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Dry eye disease – more than tear deficiency. The role of inflammation, parainflammation, and immunological mechanisms: current insights and their practical implications

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Summary: Dry eye disease is a multifactorial, symptomatic condition resulting from a loss of homeostasis in the tear film and/or the ocular surface. The modern understanding of this disease goes far beyond the outdated model of simple tear deficiency. It encompasses tear film instability, hyperosmolarity, epithelial damage, glycocalyx and mucin disorders, eyelid and meibomian gland dysfunction, inflammation, neurosensory abnormalities, and the influence of environmental, iatrogenic, and systemic factors. Of particular significance is the transition from adaptive parainflammation to a chronic, self-perpetuating inflammatory process that exacerbates ocular surface damage and drives disease chronicity.

This article reviews current data on the epidemiology, pathophysiology, and immunological background of dry eye disease, as well as the role of the complement system as a potentially overlooked link between innate immunity and chronic ocular surface inflammation. The work also addresses neuropathic pain, comorbidities, iatrogenic factors, and the psychological impact of the disease. It highlights that dry eye disease measurably impairs visual quality, daily functioning, and overall quality of life; therefore, managing dry eye disease remains vital even in patients with other severe, concurrent retinal pathologies. Special emphasis is placed on practical diagnostic and therapeutic implications. Diagnosis requires the presence of both subjective symptoms and objective signs of homeostasis loss. Management should not rely solely on lubrication; instead, it must be tailored to the dominant disease mechanism. This includes tear film stabilization, evaporation protection, anti-inflammatory therapy, eyelid management, mucin and glycocalyx support, and interventions targeting the neurosensory component and comorbidities. The article also discusses the potential value of formulations combining hyaluronic acid, trehalose, and N-acetylaspartylglutamate as an example of a multi-level therapy providing hydration, osmoprotection, and anti-inflammatory benefits. Modern management of dry eye disease should therefore rely on early diagnosis, patient phenotyping, and proactive treatment of the underlying mechanisms driving the disease before it progresses to a severe, chronic, and treatment-resistant form.

Key words: dry eye disease (DED), ocular surface disease, inflammation, parainflammation, complement system, immunology, meibomian gland dysfunction (MGD), neuropathic pain, TFOS DEWS III, anti-inflammatory treatment.

Introduction

Dry eye disease (DED) is one of the most common ocular surface disorders, yet it remains a condition that is still frequently oversimplified in clinical practice. For years, it was viewed primarily as the result of insufficient tear volume or excessive evaporation. However, this perspective is inadequate, as it does not account for the complexity of symptoms, the chronic nature of the disease, the frequent mismatch between patient complaints and clinical findings, or the limited effectiveness of lubrication alone.

The modern understanding of DED, shaped by successive Tear Film and Ocular Surface Society Dry Eye Workshop reports, shifts the focus from a simple lack of tears to a loss of homeostasis within the tear film and the entire ocular surface [1–3]. In this framework, attention is directed not only to the aqueous, lipid, and mucin layers of the tear film, but also to the epithelium, glycocalyx, eyelids, meibomian glands, inflammatory mechanisms, innate and adaptive immunity, and neurosensory abnormalities. DED must therefore be regarded as a multi-mechanism condition in which disruption of a single component can trigger a self-perpetuating cycle of tear film instability, hyperosmolarity, ocular surface inflammation and damage.

This paradigm shift has clear clinical implications. DED is not merely an inconvenience or a minor age-related ailment. It can impair visual quality, interfere with reading, computer work, and driving, affect psychological well-being, and reduce satisfaction with ophthalmic care. This also applies to patients treated for other ocular diseases, such as glaucoma, cataracts, or age-related macular degeneration (AMD), where the state of the ocular surface influences treatment tolerance, the accuracy of clinical measurements, surgical outcomes, and the patient's subjective visual experience.

The aim of this article is to present a modern, practical perspective on DED as a disease involving loss of ocular surface homeostasis. Particular emphasis is placed on the role of inflammation, parainflammation, immunological mechanisms, the complement system, and the neurosensory component, and on how these elements translate into diagnostic and therapeutic decisions tailored to the dominant disease mechanism.

Methodology

This article is a **narrative review of the literature** dedicated to the modern understanding of DED, with a particular focus on inflammation, parainflammation, and immunological mechanisms, as well as their practical relevance for ophthalmologists.

Epidemiology

Assessing the epidemiology of DED remains challenging, as the prevalence of the disease varies depending on the definition adopted, the diagnostic tool used, and whether diagnosis relies on subjective symptoms, objective signs, prior clinical diagnosis, or

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administrative data. This methodological heterogeneity explains the wide variation in findings across published studies and complicates direct comparisons between populations.

Nevertheless, available data consistently show that DED is a common disorder whose prevalence increases with age and is higher in women. Population-based studies indicate that prevalence rises from low rates in young adults to approximately 30% in individuals over 80 [4]. A particularly sharp increase is observed in the 40–50 age range, which is linked to factors such as hormonal changes, a higher incidence of autoimmune diseases in women, and involutional changes in the lacrimal glands, eyelids, and ocular surface [5]. At the same time, newer data demonstrate that DED is not uniquely a disease of older adults. Young adults are becoming increasingly significant epidemiologically. In this demographic group, dry eye symptoms are often linked to contact lens wear, prolonged screen time, reduced blink rates, and a higher proportion of incomplete blinks [6].

A critical component of DED epidemiology is meibomian gland dysfunction (MGD), representing one of the primary mechanisms of the evaporative form of the disease. According to TFOS DEWS III, the prevalence of MGD rises markedly after age 40 and can reach very high levels in older adults, particularly in men [3]. Epidemiological reviews indicate that MGD symptoms occur in about 30–35% of Caucasians and 33–50% of East Asian populations, with prevalence exceeding 50% after the age of 65 [6]. Clinically, it is also important to note that up to two-thirds of MGD cases may be asymptomatic, contributing to underestimation of the true burden.

