: hydroxypropyl guar; PRGF: plasma rich in growth factors; PVA: polyvinyl alcohol.

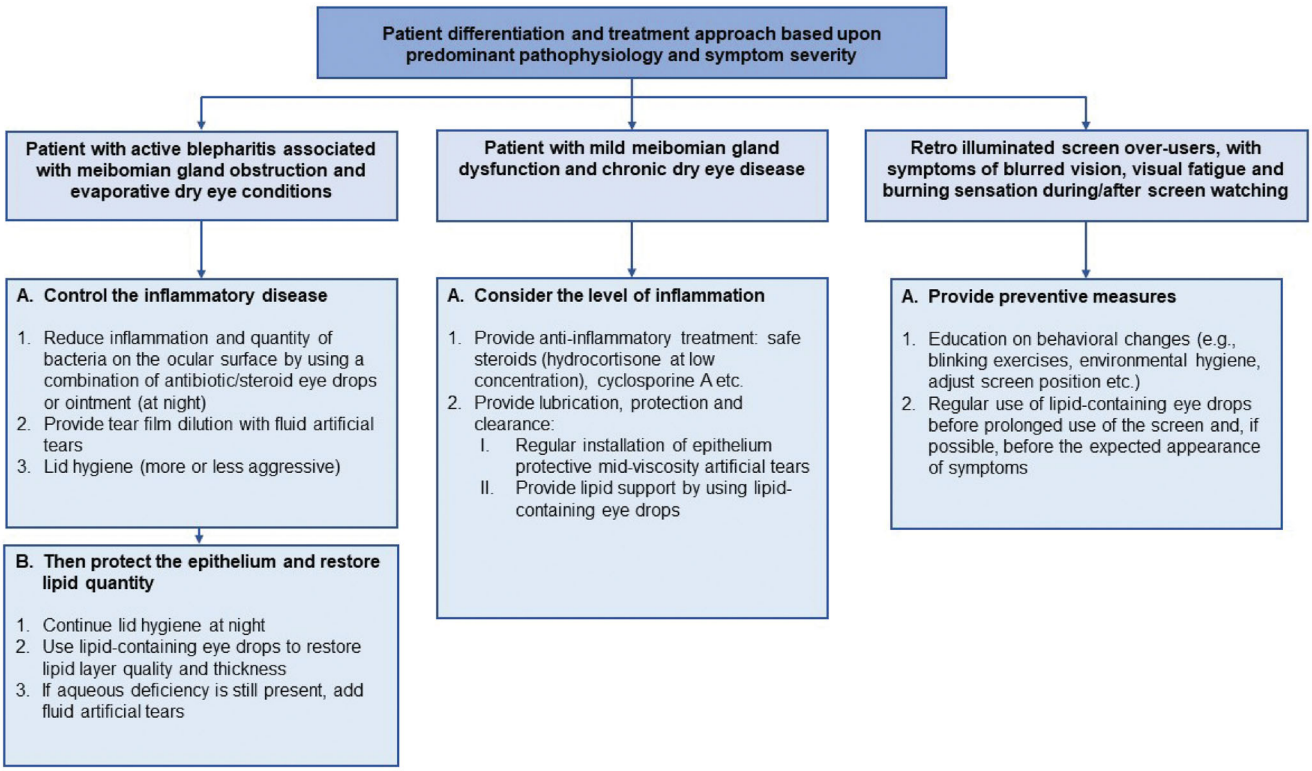

Figure 5. Management algorithm for customized treatment based upon patient differentiation according to predominant pathophysiology and symptom severity.

the flow of treatments is provided in Figure 5. Preventive measures that include behavioral changes and the regular use of lipid-containing eye drops are outlined with relevance to screen over-users with DED symptoms who tend to have a lower blink rate and incomplete blinking which leads to longer evaporation time and reduced expression of lipids from meibomian glands (Figure 5). Tear substitutes are traditionally used for the treatment of DED to improve tear volume. While ocular lubricants are a mainstay of therapy, they generally provide only temporary symptom relief and do not target the underlying pathophysiology. Artificial tears with higher viscosity (e.g., gels) may be preferred for their

extended efficacy due to enhanced ocular residence; however, they can be associated with decreased tear clearance and blurred vision.[60]

