

# Management of ocular surface disorders according to the guidelines of the Tear Film & Ocular Surface Society Dry Eye Workshop (DEWSII) Report



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## HIGHLIGHTS

Only modern approach to ocular surface disease, combining pharmacotherapy, neuromodulation, and advanced technologies, may give relieve from daily chronic pain.

## ABSTRACT

Ocular surface disorders, including dry eye disease, affect 5–50% of the population, with prevalence increasing with age, especially among women. Symptoms such as dryness, burning, and eye fatigue significantly reduce quality of life. The tear film consists of aqueous-mucin and lipid fractions, providing protection and hydration for the eye. Meibomian gland dysfunction, which disrupts the lipid layer, accounts for most cases of dry eye disease by causing excessive tear evaporation. A modern approach to ocular surface disorder therapy, combining pharmacotherapy, neuromodulation, and advanced technologies, may relieve daily chronic eye pain.

**Key words:** ocular surface disease, dry eye, DEWS II, Meibomian gland dysfunction

## INTRODUCTION

According to the 2017 definition of the updated Dry Eye Workshop Report published by the Tear Film and Ocular Surface Society (DEWS II), ocular surface disease (DED, dry eye disease) is a multifactorial ocular surface disorder characterized by abnormal tear homeostasis and associated ocular discomfort caused by multiple etiologic factors, the most important of which are tear film instability and hyperosmolarity, inflammation and damage of the ocular surface, and neurosensory dysfunction [1].

According to Craig et al. [2], tears are classified as:

- Basal (occurring when the eyelids are open) – tears that cover the ocular surface; their deficiency is the main cause of ocular surface disorders due to insufficient production of the aqueous layer (ADDE, aqueous deficient dry eye).
- Reflex – their secretion is triggered by irritation of the ocular surface (e.g. fumes from cutting onions) or stimulation of the reflex arc.
- Emotional – secreted in response to emotions.
- Under the closed eyelid – tears that can be collected for analysis immediately after waking up.

Basal tears, reflex tears and emotional tears are produced by the lacrimal gland as a result of stimulation of the nerve arc, but they differ, for example, in the concentration of proteins [3]. During sleep, the secretion of the lacrimal gland is reduced, so there is a higher concentration of proteins (from serum) in the tear preparations collected immediately after waking up, which come from the blood vessels of the conjunctiva [2].

## EPIDEMIOLOGY OF OCULAR SURFACE DISORDERS

One in seven patients between the ages of 65 and 84 report intermittent or chronic symptoms of DED [4]. According to some studies, signs resulting from ocular surface disorders affect 40 million patients worldwide each year and are among the main reasons for visits to ophthalmologists' offices [5]. Unfortunately, due to the multiplicity of diagnostic criteria and the ambiguity in the classification of ocular surface disorders, epidemiologic studies are very difficult to perform. Many studies have been published in the world literature; however, their methodologies are not systematized, and meta-analyses are also lacking. According to an updated report of the Dry Eye Workshop published by the Tear Film and Ocular Surface Society, the prevalence of DED ranges from 5% to 50% depending on the studied population, and the percentage increases with age [6]. In studies assessing the prevalence of clinical symptoms only, the percentage is higher, reaching as high as 75% in some populations (including Asian and Caucasian) and contact lens wearers [1]. The gender difference in the prevalence of

DED also increases with age, being 1.33–1.74 times higher in women than in men [7–11]. A high incidence of DED has been reported in school-aged children, highlighting the need for future studies evaluating risk factors such as smartphone use. Population-based studies in the southern hemisphere have not been conducted in the last decade, making it impossible to properly assess socioeconomic and environmental risk factors [7–9, 12, 13].

## STRUCTURE OF THE TEAR FILM

The ocular surface includes the cornea, the conjunctiva of the eyelid and eyeball, the goblet cells, the lacrimal glands and the accessory glands of the eyelid, and the Meibomian glands and eyelashes within them. These structures form a functional unit whose function is to produce the tear film, commonly known as tears [14].

