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+15878858911
editorial-office@sciformat.ca

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CURRENT CONCEPTS IN THE DIAGNOSIS AND MANAGEMENT OF DRY EYE DISEASE - A NARRATIVE REVIEW

Aleksandra Anna Kuls (Corresponding Author, Email: aleksandra.kuls@gmail.com)

Polish Red Cross Maritime Hospital, Gdynia, Pomerania, Poland

ORCID ID: 0009-0003-3808-7631

Martyna Kadłubańska

Polish Red Cross Maritime Hospital, Gdynia, Poland

ORCID ID: 0009-0003-7074-657X

Sonia Zembrzuska

Polish Red Cross Maritime Hospital, Gdynia, Pomerania, Poland

ORCID ID: 0009-0007-3594-6591

Anna Maria Kowalska

Szpital Tczewskie SA, Tczew, Poland

ORCID ID: 0009-0002-0716-9901

Justyna Maria Wiktorowicz

COPERNICUS, Saint Adalbert Hospital in Gdańsk, Poland

ORCID ID: 0009-0001-9633-6873

Bogusław Pabis

University Clinical Centre, Gdansk, Pomerania, Poland

ORCID ID: 0009-0009-8833-1579

Nicole Bulińska

University Clinical Centre, Gdansk, Pomerania, Poland

ORCID ID: 0009-0001-6449-6450

Zofia Sinczak

Szpital św. Wincentego a Paulo in Gdynia, Poland

ORCID ID: 0009-0008-3516-4044

Aleksandra Zofia Sobol

Szpital św. Wincentego a Paulo in Gdynia, Poland

ORCID ID: 0009-0005-9614-3472

Stanisław Bajerski

Gdański Uniwersytet Medyczny, Marii Skłodowskiej-Curie 3a, 80-210 Gdańsk, Poland

ORCID ID: 0009-0004-3815-8396

ABSTRACT

Dry eye disease (DED) is a chronic, multifactorial disorder of the ocular surface, the prevalence of which is steadily increasing with population aging and changes in lifestyle. The aim of this study was to review current knowledge on the epidemiology, pathophysiology, risk factors, symptoms, diagnosis, and treatment of DED, with particular emphasis on emerging therapeutic approaches.

This is a review paper based on an analysis of available scientific literature from databases such as PubMed and Google Scholar. Original studies, systematic reviews, meta-analyses, and expert reports were included, including the TFOS DEWS II guidelines.

The collected data indicate that DED affects between 5% and 50% of the population and occurs more frequently in women and older individuals. The pathogenesis of the disease involves disruption of ocular surface homeostasis, tear film instability and hyperosmolarity, and chronic inflammation, coexisting with neurosensory abnormalities. Environmental and behavioral factors play a significant role, particularly prolonged use of digital devices. Diagnosis remains challenging due to the weak correlation between symptoms and clinical findings. Management is multifaceted and includes symptomatic and anti-inflammatory therapy as well as lifestyle modifications; however, it often does not eliminate the underlying causes of the disease.

The conclusions indicate that DED constitutes a significant clinical problem, and the development of targeted therapies and modern drug delivery systems may contribute to improved treatment efficacy in the future.

KEYWORDS

Dry Eye Disease; Tear Film; Pathophysiology; Risk Factors; Diagnosis; Treatment

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1. Introduction

Dry eye disease (DED) is one of the most common ocular surface disorders and constitutes a significant clinical and public health problem worldwide (46, 50). This condition is multifactorial in nature and involves abnormalities of the tear film and ocular surface, leading to symptoms of discomfort, visual disturbances, and tear film instability (12, 37). Contemporary definitions also emphasize the role of loss of ocular surface homeostasis, hyperosmolarity, and chronic inflammation as key elements in the pathogenesis of the disease (11, 37).

The prevalence of dry eye disease is steadily increasing, which is associated both with population aging and changes in lifestyle, particularly increased exposure to digital devices and adverse environmental factors (46, 61). Despite a large number of epidemiological studies, available data show considerable variability, partly due to differences in diagnostic criteria and study methodologies (40). An additional challenge is the frequently observed discrepancy between the severity of symptoms reported by patients and clinical findings, which complicates both diagnosis and the assessment of treatment efficacy (13).

The complex pathophysiology of DED, involving the interplay of inflammatory, immunological, and neurosensory factors, makes this disease a significant therapeutic challenge (11, 52). Despite the availability of numerous treatment options, many of them are primarily symptomatic, and their effectiveness is often limited. In recent years, there has been growing interest in therapies targeting underlying pathogenic mechanisms as well as in advanced drug delivery systems (34, 40).

The aim of this paper is to review current knowledge on the epidemiology, pathophysiology, risk factors, symptoms, diagnosis, and therapeutic options for dry eye disease, with particular emphasis on emerging treatment strategies.