From the standpoint of risk factors, two elements remain the most consistent: age and female sex. DED occurs more frequently in women, and the risk escalates with advancing age [3, 4, 7–9]. Furthermore, environmental and digital factors are playing an increasingly prominent role in the epidemiology of the disease (Tab. I). Low humidity, extreme temperatures, wind, air pollution, and prolonged screen time are currently recognized as significant risk or exacerbating factors for this disease [8]. In the case of screen-based work, a decrease in blink rate and an increase in incomplete blinks are particularly critical, as they promote tear film instability and increase evaporation [10]. Britten-Jones et al. reported that each additional hour of daily screen time is associated with an increase in the odds ratio for DED of approximately 1.14. It is precisely this area that most likely explains the increasing prevalence of dry eye symptoms and visual fatigue also among younger age groups [6].

Category	Key risk factors	Clinical significance / possible mechanism
Non-modifiable factors	Age, female sex, Asian ethnicity, genetic predisposition	DED risk increases with age; it is more common in women; genetic and ethnic background also influences susceptibility
Systemic diseases	Sjögren's disease, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, thyroid diseases, sarcoidosis, inflammatory bowel disease, psoriasis, diabetes mellitus	These diseases can impair tear secretion, exacerbate ocular surface inflammation, and contribute to DED
Hormonal and metabolic disorders	Androgen deficiency, polycystic ovary syndrome, thyroid diseases, menopause, diabetes mellitus	Hormones affect all layers of the tear film; metabolic disorders can impair tear secretion and corneal nerve function
Skin diseases and allergies	Rosacea, atopic dermatitis, eczema, asthma, allergies, allergic conjunctivitis	Chronic inflammation of the eyelids and ocular surface, tear film instability, and frequent coexistence of MGD
Neurological and psychiatric factors	Depression, anxiety, stress, burnout, PTSD, chronic pain syndromes, migraine	They may increase symptom perception, promote neuropathic pain, and are associated with poorer patient functioning
Sleep disorders	Obstructive sleep apnea, insomnia, poor sleep quality	They may coexist with ocular surface inflammation, corneal exposure, and MGD
Ophthalmic conditions	MGD, blepharitis, allergic conjunctivitis, pterygium, pinguecula, conjunctivochalasis	MGD is one of the most significant risk factors for DED, particularly the evaporative subtype
Glaucoma and its treatment	Chronic use of glaucoma eye drops, especially those containing preservatives; history of glaucoma surgery	Both active ingredients and preservatives can damage the ocular surface and destabilize the tear film
Ophthalmic procedures and surgeries	Refractive surgery, cataract surgery, intravitreal injections, eyelid and periocular procedures	Corneal nerve damage, ocular surface trauma, eye drop toxicity, and intraoperative ocular desiccation can induce or exacerbate DED
Systemic medications	Anticholinergic drugs, antihistamines, certain antidepressants, antiarrhythmics, antiparkinsonian drugs, retinoids, oncological treatment, hormone replacement therapy	They can reduce tear secretion, disrupt the mucin and lipid layers, and exert toxic effects on the ocular surface
Topical medications	Preserved eye drops, long-term topical treatment	They can damage the epithelium, destabilize the tear film, and worsen chronic inflammation
Environmental factors	Low humidity, air conditioning, wind, high and low temperatures, air pollution	They promote tear evaporation and tear film instability
Lifestyle	Prolonged screen time, reduced blink rate, contact lens wear, periocular cosmetics	These factors increase tear evaporation, disrupt Meibomian gland function, and exacerbate ocular surface symptoms
Nutritional factors	Deficiencies in vitamins A, C, B12, D, and omega-3 fatty acids	They can adversely affect ocular surface homeostasis, though the significance of some remains subject to further research

Tab. I. Key risk factors for dry eye disease [8].

The epidemiological significance of DED extends far beyond its prevalence. It is a chronic condition that impacts visual comfort, daily functioning, productivity, and psychological well-being [11]. It also carries a substantial economic burden: in the United States, annual direct costs of treating DED are estimated at approximately $3.8 billion, and after accounting for physician visits and lost productivity, the total societal burden approaches $55.4 billion annually [6]. Dry eye disease must therefore be viewed not merely as a common ophthalmic complaint, but as a major and growing public health issue.

Modern understanding of dry eye disease

The understanding of DED has undergone a fundamental shift over the last few decades. For a long time, the disease was viewed primarily as a consequence of insufficient tear volume or excessive evaporation, and treatment focused predominantly on replacing the tear film. While this model remains partially useful, it proved too narrow to explain the complexity of symptoms, the heterogeneity of the clinical presentation, and the limited efficacy of lubrication alone.

Successive *Tear Film and Ocular Surface Society Dry Eye Workshop* reports clearly reflect this evolution in thinking. Of particular importance was the shift in focus from tear quantity to tear film homeostasis, and subsequently (in the latest TFOS DEWS III framework) to homeostasis of the entire ocular surface [1–3]. According to the current definition, DED is a multifactorial symptomatic disease characterized by a loss of homeostasis of the tear film and/or the ocular surface. Key factors contributing to the pathogenesis of DED include tear film instability, hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities. This definition explicitly shifts the perspective on DED from a simple shortage of tears to a disorder affecting the entire functional microenvironment of the ocular surface [12].

The modern model assumes that the tear film does not function independently of the tissues that produce and stabilize it. Its proper function depends on the interplay between the aqueous, lipid, and mucin layers, the corneal and conjunctival epithelia, goblet cells, the glycocalyx, the eyelids, the meibomian glands, and corneal innervation. Disruption of any of these components can destabilize the entire system [13].

The ocular surface epithelium is of particular importance. It is not merely a passive mechanical barrier, but a biologically active tissue responding to hyperosmotic, mechanical, environmental, and inflammatory stress. Epithelial cells contribute to the local immune response by producing inflammatory mediators and supporting the integrity of the ocular surface barrier [14].