Tear film covers the curvature of the cornea, serves to nourish and moisturize the eyeball, and participates in the transport of oxygen to the cornea. In addition, tears contain antimicrobial peptides, proteins and dissolved immunoglobulins that form a protective layer on the eyeball to protect it from microorganisms. DED is immunologically heterogeneous. Using modern proteomic methods, more than 2,000 proteins and more than 200 peptides have been identified in the tear film [15–17]. The proteins and peptides clear the ocular surface of dead corneal epithelial cells. The tear film provides an inert environment for the cornea. Due to the difference in refractive indices between air (1.0000) and the tear film (1.3369), the air-tear film interface is the primary refractive power in the human eye with a focusing power of approximately 42 D [18]. The average pH of tears is between 6.8 and 8.2, and gender has no effect on its value. The pH is dependent on age, time of day, eye closure, blinking and tearing [19–25].

According to the model proposed by Wolff et al. [26, 27], the tear film is composed of:

- The mucin layer composed of high molecular weight glycoproteins produced by the disc and sternal goblet cells. This fraction directly covers the epithelium lining the anterior surface of the cornea.
- The aqueous layer, which consists of the secretions of the main lacrimal glands and the Wolfring and Krause secondary lacrimal glands. This fraction is the largest volume component of the tear film.
- The lipid layer, produced by the Meibomian, Zeiss and Moll's glands.

According to the 2017 DEWS II report, there are 2 fractions of the tear film [1]:

- mucin-water fraction
- lipid fraction.

In terms of dynamics, these fractions behave as a coherent functional unit [28]. The thickness of the tear film covering the cornea, as measured by optical coherence tomography, is approximately 2.0–5.5  $\mu\text{m}$  [29–33]. This value is consistent with the results of studies using interferometric techniques. The thickness of the tear film covering the conjunctiva has not been clearly measured [29, 34]. Physiological daily secretion is approximately 1.5–2 mL of tears with a volume of 8 ( $\pm 3$ )  $\mu\text{L}$  [35, 36]. The fluid is released into the conjunctival sac and is drained during the blink reflex. Tears are drained into the nasal cavity through the lacrimal punctum, lacrimal ducts, lacrimal sac and nasolacrimal duct. Only 16% ( $\pm 5\%$ ) of tears per minute are drained through the lacrimal ducts, with the remainder evaporating [36, 37]. Tear secretion is controlled by the parasympathetic nervous system. Protein and electrolyte secretion is regulated by the sympathetic nervous system [38].

### Fractions of the tear film

The normal tear film is a non-Newtonian emulsion consisting of a mucin-water fraction and a lipid fraction.

#### Mucin-water fraction

Mucins are found not only on the surface of the eye, but also in other organs of the human body, including the lining of the respiratory epithelium or the epithelium lining the stomach. The mucin fraction consists of mucopolysaccharides produced by goblet cells and conjunctival and corneal epithelial cells. There are two groups of mucins based on their size: large gel-forming mucins (including MUC5AC) and small non-gel-forming soluble transmembrane mucins (including MUC1, MUC6, MUC4). Mucins are also classified according to their transmembrane and secretory forms. Their concentration decreases with distance from the epithelial cells. Mucins contain protein domains rich in serine and threonine and are glycosylated by attachment of O-glycans (glycan chains make up to 80% of the mass of mucins).

The main functions of this mucosal component are to minimize frictional forces and tightly fill intercellular spaces. Its gel-like consistency provides a barrier to pathogens. It is hydrophilic in nature, unlike the hydrophobic corneal epithelium. The aqueous component after a full blink (i.e., when both eyelids close tightly) divides into an upper and lower meniscus. It is composed of 95% lacrimal gland secretions, with the remaining 5% being secretions from the secondary lacrimal glands of Wolfring and Krause. This fraction consists mainly of water, electrolytes, and dissolved mucins and proteins. It carries nutrients, immune proteins and maintains the proper osmolarity of the tear film. It contains soluble immunoglobulins, sodium, potassium, chloride, calcium, magnesium, bicarbonate, glucose, lactate, amino acids and urea [39].

Mucin disorders cause both tear instability and ocular surface damage.

#### Lipid fraction

According to studies, the thickness of the lipid fraction ranges from 15 nm to 157 nm, with an average thickness of 42 nm [40]. The lipid layer reduces the surface tension of the tear film and is mainly produced by Meibomian glands. The thickness of the tear film is not uniform over the entire surface. The lipid layer protects the pre-corneal tear film from excessive evaporation [41, 42]. The exact structure of the lipid layer of the tear film is not known. Hypothetically, it consists of surfactant molecules at the interface with the mucin-water fraction and lipophilic molecules at the interface with the air.