2. Methodology

This study is a narrative review based on an analysis of the available scientific literature on dry eye disease (DED). Its aim was to compile current data on the epidemiology, pathophysiology, risk factors, clinical presentation, diagnosis, and management of DED, with particular emphasis on emerging therapeutic approaches (11, 37, 50).

The literature search was conducted using electronic databases, including PubMed and Google Scholar, as well as authoritative online sources such as Medscape, AAO EyeWiki, and official guidelines from professional societies (2, 8, 14, 48). Publications included were primarily from 2003 to 2025, though earlier seminal studies were also considered to provide historical context and foundational understanding (6, 7, 37, 41).

The search strategy employed a combination of keywords, including: “dry eye disease,” “keratoconjunctivitis sicca,” “tear film,” “meibomian gland dysfunction,” “dry eye epidemiology,” and “dry eye treatment” (3, 9, 50).

The analysis incorporated original research articles, systematic reviews, meta-analyses, and narrative reviews, published primarily in English (24, 50, 57). Reports from international expert groups were also included, notably the International Dry Eye WorkShop (DEWS, 2007) (37), TFOS DEWS II (2017) (11), and the Asia Dry Eye Society consensus report (2017) (61), which provide the basis for contemporary definitions and classifications of DED.

Inclusion criteria consisted of publications addressing the pathophysiology, epidemiology, risk factors, diagnosis, or management of DED. Studies were excluded if they were not directly related to DED, of limited methodological quality, or inaccessible in full text. Both clinical studies and experimental research were reviewed to provide a comprehensive overview of the mechanisms and clinical aspects of dry eye disease (3, 30, 49).

The literature was synthesized in a descriptive, narrative manner, consistent with the nature of this review. Emphasis was placed on risk factors, underlying pathophysiology, and novel therapeutic directions, reflecting both established knowledge and current trends in DED research.

3. Epidemiology of Dry Eye Disease

Dry eye disease is a multifactorial disorder of the ocular surface and tear film, leading to tear film instability and the occurrence of ocular discomfort. Various terms are used in the literature to describe this condition, including keratoconjunctivitis sicca, sicca syndrome, keratitis sicca, xerophthalmia, dysfunctional tear syndrome, or ocular surface disease. A particular form of the disease is Sjögren’s syndrome, characterized by reduced tear production due to lacrimal gland dysfunction (50).

According to the International Dry Eye Workshop (2007), dry eye disease is a multifactorial disorder involving abnormalities of the tear film and ocular surface, resulting in discomfort, visual disturbances, and tear film instability, accompanied by hyperosmolarity and inflammation (37). The TFOS DEWS II report (2017) additionally emphasized the role of loss of ocular surface homeostasis and the importance of factors such as tear film instability, hyperosmolarity, inflammation, and neurosensory abnormalities, which together create a vicious cycle of disease (11). An alternative definition was proposed by the Asian Dry Eye Society, highlighting tear film instability as the main factor responsible for symptoms and visual disturbances (61).

A healthy tear film, composed of water, lipids, mucins, electrolytes, and proteins, plays a key role in maintaining ocular surface integrity by providing hydration, protection from external factors, and optimal optical conditions (40). Disruptions in its composition or stability, caused by intrinsic and environmental factors, contribute to the development of dry eye disease. The condition is among the most common reasons for patients to consult an ophthalmologist. While it may be asymptomatic in some individuals, many patients report discomfort such as a foreign body sensation, dryness, burning, irritation, photophobia, pain, and decreased visual acuity (12, 46).

Two main types of dry eye disease are distinguished: aqueous-deficient and evaporative. The aqueous-deficient type is associated with reduced tear production by the lacrimal gland, whereas the evaporative type primarily results from Meibomian gland dysfunction. The evaporative form has been shown to be strongly associated with aging (13). Age is one of the most important risk factors for disease development; therefore, the prevalence of DED is expected to increase with the aging population (52).

Contemporary research indicates that dry eye disease has an inflammatory component and shares features with autoimmune disorders. Factors contributing to ocular surface stress, such as infections, environmental stressors, endogenous stress, genetic predisposition, and antigen presence, play a significant

role in pathogenesis (33, 34). The disease is usually chronic and occurs more frequently in older adults; however, appropriately tailored treatment can reduce symptom severity and the risk of ocular surface damage (40).

The prevalence of dry eye disease in the general population varies, ranging from 5% to 50% according to different studies, while in individuals over 40 years of age, it may reach up to 75%. The condition is more common in women. Among younger adults (18-45 years), prevalence is much lower, approximately 2.7% (24).