In this context, the glycocalyx (a thin, glycoprotein- and mucin-rich layer covering the surface of corneal and conjunctival epithelial cells) plays a crucial role. Acting as the interface between the epithelium and the tear film, it makes the ocular surface hydrophilic, facilitates tear film adherence and even distribution, reduces friction during blinking, and supports the epithelial protective barrier [15]. Disruption of the glycocalyx can lead to tear film instability and DED symptoms even when tear volume appears relatively preserved [16].

Equally critical to the pathogenesis of the disease are the eyelids and meibomian glands. Meibomian gland dysfunction is one of the most common mechanisms leading to evaporative DED. Incomplete blinking, improper eyelid closure (lagophthalmos), blepharitis, keratinization of the gland orifices, and alterations in

Main group of mechanisms	Subtype / dominant feature	Examples of disorders	Clinical significance
Deficiencies in tear film components	aqueous layer deficiency	impaired tear secretion by the lacrimal gland, Sjögren's disease, autoimmune diseases, impaired reflex tearing, side effects of systemic medications	causes insufficient lubrication and clearance of the ocular surface, hyperosmolarity, and epithelial damage
	lipid layer deficiency / dysfunction	meibomian gland dysfunction, blepharitis, altered meibum quality, gland orifice obstruction	increases tear evaporation and leads to tear film instability
	mucin layer and glycocalyx deficiency / dysfunction	loss of goblet cells, secretory and membrane-associated mucin disorders, glycocalyx damage, MUC1 / MUC4 / MUC16 abnormalities	impairs epithelial wettability and uniform tear film distribution; symptoms may occur despite apparently preserved tear volume
Eyelid abnormalities	blinking disorders	infrequent or incomplete blinking, digital screen use, neurological disorders, reduced blink force	promotes tear film instability, increased evaporation, and poorer meibum expression
	eyelid closure and malposition disorders	lagophthalmos, ectropion, entropion, floppy eyelid syndrome, facial nerve palsy, post-eyelid surgery alterations	leads to ocular surface exposure, epithelial desiccation, and chronic damage
	lid margin diseases	blepharitis, Demodex infestation, keratinization of meibomian gland orifices	exacerbates MGD, destabilizes the lipid layer, and perpetuates inflammation
Ocular surface abnormalities	ocular surface cellular damage	corneal and conjunctival epithelial damage, reduced goblet cell count, toxicity from topical medications and preservatives	weakens the epithelial barrier, exacerbates inflammation, and perpetuates the dry eye disease vicious cycle
	primary inflammation and oxidative stress	autoimmune diseases, allergy, chronic irritation, environmental pollution, hyperosmolarity	activates the ocular surface inflammatory response and can lead to chronic disease
	neurosensory disorders	corneal hyperalgesia, neuropathic pain, impaired corneal sensation, symptom–sign disparity	explains patients with severe symptoms despite minimal clinical signs, or conversely, severe ocular surface damage with minimal symptoms
	ocular surface anatomical disorders	conjunctivochalasis, pterygium, pinguecula, conjunctival scarring, ocular surface irregularity	impedes uniform tear film distribution and promotes localized instability

Tab. II. Classification of dry eye disease according to TFOS DEWS III [3].

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the quality of their secretion lead to destabilization of the lipid layer and increase tear evaporation [17].

The classification of the disease has also evolved. The TFOS DEWS III guidelines move away from an overly simplified division into purely aqueous-deficient and evaporative forms, proposing instead an approach based on predominant etiological mechanisms. This model encompasses deficiencies in individual tear film components, eyelid abnormalities, and ocular surface disorders (Tab. II). This approach better reflects clinical reality, where lipid deficiency, mucin and glycocalyx disorders, incomplete blinking, epithelial damage, oxidative stress, inflammation, and a neurosensory component often coexist in a single patient [3, 12].

Pathophysiology

The pathophysiology of DED cannot be reduced to decreased tear volume. It is a dynamic, self-perpetuating disease rather than a simple tear deficiency.

One of the earliest and most critical elements of DED pathophysiology is **tear film instability**. Under normal conditions, tear film forms a dynamic protective layer with optical, trophic, immunologic, and anti-inflammatory functions. When any component is disrupted, the tear break-up time (TBUT) shortens, exposing the ocular surface to repeated episodes of localized dehydration [13].

The consequence of tear film instability is hyperosmolarity, recognized as one of the central noxious stimuli in DED. Increased tear film evaporation or reduced tear volume leads to an elevated concentration of electrolytes and other tear components, which in turn disrupts the osmotic balance on the ocular surface. Water then moves from corneal and conjunctival epithelial cells into the more concentrated external environment, causing cell dehydration, shrinkage, and the activation of cellular stress pathways [18]. If the decrease in cell volume exceeds the cell's adaptive capacity, irreversible apoptotic mechanisms are triggered, leading to cell death and further weakening of the epithelial barrier [19]. Concurrently, hyperosmolarity activates inflammatory response pathways, increasing the production of pro-inflammatory cytokines, chemokines, and metalloproteinases. Hyperosmolarity is therefore not merely a disease marker, but an active mechanism that translates physicochemical disruption into biological damage to the ocular surface.

These processes result in the **impairment of the ocular surface barrier**. Under normal conditions, the corneal and conjunctival epithelia, cellular tight junctions, the mucin layer, and the glycocalyx form an integrated protective barrier. In DED, this barrier becomes compromised, and increased matrix metalloproteinase activity (particularly MMP-9) elevates epithelial permeability, facilitating the further penetration of irritants and inflammatory mediators [20]. **Clinically**, this manifests as ocular surface staining and increased sensitivity to environmental factors.