For 24-hour DED management, daytime use of artificial tears to protect the eye from aggravating environmental factors in combination with night-time use of gels to relieve more severe symptomatology is recommended.[61] To increase *tear film stability*, polymers containing hyaluronic acid are considered the gold standard.[47,62,63] For *epithelial protection*, trehalose is demonstrated to have a bioprotective effect on ocular surface alterations resulting from preservation of the integrity of proteins and lipids, and protection against oxidative stress, hypoxia, and apoptosis.[47] If *inflammation* is clinically evident, initiation of treatment with a corticosteroid plus cyclosporine is advised to reduce production of proinflammatory substances to obtain a rapid response followed by maintenance of response with cyclosporine alone.[47] Omega-3 fatty acids are useful to treat inflammation through the formation of potent anti-inflammatory and pro-resolving lipid mediators..[17]Eye drops containing n-3 eicosapentaenoic (EPA) and docosahexaenoic acids (DHA) have a positive effect on the ocular surface and may have *neuroprotective properties*.[64,65] Dietary modification to treat DED with essential fatty acid supplementation has been the focus of some research[65–67]. However, a randomized controlled trial for oral daily doses of EPA and DHA versus olive oil (placebo) found no significant differences between treatment groups for both the signs and symptoms of DED over 12 months.[68] although, the polyphenols present in olive oil have demonstrated anti-inflammatory effects, which may have been a cofounder in this study[69–71]. A recent systematic review and meta-analysis concluded that long-chain omega-3 supplements may have little to no benefit on dry eye symptoms relative to placebo, although there was some improvement on clinical signs.[72]

For patients with a *significant component of EDE and MGD*, procedures targeting clearance of meibomian gland obstructions can be employed using heat or mechanical energy (e.g., warm compresses, self-administered lid massages, eye-warming devices, thermal pulsation treatment or intraductal meibomian gland probing) to restore natural flow of meibum.[10,73] In addition to interventional procedures, the use of topical and systemic antibiotics (tetracyclines, macrolides, fluoroquinolones) can help to regulate bacterial flora, decreasing the secretion of bacterial lipases that act on altered lipid secretions and release fatty acids that are irritating to the glandular ducts.[47] The interventional procedures may also be supplemented with topical medicines including artificial tears and lipid-containing eye drops as and when required to break the cycle of chronic MGD (Figure 5).

Lipid-based treatments

Lipid-containing eye drops are proposed as a step closer to natural tears because they more closely mimic the aqueous and lipid layers. Lipid-containing eyedrops potentially have a longer-lasting lubricating effect while minimally interfering with patient's vision.[74] Such lipid-based agents would be expected to benefit patients with EDE as well as related ocular surface diseases. Topical lipid-based products are designed to restore the lipid layer of the tear film to reduce tear evaporation rate and restore tear film stability thereby improving signs and symptoms of MGD.[74,75] Historically, lipid-containing lubricant eye drops have not been widely used as they tended to induce blurred vision; however, in recent years newer formulations have been better accepted.[76] Lipid-containing artificial tears may be superior to sodium hyaluronate-containing drops in terms of improving optical quality and ocular surface parameters in patients with significant MGD.[77] Agents used to control inflammation may be used in combination with lipid-containing artificial tears to increase tolerability, although the combination should be avoided in the presence of significant inflammation. There is a pro-inflammatory activity of phospholipids in an inflammatory environment whereby phospholipases produce polyunsaturated lisophopholipid molecules which are involved in the progression of inflammation.[78]

Lipid-based eye drops are demonstrated to decrease tear film osmolarity and improve tear film stability more effectively than water-based eye drops in patients with mild to moderate EDE.[75] A systematic literature review found lipid-containing lubricant eye drops to be effective on improving selected signs of dry eye and thus they could be recommended for treatment.[74] Lipids used in artificial lubricants include, mineral oil, castor oil, polar phospholipid surfactant, glycerin, soy oil, phospholipid liposomes.[9,76,79] Liposomal lid sprays, emulsion eye drops, gels, and other lipid-based carriers have shown favorable tolerability and efficacy in improving symptoms of dry eye.[9,80,81] Oil-in-water emulsions reduce the signs and symptoms of all types of dry eye, but are particularly recommended for lipid-deficient dry eye patients.[82]

To counteract the effects of hyperosmolarity, components in the aqueous phase of the emulsions, such as polyols (glycerol), disaccharides (trehalose), and some amino acids may provide additional effect on the ocular surface (e.g., lubrication, osmoprotection), and may be recommended to protect ocular epithelial cells.[9,83] Cationic emulsions may provide optimal ocular spreading and residence time with ocular surface benefits to improve DED, especially in MGD patients.[84,85] Anionic polar phospholipids in lubricant drops act as surfactants and provide a stable interface between neutral nonpolar lipids and the aqueous layer thereby replenishing and stabilizing the lipid layer, improving lipid layer thickness, and meibomian gland functionality.[86]

Lipid-containing lubricant eye drops are shown to improve tear film breakup time, reduce ocular discomfort, and are well tolerated in patients with lipid-deficient DED.[86] More recently an eye drop formulated as a nanoemulsion (composed of particles that are generally 10-1000 nm in size and packed with both oil and aqueous components) increased average lipid layer thickness in subjects with low baseline levels and improved symptoms of DED.[87] The nanoemulsion formulation allows for the components of the drop to be dispersed onto the surface of the eye similarly to