An epidemiological analysis conducted by the Epidemiology Subcommittee within the Dry Eye Workshop reported that the prevalence of both symptoms and clinical signs ranges from 8.7% to 30.1% (57). It is also estimated that about 14.4% of individuals over 50 years of age experience dry eye symptoms, with women being affected more frequently (25). Significant variability in reported prevalence is likely due to differences in diagnostic criteria, study methodologies, and characteristics of the populations studied.

Dry eye disease is also associated with a substantial economic burden. The annual cost of treating a single patient is estimated at \$687-\$1,267, depending on disease severity, while total costs for the U.S. economy are approximately \$3.8 billion per year (4, 24). These costs include expenses related to pharmacological treatment, over-the-counter products, and procedures such as punctal plug insertion (9).

4. Pathophysiology and Disease Mechanisms

Dry eye disease (DED) is a complex, multifactorial disorder of the tear film and ocular surface, leading to loss of tear film homeostasis, ocular discomfort, visual disturbances, and potential damage to the corneal epithelium and stroma (29).

A central role in the pathogenesis of DED is played by tear film hyperosmolarity and chronic ocular surface inflammation. A healthy tear film provides protective, lubricating, and nourishing functions and participates in light refraction. It consists of three layers: lipid, aqueous, and mucin. The lipid layer, produced by the Meibomian glands, limits evaporation; the aqueous layer, which constitutes approximately 90% of the tear film thickness, ensures ocular surface hydration; and mucins, secreted by conjunctival goblet cells, stabilize the tear film and exert protective effects (36). Disruptions in any of these layers lead to increased tear film osmolarity and promote chronic inflammation (47).

The core pathogenic mechanisms include hyperosmolarity and tear film instability, which mutually reinforce each other, creating a vicious cycle of inflammation and epithelial damage (3). Hyperosmolarity can result from either aqueous tear deficiency (ADDE - aqueous- deficient dry eye) or excessive tear evaporation (EDE - evaporative dry eye). It triggers activation of inflammatory pathways, including MAPK and NF- κ B, leading to increased production of proinflammatory cytokines (IL-1, IL-6, IL-8), TNF- α , chemokines (e.g., CCL5/RANTES), and matrix metalloproteinases, particularly MMP-9 (49). Tear film instability may result from Meibomian gland dysfunction, mucin deficiency, epithelial damage, or altered blinking patterns, which further exacerbates evaporation and hyperosmolarity (47).

Hyperosmolar stress activates both innate and adaptive immune responses. Dendritic cells present antigens and activate CD4⁺ T lymphocytes, including Th1 and Th17 subpopulations, which infiltrate the ocular surface and lacrimal glands, secreting effector cytokines such as IFN- γ and IL-17. Concurrent dysfunction of regulatory T cells (Treg) contributes to the persistence of inflammation and disease progression (47).

Pathogenic mechanisms differ depending on the disease subtype. In aqueous-deficient DED (ADDE), the primary issue is reduced tear production, often associated with autoimmune diseases such as Sjögren's syndrome. In evaporative DED (EDE), excessive tear evaporation, most commonly due to Meibomian gland dysfunction (MGD), is the key factor. Reduced lipid content promotes hyperosmolarity, inflammation, and tear film destabilization (8).

Chronic inflammation leads to structural changes in the ocular surface, including disruption of the corneal barrier, epithelial cell desquamation, loss of goblet cells, and squamous metaplasia (48). Neurosensory alterations, such as corneal hypersensitivity or decreased sensation, often accompany these changes. Neuropeptides and nerve alterations enhance leukocyte infiltration, immune cell chemotaxis, and neurogenic inflammation (30). The TRPV1 receptor also plays a significant role, acting as an osmosensory sensor that, through activation of MAPK and NF- κ B pathways, amplifies proinflammatory cytokine production and sustains the disease's vicious cycle (27).

Hormonal factors also influence disease development and progression. Androgen deficiency and hormonal changes during menopause can impair lacrimal and Meibomian gland function and exacerbate inflammation. Additionally, reductions in protective tear film components such as lysozyme, lactoferrin, and lacritin, further destabilize the tear film and increase ocular surface susceptibility to damage (14).

Comorbidities, including thyroid disorders (e.g., thyroid eye disease), premature ovarian failure, leprosy, and graft-versus-host disease (GVHD), can lead to decreased tear production and chronic ocular surface inflammation (55).

Environmental factors contributing to DED include low humidity, wind, air conditioning, tobacco smoke, prolonged use of electronic devices, and driving, all of which reduce blink rate (36). Iatrogenic factors are also important, including chronic contact lens wear and certain medications such as β -blockers, diuretics, selective serotonin reuptake inhibitors, antihistamines, tricyclic antidepressants, antipsychotics, antiparkinsonian drugs, oral hormonal contraception, and isotretinoin. Topical ophthalmic drops containing benzalkonium chloride have an additional detrimental effect by damaging goblet cells responsible for the mucin layer of the tear film (47).