The most useful model for explaining the chronicity of DED remains the concept of the "**vicious cycle**". Tear film instability leads to hyperosmolarity, which induces cellular stress and the release of inflammatory mediators. The resulting inflammation damages the epithelium and the ocular surface, further degrading tear film quality and exacerbating its instability. In this manner, each element simultaneously becomes both a consequence and a driver of the next, transforming the disease into a self-perpetuating **chronic process**. These interrelationships are illustrated in Figure 1 [21].

The pathophysiology of the disease can vary depending on the phenotype. In more **evaporative** forms, primarily associated with MGD, incomplete blinking, and increased evaporation, the dominant factors are tear film instability, eyelid inflammation, and lipid layer dysfunction [22]. Conversely, in **aqueous-deficient** forms, particularly severe and autoimmune cases, inflammation,

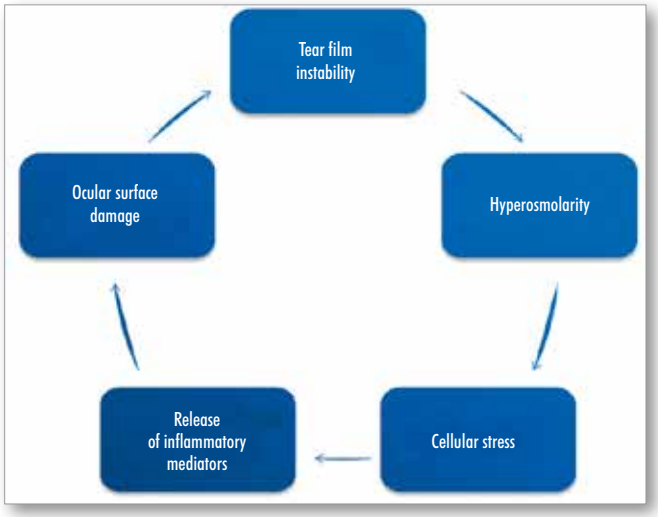

Fig. 1. The vicious cycle in the pathogenesis of dry eye disease [21].

epithelial damage, and deeper lacrimal gland dysfunction predominate [12]. From a clinical standpoint, this distinction is crucial. It prevents a simplistic approach where every patient with DED is thought to require the exact same therapy. For a patient with prominent MGD and a short TBUT, treatment focuses primarily on tear film evaporation, blepharitis, and lipid layer restoration. In contrast, for patients with a more severe aqueous layer deficiency, especially one with an autoimmune etiology, it is essential to consider more aggressive anti-inflammatory treatment and ocular surface regeneration.

Inflammation and parainflammation

The current understanding of DED requires a shift away from viewing inflammation as a late-stage phenomenon present only in severe or autoimmune forms of the disease. Both inflammation and parainflammation play key roles across the entire DED spectrum: from seemingly mild, primarily evaporative forms to severe, aqueous-deficient, and autoimmune phenotypes. What varies is the severity, the dominant mechanisms, and the involvement of specific immune pathways, rather than the presence of an inflammatory response itself.

Parainflammation can be understood as an adaptive, low-grade, and initially controlled immune response to chronic or repeated noxious stimuli, aimed at restoring tissue homeostasis. It is not yet full-blown inflammation, nor is it a state of physiological equilibrium. Instead, it represents an intermediate state triggered when the ocular surface experiences environmental, osmotic, oxidative, or mechanical stress. In its well-controlled form, parainflammation **is protective** [23]. It involves, among others, epithelial cells, tissue macrophages, cytokines, **and components of the complement system**. Their purpose is not to elicit a full-scale inflammatory reaction, but to promote regeneration, clear damaged structures, and restore balance to the ocular surface. In this sense, parainflammation can be viewed as a "work-in-progress repair" attempt – a reaction meant to halt disease progression before permanent tissue damage occurs. On the ocular surface, this response fulfills an essential biological function. The eye is constantly exposed to numerous damaging factors, including air, wind, fluctuating temperatures, low humidity, pollutants, and tear film evaporation. Under these conditions, a complete absence of an adaptive response would be impossible. Parainflammation thus helps maintain epithelial function, supports ocular surface cell repair, and limits the impact of minor but repetitive damage. The problem arises when the damaging stimulus is too severe or prolonged, or when regulatory mechanisms become overwhelmed. At that point, the adaptive response loses its protec-

tive nature and transitions into a "standard" chronic inflammatory process, perpetuating the damage. The ocular surface no longer returns to equilibrium but enters a state of sustained dysregulation, in which the mechanism originally meant to protect the tissue becomes the mechanism that drives its injury. Rolando et al. emphasize that in the presence of low-intensity damaging stimuli, parainflammation enables ocular surface cells to maintain viability. At this stage, the disorders remain adaptive and potentially reversible [24]. Clinically, this means that even at an early stage, treatment should not only alleviate symptoms but also inhibit the escalation of the inflammatory response before the protective mechanism transitions into a chronic disease process.

A key stage in the pathogenesis is the translation of local ocular surface stress into an immune response. Tear film instability and hyperosmolarity damage the corneal and conjunctival epithelium, triggering the release of inflammatory mediators [25]. This is followed by the activation and maturation of antigen-presenting cells (APCs), which migrate to regional lymph nodes and initiate a T-cell-mediated response. Activated T-helper type 1 (Th1) and type 17 (Th17) cells then return to the ocular surface, where they secrete proinflammatory cytokines, including interferon-gamma and interleukin-17. In this way, an initial tear film disturbance can evolve into a chronic immune-mediated process [25, 26].

Understanding this transition is fundamental to explaining the chronicity of DED. Inflammation becomes both a consequence and a cause of the disease: primary tear film instability triggers an inflammatory response, and sustained inflammation causes secondary epithelial damage, exacerbates goblet cell loss, impairs mucin quality, increases hyperosmolarity, and further destabilizes the tear film [27]. This initiates the immunological vicious cycle that drives the disease. It is particularly important to identify the stage before the localized inflammatory response becomes permanent through full activation of the APC–lymph node–effector lymphocyte axis [14]. **Consequently, anti-inflammatory treatment is essential even in the early stages of the disease.**

It is vital to emphasize that inflammation and parainflammation are not phenomena reserved exclusively for severe forms of DED. In fact, the question is not whether inflammation is involved in the pathogenesis, but rather what its intensity, timing, and dominant components are.

