Review Article

Modern Approach to the Treatment of Dry Eye: A Complex Multifactorial Disease

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Abstract

Dry eye disease (DED) is a growing public health concern affecting quality of life and visual function, with a significant socio-economic impact. It is characterized by the loss of homeostasis, resulting in tear film instability, hyperosmolarity and inflammation of the ocular surface. Treatment of DED should be aimed at the restoration of the homeostasis of the ocular surface system. A proper diagnostic approach is fundamental to define the relevance and importance of each DED main pathogenic factor, namely tear film instability, epithelial damage and inflammation. All the factors that maintain the vicious circle of DED in the patient's clinical presentation have to be considered and possibly treated simultaneously. The treatment should be long-lasting and personalized since it has to be adapted to the different clinical conditions observed along the course of the disease. Since DED treatment is frequently unable to provide fast and complete relief from symptoms, empathy with patients and willingness to explain to them the natural history of the disease are mandatory to improve patients' compliance. Furthermore, patients should be instructed about the possible need to increase the frequency and/or change the type of treatment according to the fluctuation of symptoms following a preplanned rescue regimen.

Keywords: Dry eye disease, Ocular surface homeostasis.

Introduction

Dry eye is one of the most frequently encountered ocular morbidities, a growing public health problem and one of the most common conditions seen by eye care practitioners.[1] In light of new knowledge about the roles of ocular surface inflammation and tear hyperosmolarity in dry eye and the effects of dry eye on visual function, the International Dry Eye Workshop (DEWS) defined dry eye as a "multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased tear film osmolarity and ocular surface inflammation.[2]

Dry eye disease is characterized by tear film instability, which can be due to insufficient tear production or poor quality of tear film, resulting in increased tears' evaporation. Dry eye, therefore, can mainly be divided into two groups (Flowchart 1).

(1) Aqueous production deficient dry eye disease;
(2) Evaporative dry eye disease.

Risk Factors for Dry Eye Disease

Several risk factors have been linked to DED (Table 1), including personal, environmental, clinical illnesses, medications, and ocular factors (Gomes *et al*., 2017; Milner *et al*., 2017; Sullivan *et al*., 2017). Women are more likely to experience DED, with increased prevalence after menopause. The use of estrogen alone or with progestin can worsen symptoms (Alawlaqi & Hammadeh, 2016), and androgen treatment improves dry eye symptoms (Sriprasert *et al*., 2016). Low dietary intake of omega-3 fatty acids and continuous positive airway pressure device use are additional risk factors associated with DED (American Academy of Ophthalmology [AAO], 2013; Downie & Keller, 2015).

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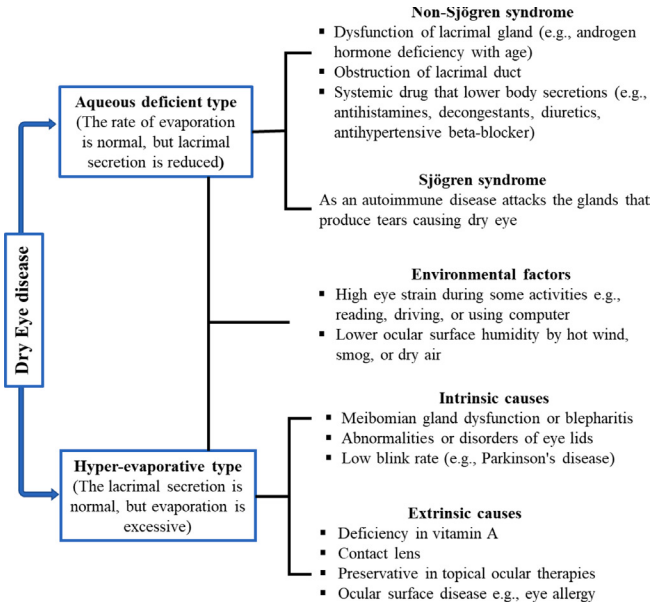

Flowchart 1: Types of dry eyes

Classification

On the basis of severity, dry eye disease has been graded as mild, moderate and severe with following features as shown in Figure 1.

Management

The management of DED is highly complicated because of its multifactorial etiology associated with many mechanisms.[3] Therefore, while diagnosing a patient with DE, clinicians should carefully determine the underlying etiology, such as evaporative or aqueous deficiency DE, which are the mechanisms that cause DED, and/or other OSDs, and they should administer relevant treatments accordingly.[4,5] The ultimate goal of DED treatment is to restore homeostasis of the ocular surface and tear film by breaking the vicious cycle of the disease.[6] Besides short-term therapies, it is always necessary to consider long-term treatment by taking into consideration the sequelae that can occur during the chronic DEs. Various management algorithms are structured to propose a series of treatment protocols according to disease stage. The management and therapeutic algorithm implementation according to disease severity can be summarized in four steps.