In summary, dry eye disease is a condition in which hyperosmolarity and tear film instability initiate an inflammatory cascade that leads to chronic ocular surface damage. In the course of the disease, inflammatory, neurosensory, and environmental factors mutually reinforce each other, perpetuating a pathogenic vicious cycle. Understanding these mechanisms provides the basis for developing therapies that target the underlying causes of DED rather than merely alleviating symptoms (36).

5. Risk Factors

Dry eye disease is a condition with a complex etiology in which sociodemographic, environmental, and medical factors play a significant role. Their coexistence may substantially influence symptom development and patients' quality of life.

A systematic review analyzed the association between multiple potential risk factors and the occurrence of dry eye disease in order to develop a predictive model enabling early diagnosis and reduction of complications. The analysis included six studies meeting the eligibility criteria, encompassing a total of 48 variables. Among these, seven were identified as the most common risk factors: female sex, contact lens use, intensive computer use, thyroid dysfunction, arterial hypertension, and the use of antidepressants and antihistamines. Sociodemographic factors predominated in the analyzed studies, whereas evidence for some other potential determinants was insufficient to confirm a clear association (28).

Numerous epidemiological studies emphasize age and female sex as the main predisposing factors for dry eye disease. The risk is particularly increased in postmenopausal women, patients undergoing estrogen therapy, and individuals after ocular surface surgery (63). An important environmental factor is the use of visual display terminals (VDTs), which reduces blink frequency and increases the number of incomplete blinks, thereby increasing ocular surface exposure to environmental factors. An association has also been demonstrated with exposure to sunlight and air pollution, particularly in tropical countries (1, 10). Additionally, vitamin D deficiency and diabetes mellitus (DM) have been identified as potential risk factors (39, 64).

Female sex remains one of the most well-documented risk factors (43, 53, 56). The higher prevalence of the disease in women may be related to the influence of sex hormones on lacrimal and Meibomian gland function, goblet cell density, and ocular surface sensitivity (43, 58). Hormonal imbalance contributes to tear film instability and increases susceptibility to inflammatory processes. However, some studies have not demonstrated a significant association between sex and the occurrence of dry eye disease, which may be due to the inclusion of predominantly older populations, in whom androgen levels are reduced in both women and men (38, 54).

Age is another important risk factor. Numerous studies indicate a relationship between aging and an increased prevalence of dry eye symptoms (53). This phenomenon may result from the progressive decline in lacrimal gland secretory function with age (35, 62). At the same time, a comparable prevalence of symptoms in younger adults may be associated with frequent contact lens use, intensive use of electronic devices, and the growing number of refractive surgical procedures.

Lifestyle-related factors include computer use and contact lens wear, both of which increase tear evaporation by reducing blink frequency and destabilizing the tear film (6, 41). The impact of smoking and alcohol consumption remains inconclusive. In most studies, these factors did not show a significant association with symptom occurrence, although some reports suggest a potential role in symptom exacerbation (41, 44).

Systemic diseases also play an important role. Thyroid dysfunction and arterial hypertension may contribute to the development of symptoms. In thyroid disorders, increased risk is associated with exophthalmos, incomplete eyelid closure, and widening of the palpebral fissure, all of which increase ocular surface exposure and tear evaporation (23). Although this association has been demonstrated in some studies

(43), the literature remains inconsistent regarding its confirmation (32). Arterial hypertension may increase the risk of symptoms, particularly in patients receiving antihypertensive therapy (43).

Among pharmacological factors, antidepressants and antihistamines are of particular importance, as they show a strong association with dry eye symptoms. The use of antidepressants has been shown in numerous studies to increase the risk of disease development (7, 45). The mechanism may involve muscarinic and adrenergic receptors in the conjunctival epithelium, which regulate ocular surface function. Similarly, an association has been demonstrated between the use of antihistamines and steroids and the occurrence of symptoms (44, 45).

In summary, the development of dry eye disease depends on the interaction of multiple factors, including demographic characteristics, systemic diseases, lifestyle, and pharmacological treatment. Their cumulative effect leads to disruption of tear film homeostasis and increases the susceptibility of the ocular surface to chronic disease. Identification of these factors is crucial for early diagnosis, prevention, and appropriate therapeutic management.

6. Symptoms and Diagnosis of Dry Eye Disease

The symptoms of dry eye disease (DED) are heterogeneous in nature and severity, including sensations of burning, stinging, or scratching in the eyes, a feeling of a foreign body or sand under the eyelids, conjunctival redness, and the presence of mucous discharge (22). Patients frequently report photophobia, intermittent visual disturbances, eye fatigue, and discomfort when wearing contact lenses. Some individuals experience difficulty driving at night or maintaining prolonged visual focus (36).