In this context, anti-inflammatory treatment for DED is **not merely a therapy reserved for "severe cases"**, but a strategic intervention aimed at disrupting the mechanisms driving the progression from an adaptive ocular surface response to a chronic disease [27].

Immunological background of DED

During DED, localized ocular surface stress triggers a complex immune response involving both innate and adaptive immunity. Innate immunity is involved in the initial stages of the disorder. The process typically begins with activation of epithelial cells and pattern-recognition receptors, followed by complement activation and the release of cytokines, chemokines, and metalloproteinases [20]. One of the most important stages in the immunopathogenesis of DED is the transition from innate to adaptive immune response. Antigen-presenting cells play a key role here, initiating a lymphocyte response primarily involving Th1 and Th17 cells. As inflammatory stimuli persist, immunological memory cells develop, capable of rapid reactivation during subsequent ocular surface stress. This mechanism can perpetuate the disease and account for its recurrent and self-sustaining nature (14). From a practical standpoint, this implies that a recurrent course of DED is not always caused simply by the eye "drying out" again. In a subset of patients, it reflects a well-established reprogramming of the immune response. This helps explain why the disease can recur even in response to a seemingly minor trigger.

Complement as an underappreciated component of DED pathogenesis

The complement system is one of the most fundamental yet underappreciated elements of innate immunity. Classically, it is described as a cascade of plasma proteins involved in opsonization of microorganisms, amplification of inflammation, and direct destruction of certain pathogens through formation of the membrane attack complex. This description is accurate, but incomplete. Complement is not merely an "adjunct" to antibodies or a defense system activated solely during infection. It is a continuously active immune surveillance system, whose low-level activity – when properly regulated – contributes to tissue homeostasis.

Complement components and regulatory proteins have been identified in tissues including the cornea, aqueous humor, and tear film. Under normal conditions, complement participates in immune surveillance, pathogen defense, and maintaining the balance between protection and tolerance. Precise regulation of its activity is particularly critical here, as the eye must maintain its immune defense capacity while protecting delicate, transparent structures from sterile inflammatory damage [28].

The problem is therefore not the mere presence of complement, but its **dysregulation** – the loss of control over activation, amplification, and termination of the response. In a healthy eye, host tissues are protected by numerous complement regulators, including membrane-bound proteins such as CD46, CD55, and CD59, as well as soluble factors like Factor H and Factor I [29]. If the balance between activation and inhibition is disrupted, complement can shift from a protective system to a mechanism that exacerbates inflammation and tissue damage. This model is already well-documented in other eye diseases, most notably AMD, but also in glaucoma, diabetic retinopathy, uveitis, corneal diseases, and allergic ocular surface diseases.

In the context of DED, complement activation products present in the tear film, particularly C3a and C5a, are especially relevant. These anaphylatoxins increase vascular permeability, recruit and activate inflammatory cells, and reinforce the local cytokine environment. Maehara *et al*. found that C3a and C5a concentrations were higher in the tears of patients with MGD and in those with concurrent DED and MGD compared with control subjects. The authors interpreted these findings as evidence of localized innate immune deregulation associated with the development of MGD and DED in older adults. This observation is significant because it indicates that DED does not merely involve a nonspecific rise in inflammatory mediators, but rather targeted activation of a specific innate immune pathway [28].

The significance of the complement system may lie primarily in its ability to amplify chronic ocular surface inflammation. The anaphylatoxins C3a and C5a can enhance the recruitment of neutrophils, monocytes, and other effector cells, increase tissue permeability, and sustain the vicious cycle of inflammation.

The complement system does not have to be the primary driver of DED in every patient. It is more likely that, in some individuals, it acts as an amplification mechanism – intensifying the inflammatory response, linking innate and humoral immunity, promoting goblet cell loss, and contributing to disruption of the ocular surface barrier. In this sense, it may be one of the missing links explaining why an apparently local disturbance of the tear film progresses, in some patients, into a chronic, self-sustaining inflammatory disease.

Neuropathic pain and neurosensory abnormalities

Dry eye disease also encompasses neurosensory abnormalities. This has important clinical implications, as it explains situations in which patients report severe burning, stinging, pain, or photopho-

bia despite relatively mild findings on examination. In the early stages of DED, symptoms are typically nociceptive, arising from actual tissue irritation caused by tear film instability, hyperosmolarity, friction during blinking, epithelial damage, and inflammation. However, when these stimuli persist chronically, sensitization may develop, leading to hyperexcitability of the sensory nervous system. Inflammatory mediators play a key role in this process: they sensitize corneal and conjunctival nerve endings, lowering the pain threshold. As a result, previously neutral stimuli – such as wind, light, air conditioning, blinking, or the instillation of eye drops – can be perceived as painful. This phenomenon is known as allodynia [30].

If this process is not interrupted, peripheral sensitization can become entrenched and progress to central sensitization, in which abnormal stimulus processing occurs within the central nervous system. At this stage, symptoms become less dependent on the current state of the ocular surface, and improvements in the tear film or staining scores do not always lead to symptom relief. Therefore, early anti-inflammatory treatment is crucial not only for protecting the epithelium and breaking the dry eye disease vicious cycle, but also for reducing the risk of a persistent, long-term pain component [31].

