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# Exploring new Frontiers in dry eye Disease: Treatments, mechanisms, and diagnostic innovations a comprehensive review

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ABSTRACT

Dry Eye Disease (DED) significantly impacts quality of life through tear film instability and ocular surface inflammation. This review highlights advancements in treatments, mechanisms, and diagnostics. Emerging pharmacological therapies, including novel anti-inflammatory agents, secretagogues, corticosteroids, and autologous serum eye drops, alongside innovative devices like punctal plugs, thermal pulsation devices, and meibomian gland expression techniques. Lifestyle modifications and nutritional supplements, such as omega-3 fatty acids and antioxidants, are also explored.

Mechanistic insights cover tear film instability, inflammatory pathways, neuropathic pain, and meibomian gland dysfunction, emphasizing recent findings on the ocular surface microbiome, genetic and epigenetic factors, and chronic inflammation. Diagnostic innovations include AI and machine learning integration, advanced imaging techniques, tear film analysis, and functional tests, enhancing early detection and monitoring.

Emerging research on gene therapy, stem cell therapy, ocular surface microbiota, and gene editing technologies like CRISPR is examined for future treatment potential. Personalized medicine approaches, incorporating genomic and proteomic profiling and patient-reported outcomes, are emphasized for tailored therapies.

Environmental and lifestyle factors, including pollution, climate change, diet, and behavioral modifications, are considered for their impact on DED management. Integrating these advancements into clinical practice aims to improve patient outcomes and quality of life, highlighting the future potential of cutting-edge research and innovations.

## 1. Introduction

Dry Eye Disease (DED) is a complex and prevalent condition affecting millions worldwide, characterized by tear film instability, ocular surface inflammation, and symptoms such as dryness, irritation, and visual disturbances that significantly impact quality of life (Wang et al., 2024; Barabino et al., 2016; Tsubota et al., 2020; Cutrupi et al., 2023). Given its multifactorial nature, effective management requires advancements in treatment, a deeper understanding of its mechanisms, and innovative diagnostic technologies (Wang et al., 2024; Zhang et al., 2024).

Recent therapeutic advancements include novel anti-inflammatory agents, secretagogues, corticosteroids, and autologous serum eye drops, alongside procedural interventions like punctal plugs, thermal pulsation devices, and meibomian gland expression techniques. Additionally, lifestyle modifications and nutritional supplements, such as omega-3 fatty acids and antioxidants, contribute to symptom relief (Colligris et al., 2014; Wu et al., 2022; Nguyen et al., 2023; Gupta et al., 2024; Shahraki et al., 2024).

Understanding the underlying mechanisms of DED tear film instability, inflammation, neuropathic pain, and meibomian gland dysfunction has driven research into the roles of the ocular microbiome, genetic predisposition, and chronic inflammation. Concurrently, diagnostic advancements, including imaging techniques, tear film analysis, and biomarker studies, are enhancing early detection and personalized treatment, with artificial intelligence further refining diagnostic

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precision.

Emerging research is exploring novel interventions such as gene and stem cell therapies, ocular microbiota studies, and CRISPR-based gene editing, offering promising future directions (Dubey and Mostafavi, 2023). Personalized medicine approaches integrating genomic and proteomic profiling aim to tailor treatment strategies to individual needs.

This review synthesizes recent advancements in DED treatment, underlying mechanisms, and diagnostic innovations, emphasizing the transformative potential of emerging research in improving patient care and quality of life.

## 2. Understanding the mechanisms underlying dry eye disease (DED)

Dry Eye Disease (DED) is a multifactorial condition with complex underlying mechanisms that drive its onset and progression. A key feature is tear film instability, resulting from an imbalance in tear production, distribution, and evaporation (Vidal-Rohr et al., 2024). Increased tear evaporation, influenced by environmental factors, reduced blink rate, and ocular surface abnormalities, further exacerbates instability (Muñoz-Villegas et al., 2024).

Another critical factor is aqueous deficiency, often linked to lacrimal gland dysfunction due to systemic diseases, medications, or age-related changes (Jackson et al., 2023). Understanding these mechanisms is crucial for developing effective treatment strategies that address both evaporative and aqueous-deficient forms of DED.