Paradoxically, excessive tearing may also occur as a symptom, resulting from reflex tear secretion in response to ocular surface irritation. These “reflex tears” are predominantly aqueous, lack the full composition of a normal tear film, and evaporate rapidly, failing to provide adequate ocular surface lubrication (5).

Symptom severity varies from mild discomfort to significant visual impairment and reduced quality of life (16). Symptoms may be intermittent or chronic, and their intensity depends on environmental factors and individual patient susceptibility (19). Factors that exacerbate symptoms include prolonged use of digital devices, exposure to air-conditioned or heated environments, exposure to tobacco smoke, wind, or dry air, as well as reading or contact lens wear (18, 21).

Visual disturbances result from tear film instability and irregularities of the corneal surface. Patients may experience transient blurred vision, fluctuations in visual acuity throughout the day, and difficulty with night driving. In more severe cases, episodes of diplopia may occur, which may partially resolve after blinking (17, 31).

The course of DED is typically chronic and may show gradual progression. The literature distinguishes four stages of the disease:

- **Stage I** – mild symptoms: burning, itching, intermittent blurred vision.
- **Stage II** – moderate symptoms: pronounced dryness, ocular surface roughness, and conjunctival redness (59, 60).
- **Stage III** – more severe symptoms associated with tear film hyperosmolarity and increased ocular surface inflammation, leading to significant visual disturbances (60).
- **Stage IV** – severe burning, foreign body sensation, photophobia, and marked deterioration in visual quality (59, 60).

Approximately 80% of patients experience periodic exacerbations (“flare-ups”), characterized by increased burning, redness, tearing, and fluctuations in visual acuity (2). DED is an inflammatory condition, the pathogenesis of which involves ocular surface stress induced by infections, environmental factors, endogenous stress, genetic predisposition, or the presence of antigens (42, 51). The disease is most often chronic, particularly in older individuals; however, appropriately selected treatment can reduce symptom severity and prevent ocular surface damage (40). In severe and untreated cases, complications such as keratitis, corneal ulceration, or scarring may occur, increasing the risk of infection and permanent visual impairment (20, 22, 26).

Symptoms also have a significant impact on daily functioning, impairing activities such as reading, computer work, and driving, while chronic discomfort may reduce quality of life and concentration (15).

7. Diagnosis

The diagnosis of dry eye disease (DED) requires a comprehensive approach that takes into account both subjective patient-reported symptoms and objective clinical findings (36). It is based on a detailed medical history, including the nature, severity, and duration of symptoms, environmental factors, comorbidities, and current pharmacological treatment. Assessment of lifestyle factors, such as prolonged screen exposure and time spent in air-conditioned environments, is also important (47).

Validated questionnaires, such as the Ocular Surface Disease Index (OSDI) and the Dry Eye Questionnaire (DEQ-5), are used to assess symptom severity, enabling initial diagnosis and monitoring of treatment outcomes. These tools evaluate symptom frequency, their impact on vision, and the role of environmental factors (47). The correlation between subjective symptoms and clinical findings is often weak, which justifies the use of multiple diagnostic methods (50).

Clinical examination includes slit-lamp evaluation of the anterior segment of the eye, assessing the eyelids, conjunctiva, cornea, and tear film. Particular attention is paid to conjunctival hyperemia, corneal epithelial damage, and Meibomian gland function (36). Evaluation of eyelid closure, as well as blink rate and completeness, helps identify mechanisms contributing to increased tear evaporation (47).

Key diagnostic tests include:

- TBUT (tear break-up time) – a measure of tear film stability; values < 10 seconds indicate instability, while < 5 seconds may support the diagnosis of DED (61).
- Ocular surface staining – using fluorescein, lissamine green, or rose bengal; allows assessment of epithelial damage and disease severity (36).
- Schirmer test – a quantitative assessment of aqueous tear production; reduced values are characteristic of aqueous-deficient DED (47).
- Tear meniscus height – evaluation of tear volume on the ocular surface (36).
- Tear osmolarity measurement and inflammatory markers, such as MMP-9 (36).
- Assessment of Meibomian gland structure and function – particularly important in evaporative DED (36).

Based on diagnostic findings, two main forms of DED are distinguished: aqueous-deficient (ADDE) and evaporative (EDE), which determine the choice of therapeutic strategy (42). Diagnostic evaluation should include patient history, TBUT assessment, vital staining, the Schirmer test, and analysis of the eyelids and Meibomian glands (42).