that of an aqueous eye drop, theoretically adding oil to the tear film without the temporary effects that accompany highly viscous eye drops. While lipid-containing eye drops are effective, artificial lipids cannot completely replace the complexity of natural lipids, such as phospholipids, sterol esters, free fatty esters, medium-chain triglycerides, and the healthy lipid bilayer. This is an important limitation of lipid supplementation in practice. Besides, it has been observed that it is difficult to see a dry eye without lipids on the lid reservoir. The problem may not be the quantity of lipids on the surface rather the quality of the lipids and whether they spread properly on the ocular surface. Oxidative stress may have a huge part in this given it increases the rigidity of the tear film and then reduces the spreading and decreases its impermeability. A microemulsion eye drop formulation of phospholipids, triglycerides and unsaturated fatty acids containing oil droplets in sub-micron size is demonstrated to improve tear lipid barrier function by restoring the lipid layer as well as a wettability similar to that of natural tears. Topical administration of the microemulsion to patients with dry eye is shown to improve both signs and symptoms.[88,89] In a randomized trial, a similar microemulsion formulation containing natural triglycerides, a mixture of phospholipids and glycerol was shown to improve tear stability and decrease osmolarity and corneal staining, with results exceeding that of the active comparators sodium hyaluronate and hydroxypropyl methylcellulose.[75] These results are consistent with improvements in the lipid layer of the tear film resulting from prolonged use of emulsion drops.[75,90] In a 6-month comparison of the long-term improvement in dry eye symptomatology with lipid and non-lipid-based artificial tears, participants with predominantly EDE due to tear lipid insufficiency (with suboptimal lipid layer thickness at baseline; grade $\leq$3) preferentially benefited from lipid-based nanoemulsion eye drops.[91]

Lipid peroxidase can change the water permeability through a bilayer of lipids and be one of the reasons for the increased EDE. Effective control of evaporation is not dependent just on the volume of lipids but also on their quality and on the correct environment of the ocular surface system (blinking efficiency, lipids, aqueous volume and composition, mucins spreading and quality) as well as the integrity of the epithelium. Water permeability through the bilayer is increased in the presence of oxidized lipids, and water defects are observed frequently at high concentrations of oxidized lipids. Wong-Ekkabut and colleagues suggest that one mechanism of cell membrane damage is the increase in membrane permeability due to the presence of oxidized lipids.[14] The best approach may be to tackle the causes by treating the condition and restoring the natural lipids of the tear film, and to use lipid eye drops morning and evening (in the right quantity) to supplement the lipid layer, while hydrating during the day with bioprotective eye drops, such as those containing sodium hyaluronate. An oil-in-water emulsion containing soybean oil and egg yolk phospholipids administered in combination with aqueous sodium hyaluronate eyedrops was associated with significant improvement in tear volume compared with sodium hyaluronate eyedrops alone in a mouse model of DED.[90] Further, the combined administration of lipid tear substitute and hyaluronate decreased the lag time before the effect was measurable. Recent studies show that formulations of crosslinked hyaluronic acid combined with liposomes and crocin, and uncrosslinked hyaluronic acid combined with other components, such as tamarind seed polysaccharide, and are effective for management symptoms of DED.[92,93]

When selecting appropriate treatment for DED, the exclusion of preservatives from the eye drop formulation is an important consideration. Inclusion of the preservative benzalkonium chloride (BAC), the most commonly used preservative in ophthalmic solutions, is prevalent despite the noted potential for exacerbating DED. BAC is shown to induce some clinicopathological features of DED in animal models.[94] BAC is shown to cause tear film instability, loss of goblet cells, conjunctival squamous metaplasia and apoptosis, disruption of the corneal epithelium barrier, and damage to deeper ocular tissues.[95] The mechanisms are not fully elucidated but may involve immuno-inflammatory reactions as well as direct impact on the lipid components of the tear film and cell membranes. To avoid BAC-related toxicity, eye drop solutions containing alternative 'soft' preservatives have been developed (e.g., polyquaternium-1 [PQ-1], stabilized oxychloro complex [SOC]); however, there is also evidence toxicity and damages to the ocular surface with extended exposure to 'soft' preservatives and cationic agents such as cetalkonium chloride in animal studies and human cell models.[96,97] Therefore, preservative-free eye-drop formulation must be used when available for the appropriate management of EDE, especially as lipid-based products have higher viscosity which leads to longer residence time on the ocular surface.[47]

Conclusions

A recent expert group has provided consensus on a clinical definition of DED as a multifactorial disease, a definition that has been lacking leading to some misunderstanding of this disease. Clarity on the clinical definition of DED will facilitate diagnosis and early treatment, and the avoidance of progression to chronic inflammation, loss of tear film homeostasis, permanent damage of the ocular surface and treatment-refractory disease. In this review, we have summarized recent literature considering the role of the lipid layer on tear film stability, the importance of its composition and of its dynamic behavior, the link of its malfunction with the insurgence and maintenance of tear film-related diseases, and the possibility of restoring it. In addition, we have provided an assessment of the best management of lipid-deficient EDE based upon an understanding of disease pathophysiology, while indicating the flow of current treatments and possible future evolution of treatment approaches. Although EDE has become increasingly important in recent years, there is currently no consensus and no clear recommendation on how to manage the disorder. As a next step, we recommend working with a wider expert

group to develop full guidelines to enable patient-centered management and facilitate personalized medicine.

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