Symptoms and diagnostics – a practical approach

According to TFOS DEWS III, dry eye disease is a symptomatic condition, and its diagnosis requires the coexistence of subjective symptoms and objective signs of a loss of homeostasis of the tear film and ocular surface. It is important to recognize that DED symptoms extend beyond burning, dryness, stinging, grittiness, photophobia, or eye strain. **Visual disturbances** are also a significant component of the clinical presentation. An unstable tear film degrades the quality of the air–tear interface, increases light scattering, and causes image fluctuations between blinks. As a result, patients may report blurred vision, reduced acuity after several minutes of visual tasks, glare, difficulty reading, fluctuating vision quality when using a computer, or temporary improvement in image clarity immediately after blinking. This aspect is particularly important because DED can impair functional visual quality even when standard visual acuity testing remains normal [12].

OSDI-6 question	Constantly	Mostly	Often	Sometimes	Never
Have you experienced any of the following during a typical day within the last month?					
1. Eyes that are sensitive to light?	4	3	2	1	0
2. Vision blurring between blinks (with your refractive correction if needed)?	4	3	2	1	0
Have problems with your eyes limited you in performing any of the following during a typical day within the last month?					
3. Driving or being driven at night?	4	3	2	1	0
4. Watching TV, or a similar task?	4	3	2	1	0
Have your eyes felt uncomfortable in any of the following situations during a typical day within the last month?					
5. Windy conditions?	4	3	2	1	0
6. Places or areas with low humidity?	4	3	2	1	0

Scoring method: sum the points from all 6 questions.
Interpretation:
- 0–3 points – normal result
- 4–8 points – mild to moderate symptom severity
- >8 points – severe symptom severity

Screening threshold for DED: ≥4 points

Tab. III. Questionnaire of the abbreviated Ocular Surface Disease Index (OSDI-6) [32].

Test / assessment element	What it evaluates	Practical relevance
NIBUT (non-invasive tear break-up time)	tear film stability	preferred test for stability; a result of <10 s indicates a loss of homeostasis
FBUT (fluorescein tear break-up time)	tear film stability after dye administration	useful when NIBUT is unavailable; a result of <5 s is abnormal
Corneal fluorescein staining	corneal epithelial damage	demonstrates a breach in the ocular surface barrier
Conjunctival lissamine green staining	conjunctival and mucin layer damage	particularly useful in evaluating chronic ocular surface disease
Lid margin /lid wiper staining	friction from blinking and early surface damage	can be sensitive in milder and earlier forms of DED
Tear osmolarity	impairment of tear film composition	abnormal if ≥ 308 mOsm/L in either eye, or if the interocular difference is >8 mOsm/l
Eyelid and meibomian gland assessment	MGD, blepharitis, and meibum quality	critical for diagnosing the evaporative phenotype
Blink and lid closure assessment	blink completeness, exposure, and lagophthalmos	particularly important in patients with digital DED and those with morning or evening symptoms

Tab. IV. Most important diagnostic tests in the evaluation of dry eye disease [12].

The practical diagnostic algorithm can be streamlined into four steps:
1. confirming symptoms,
2. excluding conditions that mimic DED,
3. demonstrating at least one objective homeostatic disturbance,
4. determining the dominant disease mechanism.

For rapid symptom assessment, TFOS DEWS III recommends the OSDI-6, which is an abbreviated version of the OSDI (Ocular Surface Disease Index) questionnaire. It is easy to implement in an office setting, and its interpretation is presented in Table III [32]. Confirming a diagnosis of DED then requires demonstrating at least one marker of homeostatic loss, such as a shortened TBUT, elevated osmolarity, or abnormal ocular surface staining. The primary diagnostic tests are summarized in Table IV [12, 33–35].

After confirming the diagnosis, it is essential to shift the focus from asking "Does this patient have DED?" to asking "What is driving the disease in this patient?". TFOS DEWS III emphasizes the need to identify the dominant mechanism – deficiency of specific tear film components, eyelid or blinking abnormalities, MGD, ocular surface damage, inflammation, oxidative stress, or a neurosensory component. Only this approach allows for truly causal treatment rather than relying solely on nonspecific lubrication.

Dry eye disease as a shared challenge in ophthalmic care

DED is not a problem exclusive to specialized "ocular surface clinics". Like many other ophthalmic conditions – such as cataract, glaucoma, AMD, or retinal diseases – DED is more prevalent in older adults and therefore frequently coexists with these disorders in the same patients [36]. Furthermore, dry eye disease can be induced, exacerbated, or unmasked by interventions performed across nearly every ophthalmic subspecialty. Patients treated for glaucoma often use topical medications for years. These drops are frequently preserved and can damage the epithelium, destabilize the tear film, exacerbate inflammation, and worsen treatment tolerance [37]. Similarly, patients undergoing eligibility assessment for cataract surgery require a stable ocular surface, as undetected DED can compromise biometric measurements, degrade postoperative quality of vision, and increase patient dissatisfaction despite a technically flawless surgical procedure [38, 39]. In patients treated for retinal diseases, particularly those requiring repeated intravitreal injections, the ocular surface is repeatedly exposed to disinfectants, topical eye drops, and lid speculums, which can worsen dryness symptoms and reduce treatment comfort. This is particularly evident in individuals with advanced AMD. In this group, it is easy to assume that all visual complaints stem from macular pathology and that ocular surface management is of secondary importance. However, studies show that while improving the condition of the ocular surface does not alter optical coherence tomography (OCT) findings or cure macular disease, it can significantly enhance patient comfort, image stability, quality of life, and daily functioning [40]. In other words, even when the "quantity" of vision measured using an eye chart cannot be improved, its "quality" – namely the functional usefulness of vision in everyday activities – may still be enhanced. Therefore, coexisting DED should not be overlooked, even in patients with advanced retinal pathology. The primary clinical scenarios in which DED impacts diagnostics, treatment, and patient satisfaction across various ophthalmic subspecialties are summarized in Table V.