Differential diagnosis is equally important to exclude other conditions, such as infections or allergies, which may present with similar symptoms (42). Due to the lack of a single test with sufficient sensitivity and specificity, the diagnosis of DED should be based on a combination of clinical findings and multiple diagnostic modalities (50). Early diagnosis and appropriate therapeutic management help prevent complications such as ocular surface damage and deterioration of vision (36).

8. Treatment

Management of dry eye disease (DED) requires a multifaceted approach tailored to the underlying causes, severity, and presence of comorbid conditions, such as Meibomian gland dysfunction, subclinical ocular surface inflammation, or systemic diseases (36, 42). The primary goals of therapy are symptom relief, restoration of normal tear film function, and prevention of further ocular surface damage (36,50). Patient education and lifestyle modifications play a crucial role, including avoidance of cigarette smoke, dry air and air conditioning; frequent blinking during screen use; wearing sunglasses to protect against wind; and maintaining a diet rich in omega-3 fatty acid (36, 42).

The foundation of treatment is artificial tears and lubricants, which hydrate and lubricate the ocular surface. These are available as drops, gels, or ointments and may contain carboxymethylcellulose, hydroxypropyl methylcellulose, hyaluronic acid, or polyvinyl alcohol. Preservative-free formulations are recommended for frequent use to reduce the risk of irritation (36, 42, 50). In cases of Meibomian gland dysfunction, lipid-containing artificial tears are used to improve tear film stability (42).

Even moderate forms of DED are associated with subclinical inflammation, so anti-inflammatory therapy is often required. Topical corticosteroids, such as loteprednol, provide rapid symptom relief when used short-term, but prolonged use carries risks, including increased intraocular pressure and cataract formation (36, 42, 50). Topical cyclosporine A (0.05%) increases tear production, reduces inflammatory cell counts, and improves goblet cell function; its immunosuppressive effect makes it effective in moderate to severe DED. For

patients intolerant to cyclosporine, tacrolimus or pimecrolimus may be used, which also have anti-inflammatory properties (42). Anti-inflammatory therapy may also include tetracyclines and macrolides, which improve Meibomian gland function, enhance tear film stability, and reduce bacterial colonization of the eyelid margin (42, 50). Newer prescription medications, such as lifitegrast or varenicline, either block immune pathways or stimulate tear production, and short-term use of modern corticosteroids like loteprednol 0.25% reduces inflammation with a lower risk of side effects (36).

For excessive tear drainage, punctal plugs- temporary, dissolvable, semi-permanent, or permanent-can be used to block the lacrimal ducts, prolonging tear contact with the ocular surface and increasing hydration (36, 42, 50). Daily eyelid hygiene is the primary treatment for Meibomian gland dysfunction, including warm compresses, massage, and lid margin cleaning to melt blocked secretions and improve lipid delivery (36, 42). In more advanced cases, therapeutic devices such as IPL, LipiFlow, TearCare, iLux, Mibo Thermoflo, RF systems, or BlephEx can support Meibomian gland function and reduce inflammation (36).

In severe cases unresponsive to conventional treatment, autologous serum eye drops containing growth factors, vitamin A, and antibodies can promote ocular surface regeneration (36, 42, 50). Specialized contact lenses create a fluid reservoir over the cornea, protecting the ocular surface and maintaining hydration, and may serve as drug delivery platforms in the future (34, 36). Supportive therapy also includes supplementation with omega-3 and omega-6 fatty acids, which exert anti-inflammatory effects and improve tear film quality (36, 42, 50).

In the most severe cases, with corneal ulcers or risk of perforation, surgical intervention may be required, including tarsorrhaphy, amniotic membrane transplantation, salivary gland transplantation, corneal patching, or cyanoacrylate glue to seal perforations (36, 42, 50). Management of DED therefore requires individualized, combined therapies with continuous monitoring to adapt treatment to the changing ocular status and prevent complications such as corneal damage, infections, or vision deterioration (34, 36, 42, 50).

9. Emerging Therapies for Dry Eye Disease

Recent research on dry eye disease (DED) is increasingly focusing not only on symptom relief but also on improving drug delivery efficiency and targeting the underlying pathophysiological mechanisms. One of the most promising areas is advanced drug delivery systems, including colloidal carriers such as liposomes, nanoparticles, and microspheres. These platforms allow controlled release of active substances and prolong their contact time with the ocular surface. Their bioadhesive properties enable binding to the mucin layer of the tear film, reducing rapid washout and enhancing drug bioavailability (50). Polymer- and lipid-based nanoparticles are particularly promising, as they protect drugs from degradation and facilitate penetration into deeper ocular structures, potentially improving therapeutic outcomes (33). Materials like chitosan further increase adhesion to the ocular surface and transient epithelial permeability, enhancing drug absorption (33).