### MEIBOMIAN GLAND DYSFUNCTION

The term Meibomian gland dysfunction (MGD) was first used by Korb and Henriquez in the early 1980s [43]. The term is used to describe all disorders of the Meibomian glands, including those with a proliferative basis or congenital lesions [44, 45]. MGD is one of the major (approximately 80%) causes of evaporative DED. As defined by the International Workshop on Meibomian Gland Dysfunction, 31 March 2011 [14, 46]:

“Meibomian gland dysfunction is a chronic obstruction of the meibomian gland orifices accompanied by quantitative and/or qualitative changes in glandular secretions. This dysfunction leads to tear film abnormalities, DED, lid margin inflammation and ocular surface disorders”.

In most cases, MGD is bilateral and symmetrical. It is often associated with blepharitis. The symptoms of both conditions are clinically similar and often overlap [47].

In the DEWS II report, the prevalence of MGD in people over 40 years of age was estimated to be 38–68% [48]. Unstable tear film and excessive evaporation are the main causes of the disease [49]. In the early stages of the disease, the course of MGD is asymptomatic, but as the disease progresses, lid margin lesions or posterior blepharitis associated with MGD appear.

Modern therapies for ocular surface disorders are based on the administration of preparations composed of various chemicals, such as cellulose derivatives or hyaluronic acid. However, despite their good ocular surface moisturizing properties, small molecules such as trehalose, L-carnitine, erythritol are included in the preparations [50, 51]. The international literature provides information on their osmoprotective effect by regulating intracellular and extracellular osmolarity. Hyperosmolarity is one of the main causes of cell apoptosis and inflammation in ocular surface diseases [50, 52]. These substances are also characterized by cytoprotective effects [53].

Despite many years of effort, there is currently no gold standard for topical therapy of ocular surface disease, yet tear film replacement is the cornerstone of any therapeutic regimen. When lid margin hygiene and tear supplementation with lubricating drops are inadequate and in severe forms of ocular surface disease, topical anti-inflammatory treatment, including preservative-free corticosteroids or preparations containing immunomodulatory substances such as cyclosporine A, should be added to the therapy according to the recommendations of the DEWS II report [38, 54].

Cyclosporin A is a cyclic immunomodulatory polypeptide with immunosuppressive activity. It has been shown to be effective in preventing allograft rejection, including rejection of a transplanted corneal flap [55]. The drug also has anti-inflammatory effects by inhibiting cellular immune responses. In the first step of its action, cyclosporin A binds to cyclophilin, a cytoplasmic protein of T lymphocytes. In the next step, the complex formed by the combination of cyclosporin and cyclophilin binds to calcineurin (a key calcium-dependent enzyme with phosphatase properties), preventing it from activating the nuclear factor of activated T cells (NFAT) – a transcription factor that stimulates the transcription of interleukin 2 (IL-2). Dephosphorylation of NFAT causes its translocation to the nucleus and initiation of transcription of genes for selected cytokines. The action of cyclosporine leads to cellular apoptosis. Cyclosporine A reduces the secretion of lymphokines, including IL-2, IL-3, IL-4, IL-5, tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), interferon  $\gamma$  (INF- $\gamma$ ), and T-cell growth factor (TCGF). This drug blocks cellular and humoral immune responses and modifies inflammatory processes. Its action is reversible, it does not cause lymphocytotoxic effects and it does not lead to proliferative processes.

In DED, cyclosporine A prevents pathological apoptosis of the secretory epithelium by blocking nonspecific pores of the mitochondrial membrane responsible for a transient increase in their permeability to molecules causing increased production of the tear film. It is used as an anti-inflammatory and anti-apoptotic agent. In the anti-inflammatory treatment regimen of severe DES, it is recommended to use cyclosporine A for 6 months along with a 2-month course of glucocorticosteroid therapy and artificial tears. It should be noted that topical cyclosporine A is also used to prevent graft rejection in corneal transplant patients.

According to the TFOS DEWS II report guidelines, the following are recommended as first-line therapy for ocular surface disorders:

- patient education
- modification of environmental factors
- dietary modification
- elimination of harmful general and topical medications (including those containing preservatives)

- tear film replacement with preservative-free moisturizing drops
- eyelid margin hygiene.