Consequently, every ophthalmologist (whether specializing in glaucoma, cataracts, retina, refractive surgery, or inflammatory diseases) should actively consider DED as a critical factor influencing treatment outcomes, patient compliance, satisfaction, and quality of vision. In practice, this requires a brief but systematic history regarding ocular surface symptoms, current eye drop use, exposure to preservatives, contact lens wear, past procedures, and systemic medications. Identifying an iatrogenic component has direct therapeutic value: sometimes, improvement is achieved not by prescribing yet another lubricant, but by limiting preservative exposure, reducing the overall drop burden, altering the glaucoma management strategy, optimizing the ocular surface prior to cataract surgery, or proactively managing DED in patients undergoing chronic ophthalmic procedures.

Dry eye disease – a condition that severely impairs quality of life

DED remains an underappreciated ophthalmic conditions. For patients, it is not merely a "sensation of dryness", but a chronic disease that affects comfort, visual quality, daily functioning, occupational performance, and psychological well-being. The most direct and most burdensome aspect of the disease is the deterioration of everyday visual functioning. Patients with DED report difficulties with reading, computer work, watching television, driving, recognizing faces, reading price labels in stores, and performing tasks that require sustained visual attention [41]. Importantly, reduced visual quality may occur despite normal visual acuity on standard testing, because an unstable tear film disrupts the optical surface of the eye and degrades image quality between blinks [42].

The impact of DED on daily functioning is measurable. Karakus et al. reported that patients with clinically significant DED read more slowly during prolonged silent reading than individuals

Field of ophthalmology	Why DED matters	Practical consequence
Glaucoma	chronic drops, preservatives, and polypharmacy can damage the ocular surface and worsen treatment tolerance	prioritizing preservative-free formulations, reducing drop burden, considering laser therapy or surgical options, and managing DED as an integral part of glaucoma management
Cataract	an unstable tear film can alter biometry, keratometry, and post-operative quality of vision	ocular surface evaluation and treatment prior to eligibility assessment and following the procedure
Retina / AMD	repeated intravitreal injections, povidone-iodine, lid speculum use, and topical drops can exacerbate ocular surface discomfort	prophylaxis and management of DED in patients requiring chronic procedures
Refractive surgery	procedures may damage corneal innervation and induce DED or exacerbate its symptoms	careful eligibility screening, identification of patients with neurosensory risk factors
Ophthalmic allergology	symptoms of allergy and DED frequently overlap: burning, tearing, itching, and discomfort	differential diagnosis between allergy, DED, MGD, and treatment toxicity
Contact lenses	lenses can increase tear film evaporation, friction, and instability	evaluation of MGD, wear time, lens material, and care system

Tab. V. Why should dry eye disease concern every ophthalmic subspecialty? [36–38].

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without DED. Moreover, each one-point increase in corneal staining severity was associated with an additional decrease in reading speed of approximately 10 words per minute [43].

The disease also carries a substantial psychological burden. Chronic discomfort, pain, photophobia, visual fatigue, and unpredictable fluctuations in visual quality act as a persistent somatic stressor. Patients with DED more frequently exhibit low mood, anxiety, sleep disturbances, frustration, and reduced social functioning. This relationship is bidirectional: DED may worsen psychological well-being, whereas stress, depression, anxiety, and sleep disorders may amplify symptom perception and hinder treatment [44]. In quality-of-life studies, the burden imposed by DED is comparable to that observed in serious systemic conditions, such as severe angina pectoris [45]. Therefore, DED should never be dismissed as a minor ocular surface complaint, but rather addressed as a chronic disease that alters a patient's quality of life, visual performance, and mental health.

Treatment of dry eye disease – from lubrication to mechanism-targeted therapy

The treatment of DED should be practical but not schematic. There is no single 'one-size-fits-all' eye drop for dry eye, because DED is a heterogeneous condition and multiple mechanisms often coexist in the same individual. Therefore, the first step in management should be identifying the dominant disease phenotype [27]. Tear substitution remains important, but it is often insufficient if exacerbating factors are not addressed simultaneously, such as excessive evaporation, incomplete blinking, blepharitis, preservatives, topical treatment toxicity, or chronic environmental stress.

For every patient, therapy should begin with education and simple measures to reduce the burden on the ocular surface: explaining the chronic nature of the disease, optimizing visual ergonomics, encouraging conscious blinking, protecting against air conditioning, wind, and low humidity, limiting preservative exposure, and reviewing both topical and systemic medications. Lubricants should be selected according to the disease phenotype: aqueous and polymer-based formulations for aqueous-deficient disease; lipid-containing drops and evaporation stabilizers for evaporative disease; and osmoprotective formulations (such as those containing trehalose) for epithelial compromise and hyperosmolar stress [46–48]. Only preservative-free preparations should be used in DED management [49].

The most important element of modern therapy, however, is recognizing that inflammation in DED is both a cause and a consequence of the disease. For this reason, anti-inflammatory treatment should be initiated early even in patients with mild DED, alongside lubrication [27]. This includes indirect measures (tear film stabilization, eyelid disease management, reducing hyperosmolarity, eliminating toxic topical factors) as well as direct anti-inflammatory therapy: short courses of topical glucocorticosteroids, cyclosporine A, lifitegrast, and, in more severe cases, autologous serum, platelet-rich plasma, scleral lenses, or amniotic membrane. The goal is not merely the relief of discomfort, but interruption of the vicious cycle of disease before inflammatory and neurosensory processes become permanently established [27, 50, 51]. A practical overview of key therapeutic directions according to the dominant disease phenotype is presented in Table VI.

Against this background, a formulation combining lubricating, osmoprotective, and anti-inflammatory properties offers a compelling option for early intervention. One example is a preparation containing hyaluronic acid, trehalose, and N-acetyl-aspartyl-glutamic acid (NAAGA). Hyaluronic acid improves tear film retention and wetting properties, trehalose provides osmoprotection and supports ocular surface cells under stress conditions, while NAAGA is a molecule with anti-inflammatory potential attributed to, among others, mast cell stabilization, limitation of histamine release, influence on inflammatory mediators, and inhibition of complement activation [52]. From the perspective of DED pathophysiology, this combination is highly compelling. Rather than offering simple lubrication, it targets several early links in the vicious cycle to halt progression at the adaptation stage, before protective parainflammation transitions into a chronic, harmful inflammatory process.