Another innovative approach involves drug-eluting contact lenses. Hydrogel lenses can absorb therapeutic agents and release them gradually into the tear film, providing much longer drug action compared to conventional eye drops (34). Techniques such as molecular imprinting or encapsulating drugs within nanoparticles embedded in the lens structure allow precise control over release kinetics, reducing the need for frequent dosing, improving patient comfort, and minimizing side effects (34).

Novel pharmacological agents are being developed to stimulate tear film components and modulate inflammatory responses. Examples include diquafosol, which activates P2Y2 receptors to enhance tear secretion and ocular surface hydration, and rebamipide, which increases mucin production to stabilize the tear film (50). Parallel studies are investigating other anti-inflammatory and immunomodulatory molecules at various stages of clinical trials, highlighting the ongoing need for therapies that directly address the root causes of DED (50).

Alternative administration routes, such as intracameral or subconjunctival injections, are also under investigation. These methods bypass ocular barriers that limit topical drug efficacy and can significantly increase local drug concentrations. However, their use is limited by invasiveness and potential complications (33), driving interest in technologies that maximize therapeutic effectiveness while minimizing tissue disruption.

Targeted immunomodulatory therapies and strategies to maintain ocular surface homeostasis are gaining importance. Current medications, such as cyclosporine and lifitegrast, primarily modulate T-cell activation but are not effective in all patients and do not address all disease mechanisms (49). Research is ongoing into treatments that more comprehensively regulate inflammatory pathways, including interventions affecting cellular stress signaling and supporting goblet cell function for mucin production (49).

Supportive therapies, such as supplementation with omega-3 and gamma-linolenic acid, demonstrate anti-inflammatory effects and improve tear film stability. Emerging evidence also suggests a potential role for gut microbiota in DED pathogenesis, opening new possibilities for probiotic or metabolite-based interventions to modulate immune responses (49).

Overall, the future of DED treatment is likely to involve a multimodal approach, combining advanced drug delivery technologies with therapies targeting specific disease mechanisms, ultimately aiming for more effective and personalized management of this chronic condition.

10. Discussion

Dry eye disease is one of the most prevalent ocular surface disorders, with steadily increasing clinical significance. This trend is associated both with population aging and dynamic lifestyle changes, particularly prolonged exposure to digital screens (11, 24, 50). Simultaneously, significant discrepancies in reported prevalence rates, ranging from a few to several tens of percent of the population, indicate notable methodological limitations in available studies. These differences primarily arise from the lack of uniform diagnostic criteria and the poor correlation between subjective symptoms and clinical findings, which remains one of the major challenges in contemporary DED diagnostics. Furthermore, the use of diverse diagnostic tools and symptom assessment questionnaires can lead to substantial variability in epidemiological outcomes, complicating direct comparisons between studies (9, 42).

Analyses indicate that age remains one of the most important risk factors for disease development. In populations over 50 years of age, a significant increase in symptom prevalence is observed, which can be explained by both physiological changes within the Meibomian glands and a reduction in basal tear secretion (13, 25, 26). This association is supported by numerous epidemiological studies, including the Shihpai Eye Study and analyses by Schaumberg et. al. (38, 53). However, it should be emphasized that the increasingly frequent occurrence of symptoms among younger adults highlights the growing importance of environmental and behavioral factors, which may partially offset the traditional influence of age (16, 29). In this context, attention is drawn to the changing demographic structure of DED patients, where an increasing proportion are professionally active individuals exposed to chronic environmental stressors (10, 63).

Sex is another important factor influencing DED risk. Women exhibit greater susceptibility to the disease, likely due to the effects of sex hormones on the function the lacrimal and Meibomian glands, as well as on tear film stability (43, 53, 57). Hormonal changes during menopause, including reductions in estrogen and androgen levels, may result in altered tear quantity and quality (53, 58). Additionally, a higher prevalence of autoimmune disorders, such as Sjögren's syndrome, in this population may exacerbate DED symptoms (58). Nonetheless, not all studies confirm a definitive influence of sex, suggesting the involvement of additional modulatory factors, such as lifestyle or environmental exposures (28, 57).

Current evidence highlights the increasing role of environmental factors, particularly prolonged screen use. Extended monitor exposure is associated with decreased blink rate and an increased proportion of incomplete blinks, leading to tear film instability and enhanced evaporation (1, 10, 63). Notably, studies in Asian populations suggest that intensive digital device use can result in DED symptoms in younger adults at rates comparable to older individuals (1, 63), underscoring the need for preventive and educational measures early in professional life (29). Additionally, other environmental factors, such as air conditioning, air pollution, and low humidity, may further exacerbate disease manifestations (28, 50).