Diagnosis

Although the literature review provides an extensive discussion on the role and appropriateness of the currently used tests to diagnose DE, there is no gold standard test or even a panel of tests or well-established cutoff values for the available tests. The suggested sequence of DE diagnostic tests is history and examination followed by a symptom questionnaire; tear breakup time (TBUT) and ocular surface fluorescein staining; Schirmer's test; lid and meibomian morphology and meibomian expression. In Delphi Panel, the most frequently cited tests were slit lamp examination and fluorescein staining (100%) followed by TBUT and medical history (both 94%). An ideal diagnostic method should be preferably noninvasive, objective, specific, reproducible, and sustainable in terms of cost and time.[7,8] A review of diagnostic approaches is summarized in Table 2.

Table 1: Risk factors for dry eye disease

Category	Risk Factor
Personal	Sex Advanced age Asian ethnicity Contact lenses Low dietary intake of omega-3 fatty acids
Environmental	Low humidity or windy environments Air-conditioning Reading for long periods Driving extended periods Second-hand smoke exposure Prolonged exposure to display monitors (computer, tablets, etc.)
Chronic illness	Bell palsy Depression Diabetes Glaucoma Hepatitis C Parkinson disease Perennial/seasonal allergies Rosacea Thyroid disease
Autoimmune diseases	Rheumatoid arthritis Sarcoidosis Sjögren syndrome
Medications	Anticholinergics Antipsychotics Antivirals Beta-blockers Diuretics Estrogens Glaucoma medications Oral contraceptives Opioids Selective serotonin reuptake inhibitors
Injury	LASIX refractive surgical history Ocular injury

Note. Adapted from Gomes et al. (2017), Milner et al. (2017), and Sullivan et al. (2017).

Treatment

Etiology-oriented treatment has gained importance in the meetings held by ADES and TFOS, and ADES has acknowledged the "Tear Film Layers-Oriented Therapy" protocol. The ADES consensus recommends that the deficient layer of the tear film should be replaced accordingly and the underlying problem should be addressed directly (Figure 2). Since it is very difficult to classify dry eye treatment within strict rules and base it only on evidence-based studies, each patient should be evaluated individually and patient-specific treatment plans should be made.

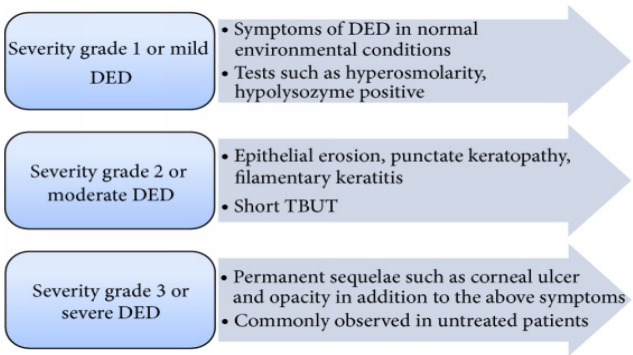

Figure 1: Classification of dry eyes on the basis of severity

Table 2: Diagnostic approaches

Stepwise diagnostic criteria and protocol	Description
Symptoms	A validated symptom questionnaire can be used at the beginning of the patient interaction
Diagnostic test recommendation and technique	OSDI, severity scale of the SANDE should be considered for repeated comfort assessment
Visual disturbance assessment	OSDI, DEQ-5, IDEEL, NEI VFQ-25, DEQS, CVSS17, functional tests - conventional distance and near visual acuity testing, aberrations, light scatter
Tear film stability	Tear film breakup time, fluorescein breakup time, noninvasive tear breakup time, thermography, osmolarity variability, tear evaporation rate
Diagnostic test recommendation and technique	Tear volume, meniscometry (tear meniscus assessment), OCT assessment of the tear meniscus, phenol red thread test, Schirmer's test, tear film osmolarity, tear film forming, ocular surface staining, impression cytology, LIPCOF, *in vivo* confocal microscopy, ocular surface sensitivity, Cochet-Bonnet or noncontact air-jet esthesiometers
Inflammation of the ocular surface	Ocular/conjunctival redness, matrix metalloproteinases, cytokines and chemokines, ocular surface immune marker, *in vivo* confocal imaging
Eyelid aspects	Anterior - Anterior blepharitis and Demodex blepharitis
	Posterior - LWE, interferometry - LipiView interferometer, meibography, meibomian gland expressibility/duct assessment, *in vivo* confocal imaging
	Dynamic - Blink/lid closure analysis, lid sensitivity