Although significant progress has been made in recent years in understanding the pathomechanisms of DED and implementing new treatment options, tear film replacement is the foundation of any DED therapy. Unfortunately, the short time a drop of a given solution remains on the ocular surface after instillation remains a challenge [34, 56–58]. As the frequency of instillation increases, the percentage of patients who fully adhere to the clinician's recommendations (patient compliance) decreases. Hypothetically, an increase in the viscosity of artificial tears should be associated with an increase in the time the products remain on the ocular surface and thus a decrease in the frequency of application [59]. Most studies on ocular surface retention have been performed in an animal model, and their methodology required the use of  $\gamma$ -scintigraphy techniques combined with radioactive particle labeling or positron emission tomography [60, 61]. As mentioned above, the ongoing challenges in the treatment of ophthalmic diseases are the bioavailability of the drug after administration and its penetration into the structures of the eyeball. In the results of these studies, products with a low molecular weight hyaluronic acid molecule had a longer retention time on the ocular surface [62, 63].

According to the definition of DED presented by TFOS DEWS II, inflammatory and immunological processes are an integral part of the pathophysiology of ocular surface disease.

If the basic treatment is not sufficient, the following are added:

- thermotherapy and massage of the meibomian glands
- therapy with terpinen-4-ol preparations [64, 65] (if demodicosis is diagnosed)
- occlusion of the lacrimal puncta [66–69]
- use of ointment or humidifier (initially only at night)
- use of IPL (intense pulse light) laser treatment and red waves – Meibomian gland revitalization with lid margin photobiostimulation in isolated MGD and associated demodicosis [70–74]
- use of antibiotic drops [75]
- use of glucocorticosteroid drops [76]
- use of tear-stimulating drops
- use of drops with immunomodulatory effects (including cyclosporine A or LFA-1 and ICAM-1 antagonists, e.g. lifitegrast) [38, 77–99]
- use of general antibiotic therapy (macrolide or tetracycline antibiotics) [100, 101]
- Meibomian gland probing [102–109]
- LipiFlow system therapy [110–114].

One of the main mechanisms responsible for the development of ocular surface inflammation is the impairment of lacrimal gland function, which leads to a decrease in the secretion of lactoferrin, which has a natural anti-inflammatory function, the release of interleukins IL-1, IL-8 and TNF- $\alpha$ , and metalloproteinases (MMP), among others. An increase in the concentration of MMP leads to the degradation of cells of the basement membrane of the epithelium. In the therapeutic regimens of anti-inflammatory treatment in DES, cyclosporine A is the drug of choice for severe and moderate cases of ocular surface disease with sicca keratoconjunctivitis. Cyclosporin A was isolated from the fungus *Tolypocladium inflatum*. It was thought to have antifungal properties. This drug is a calcineurin inhibitor and has potent immunosuppressive properties in the mechanisms of inhibition of T lymphocytes and inhibition of apoptosis of conjunctival epithelial cells. Historically, immunosuppressive effects have been observed in dogs with idiopathic keratoconjunctivitis sicca. In clinical studies, a significant reduction in the CD4+ cell count was observed in patients. Drops containing 0.05% cyclosporine A solution significantly reduced corneal fluorescein staining by approximately 46-50% and improved

Schirmer's test scores over a 6-month observation period [115]. These parameters, as well as Ocular Surface Disease Index (OSDI) questionnaire scores, also improved over an additional 6 months of follow-up [115, 116]. A decrease in the expression of the HLA-DR receptor on the surface of conjunctival cells was also observed. The above results of the Daull study [115] are consistent with the results of the SICCANOVE study [117], which confirmed the good safety profile of cyclosporine A. The use of the drug does not cause significant systemic adverse effects and is well tolerated by patients [118, 119].

## CONCLUSIONS

DED, the most common ocular surface disease, is a disease of civilization and affects everyone, regardless of gender or age. Therefore, every patient should undergo a thorough evaluation of the ocular surface and tears during a comprehensive ophthalmic examination. Non-invasive tests and questionnaires are particularly valuable. If the patient is diagnosed with symptoms suggestive of ocular surface disease, the diagnosis should be expanded according to the algorithms [120].

## CORRESPONDENCE

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