Clinical data on the hyaluronic acid + trehalose + NAAGA formulation come from a multicenter, open-label study without a control group involving 62 patients with moderate to severe DED treated for 42 days. Rapid symptom improvement was observed after 14 days, with continued improvement throughout follow-up. VAS and OSDI scores decreased, and conjunctival hy-

Phenotype / dominant mechanism	Key treatment elements
Aqueous-deficient dry eye	preservative-free lubricating and regenerative formulations; anti-inflammatory medications; consideration of punctal occlusion once active inflammation is controlled; secretagogues (including diquafosol); blood-derived products / autologous formulations for severe cases
Evaporative dry eye / meibomian gland dysfunction	lid hygiene, warm compresses, meibomian gland expression, lid margin treatment, lipid-based drops, evaporation stabilizers, anti-inflammatory medications, perfluorohexyloctane, Demodex eradication, light therapies or other in-office procedures; consideration of tetracyclines or azithromycin if ocular rosacea or clear MGD is diagnosed
Mucin and glycocalyx disturbances	formulations supporting ocular surface wettability and integrity; trehalose, osmoprotection, hyaluronic acid; mucin secretagogues (especially diquafosol); rebamipide; management of concurrent ocular surface inflammation coexisting with glycocalyx damage
Inflammation-dominant	early control of inflammation: formulations that support homeostasis and limit ocular surface stress; consideration of NAAGA (n-acetyl-aspartyl-glutamic acid) formulations in earlier stages; short courses of topical glucocorticosteroids; cyclosporine A; lifitegrast; elimination of toxic topical factors; biologic tear substitutes for more severe cases
Neurosensory dry eye	simultaneous management of the ocular surface and inflammation alongside the diagnostic evaluation of the pain component; patient education; realistic discussion of expectations; interdisciplinary collaboration and neuromodulatory treatment in selected cases, as topical drops alone may be insufficient
Severe and refractory dry eye	autologous serum, platelet-rich plasma (PRP), scleral lenses, amniotic membrane, consideration of surgical or protective interventions; intensive inflammation control, ocular surface reconstruction, management of eyelids and evaporation, and multidisciplinary care as needed

Tab. VI. Key therapies in different dry eye disease phenotypes [27].

peremia, TBUT, and ocular surface staining improved. Most patients reported noticeable relief [52]. Based on available evidence and pathophysiological rationale, the hyaluronic acid + trehalose + NAAGA combination appears to have a particularly favorable profile as an **early treatment** option, used **from the very onset** of disease in patients with mild to moderate DED, when more aggressive anti-inflammatory therapy (topical glucocorticosteroids or calcineurin inhibitors) is not yet required.

Conclusions

Dry eye disease is a **multifactorial** condition rather than a simple consequence of tear deficiency. At the core of its development lies a loss of homeostasis in the tear film and ocular surface. This involves a complex interplay of aqueous, lipid, and mucin layer disorders, eyelid and meibomian gland dysfunction, epithelial barrier damage, neurosensory abnormalities, and mechanisms activating innate and adaptive immunity. This model requires moving beyond the simplified notion of "ocular dryness" toward identifying the specific phenotype and dominant disease mechanism.

A key mechanism underlying the chronicity of DED appears to be the transition from **adaptive parainflammation** to a persistent, self-perpetuating inflammatory cycle. It is precisely at this point that the ocular surface loses its ability to return to equilibrium, and the disease becomes self-sustaining, characterized by progressive epithelial damage, goblet cell loss, tear film destabilization, and a further decline in homeostasis. In practical terms, this means that anti-inflammatory treatment must not be delayed, as failure to resolve inflammation promotes disease persistence, progression to more severe forms, and reduced treatment responsiveness.

Within this framework, the complement system gains particular relevance. It may represent an **underappreciated component of the inflammatory cascade**, linking innate immunity with chronic ocular surface inflammation. An increasing body of evidence suggests that the complement system is not merely a passive immunological background, but can actively participate in amplifying damage and perpetuating inflammation. This makes it an intriguing and potentially highly valuable therapeutic target for the future.

Dry eye disease is not a trivial matter. It is an ocular surface disorder that **substantially impairs visual quality, daily functioning, and quality of life**, even when conventional visual acuity appears normal. For this reason, the diagnosis of DED must be proactive and deliberate. It is not enough to conclude that a patient "has dry eyes". The clinician must determine whether the condition is driven predominantly by aqueous deficiency, evaporative excess, meibomian gland dysfunction, mucin and glycocalyx disorders, or an inflammatory, neurosensory, or iatrogenic component. Only such an approach enables treatment that is truly targeted rather than merely symptomatic.

Modern DED therapy should act on **multiple levels**: stabilizing the tear film, reducing damaging stimuli, improving the ocular protective structures, treating the eyelids, and, above all, controlling inflammation. Lubrication remains important, but it is often insufficient unless accompanied by interventions addressing the mechanisms that sustain the disease. There is no reason to hesitate when treating inflammation. On the contrary, its timely control may be crucial for preventing disease consolidation, progression to more treatment-resistant stages, and possibly the development of a neuropathic component.

Within this framework, combining **hyaluronic acid, trehalose, and NAAGA** is an especially promising approach. It fits perfectly into a multidirectional treatment strategy by bringing together hydration, cellular protection, and osmoprotection alongside potential anti-inflammatory and anti-complementary properties. Such an approach is especially attractive in the earlier stages of the disease, when the goal should be not only symptom relief but also halting progression at the adaptive stage, before the condition transitions into established chronic inflammation requiring more advanced anti-inflammatory therapy.

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