OSDI: Ocular surface disease index, SANDE: Symptoms analysis in dry eye, DEQ: Dry eye questionnaire, IDEEL: Impact of dry eye on everyday living, NEI VFQ-25: National Eye Institute's visual function questionnaire, DEQS: Dry eye-related quality-of-life score, CVSS: Computer-vision symptom scale, OCT: Optical coherence tomography, LIPCOF: Lid parallel conjunctival folds, LWE: Lid wiper epitheliopathy

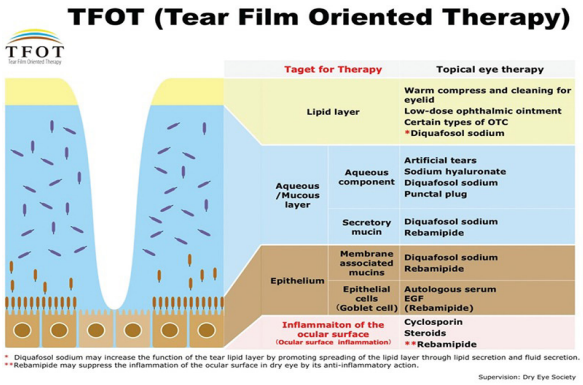

Figure 2: Tear film layers-oriented therapy

Another aspect of the management of dye eye disease involves stepwise management according to the grading or severity of the disease, which is depicted in Figure 3.

Future trends – The future of dry eye treatment

The newer treatment modalities under investigation are:
Lifitegrast 5%: Small-molecule integrin antagonist
Rebamipide: Quinolinone derivative mucin secretagogue
MIM-D3 (Mimetogen Pharmaceuticals; Gloucester, *MA, USA):* Nerve growth factor peptidomimetic, mucin secretagogue
OTX-DP: Sustained release dexamethasone-loaded punctual plug 0.4 mg
EBI 005 (Eleven Biotherapeutics): Protein-based IL-1 inhibitor
Diquafosol: P2Y2 receptor agonist
RU-101: Recombinant human serum albumin
KPI-121/LE-MMP 0.25%: Loteprednol etabonate mucus-penetrating particle, glucocorticoid receptor agonist
Ocular neurostimulator device: Intranasal lacrimal stimulator for DE

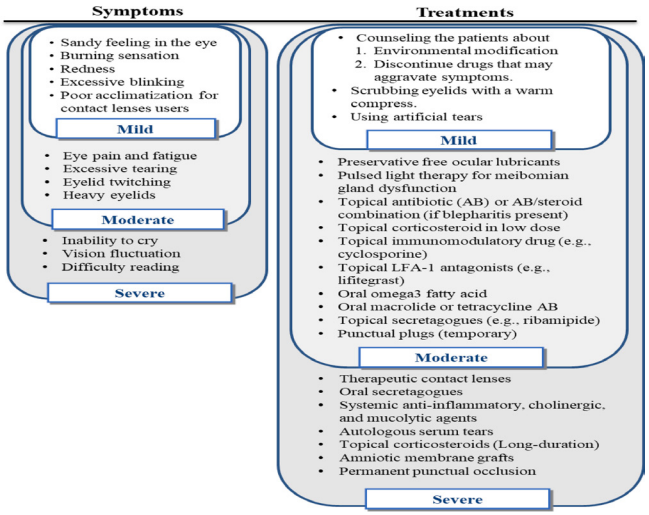

Figure 3: Stepwise management according to the grading or severity of the disease

Ocular iontophoresis with EG-437 (40 mg/mL dexamethasone phosphate solution).

Conclusion

Understanding the pathogenesis and specific cellular responses involved in different forms of DE could result in the development of other treatment strategies for better management and long-lasting results. The evidence implicating inflammation in the pathogenesis of DE has opened up new avenues for the treatment of this complex disorder. Development of additional treatment options in the form of compounds targeting specific components such as the epithelial barrier, corneal nerves, conjunctival goblet cells, or immune cells and cytokines involved in the ocular inflammatory reaction would provide hope for the millions of individuals who daily experience this deleterious condition.

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