Comorbidities also play a significant role in DED pathogenesis. Conditions such as diabetes, thyroid dysfunction, and vitamin D deficiency can affect both the quantity and quality of the tear film (23, 32, 64). These mechanisms include chronic oxidative stress, corneal epithelial damage, and modulation of inflammatory responses (39, 64). In thyroid disorders, mechanical factors such as incomplete eyelid closure and increased ocular surface exposure are particularly relevant (23, 32). The literature also emphasizes the impact of neurological diseases and systemic medications on tear secretion and ocular surface function (26, 42), highlighting the necessity of a holistic approach to patient care that accounts for systemic comorbidities in diagnostic and therapeutic strategies.

The pathophysiology of DED is complex and involves the interplay of multiple mechanisms leading to ocular surface homeostasis disruption (3, 11, 37, 49, 61). Tear film hyperosmolarity and chronic inflammation play central roles, mutually reinforcing each other and creating a self-perpetuating disease cycle. In clinical practice, purely hyposecretory or evaporative forms are rarely observed, with most patients exhibiting a mixed phenotype (3, 11, 52). Increasing attention is also being directed toward disturbances in the mucin layer of the tear film, which may compromise tear film stability even when tear volume is normal (49, 55). This has

therapeutic implications, as effective management should concurrently address multiple pathogenic mechanisms.

The role of neurosensory mechanisms in DED pathogenesis has gained growing recognition. Dysregulation of TRPV receptors and neuropeptides may influence symptom perception and explain the observed discrepancies between subjective complaints and clinical findings (27, 30, 49). This phenomenon poses significant diagnostic challenges, potentially leading to both under- and over-diagnosis, and emphasizes the need for a multidimensional diagnostic approach. In this context, assessment of patients' quality of life is increasingly considered an important complement to conventional diagnostic methods (9, 50).

Therapeutically, accurate identification of the dominant pathogenic mechanism is crucial. In clinical practice, treatment should be individualized and include both symptomatic and etiologic interventions (11, 40, 61). While traditional approaches, such as artificial tears and eyelid hygiene, remain foundational, strategies targeting inflammation reduction and improvement of Meibomian gland function are gaining prominence. Recent years have also highlighted the importance of immunomodulatory and targeted therapies capable of influencing key inflammatory pathways (40, 49). Nevertheless, it should be noted that many available treatments are primarily symptomatic and do not address the underlying causes of disease.

Emerging therapeutic directions, including nanotechnology applications, advanced drug delivery systems, and contact lenses as drug carriers, represent promising avenues for DED management (33, 34, 40). These technologies have the potential to enhance drug bioavailability and prolong therapeutic effect, although most are still in experimental or early clinical trial stages. Additionally, strategies based on ocular surface regeneration and modulation of the inflammatory microenvironment are under development, which may allow a more causative approach in the future (33, 49). Further studies are required to confirm their efficacy and long-term safety.

Lifestyle modifications and preventive measures remain essential. Patient education on proper screen ergonomics, regular breaks, and ocular surface care can significantly reduce symptom severity and improve quality of life (2, 16, 29). This is particularly important for younger patients, in whom environmental factors play a predominant role. Early intervention and symptom monitoring can help prevent disease progression and the development of complications (16, 19).

In summary, DED is a disease with complex etiology, in which interactions among demographic, environmental, immunologic, and neurosensory factors are of critical importance. Effective management requires a multidimensional approach, encompassing pharmacological therapy, lifestyle modification, and treatment of comorbidities. Ongoing research into pathophysiological mechanisms and novel therapeutic strategies may facilitate the development of more effective, causative interventions, ultimately reducing both disease symptoms and its social and economic burden (4, 11, 16, 27, 29, 30, 46, 50).

11. Conclusions

Dry eye disease is a complex, multifactorial disorder of the ocular surface, the prevalence of which is increasing due to population aging and lifestyle changes, particularly increased exposure to digital devices. The pathogenesis involves an interplay between tear film instability, chronic inflammation, and neurosensory mechanisms, which complicates both accurate diagnosis and effective treatment.

A significant clinical challenge remains the lack of concordance between patient-reported symptoms and objective diagnostic findings, highlighting the need for a comprehensive, multidimensional approach to diagnosis that incorporates both clinical parameters and patient-reported quality of life (9, 50).

Therapeutic management should be individualized and aimed at both symptom relief and the elimination of underlying causes and comorbid conditions. Lifestyle modification and patient education constitute essential components of therapy, particularly in younger populations exposed to environmental risk factors. Early implementation of preventive strategies may limit disease progression and improve treatment outcomes (16, 29).

The development of novel therapeutic strategies, including advanced drug delivery systems, targeted molecular therapies, and regenerative approaches, offers the prospect of more effective causative treatment. However, further studies are required to evaluate their long-term efficacy, safety, and feasibility for widespread clinical application (33, 40, 49).

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