## 3. Environmental factors influencing dry eye disease (DED)

Environmental conditions significantly impact tear film stability, contributing to increased tear evaporation and worsening DED symptoms. Low humidity, common in air-conditioned or heated environments, accelerates tear evaporation, particularly in winter or during prolonged indoor exposure (Chlasta-Twardzik et al., 2021). Wind exposure further dehydrates the ocular surface, affecting those frequently outdoors or living in windy regions. Additionally, direct airflow from fans and heating, ventilation and air conditioning (HVAC) systems exacerbates tear film instability (González-García et al., 2007; Ito and Takada, 2023; Arita and Fukuoka, 2024).

### 3.1. Environmental factors

Temperature extremes significantly impact tear film stability. High temperatures accelerate tear evaporation, while cold, low-humidity conditions disrupt tear film integrity, exacerbating DED symptoms (González-García et al., 2007; Britten-Jones et al., 2024). Air pollution from smoke, smog, and vehicle exhaust, dust pollution (Devarajan, R. et al., 2015) causes ocular irritation and inflammation. Chemical irritants, including industrial chemicals and cleaning products, further contribute to dryness. High-altitude regions with lower humidity and seasonal variations also influence tear evaporation and symptom severity (Fraser, 2024; Deng et al., 2024).

### 3.2. Modern lifestyle factors

Prolonged screen time reduces blink frequency, increasing tear evaporation and worsening DED (Tawfik et al., 2024). Artificial lighting, particularly fluorescent lights, adds to visual discomfort and dryness (Talens-Estarelles et al., 2023; Dyrek et al., 2024; Malik et al., 2024).

## 4. Digital device usage and occupational impact on dry eye disease (DED)

### 4.1. Impact of digital devices on DED

The widespread use of computers, smartphones, and televisions has significantly contributed to the increasing prevalence of DED (Al-Mohtaseb et al., 2021). A primary mechanism linking screen use to DED is the reduction in blink rate, which disrupts tear film stability and accelerates tear evaporation (Almuhwwis et al., 2022).

#### 4.1.1. Key contributing factors

- **Reduced Blink Rate:** Normal blinking spreads tears evenly, but screen use significantly reduces blink frequency, leading to tear instability and dryness.
- **Poor Ergonomics:** Improper screen height or prolonged downward gaze can increase tear evaporation from the lower ocular surface.
- **Dry Indoor Air:** Air-conditioning and heating systems in digital environments further accelerate tear evaporation.

### 4.2. Blue light and eye strain

While the direct impact of blue light on tear film stability remains under investigation, prolonged exposure contributes to visual discomfort and strain, exacerbating DED symptoms (Chawla et al., 2021). Given the modern dependence on digital devices, further research is warranted to understand blue light's long-term effects on ocular health.

### 4.3. Occupational hazards

Certain professions heighten DED risk due to prolonged screen use, intense lighting, and exposure to harsh environments. Office workers, and IT professionals, experience reduced blink rates and visual strain (Al-Dossary, 2024). Pilots, flight attendants, and construction workers face low humidity, dust, and debris, accelerating tear evaporation (Ay et al., 2023). Other occupations, including teachers, customer service representatives, drivers, and artists, encounter fluctuating environmental conditions that contribute to DED.

## 5. Nutritional deficiencies and DED

Nutrition plays a critical role in maintaining tear production and ocular surface health. Deficiencies in key nutrients can impair tear biosynthesis, leading to dry eye symptoms **(**Stapleton et al., 2024**)**.

### 5.1. Essential nutrients for tear stability

- **Omega-3 Fatty Acids** (fish oil, flaxseed oil): Support meibomian gland health and reduce inflammation (Giannaccare, 2019).
- **Vitamin A** (liver, dairy, eggs, and carrots): Maintains corneal epithelium and tear production (Christen et al., 2022).
- **Vitamin D** (sunlight, fatty fish, fortified dairy): Modulates immune responses and prevents inflammation (Rolando and Barabino, 2023).
- **Vitamin E** (nuts, seeds, vegetable oils): Reduces oxidative stress and inflammation (Najjaran et al., 2023).
- **Zinc** (meat, shellfish, legumes, whole grains): Supports enzymatic processes for tear production (Grahn et al., 2001).
- **B Vitamins (B6, B12)** (meat, fish, dairy, cereals): Promote nerve health and corneal function (Hyon and Han, 2022; Guo et al., 2023)
- **Hydration & Antioxidants** (fruits, vegetables, vitamin C sources): Reduce oxidative damage and inflammation (Seen and Tong, 2018; Srinivasan, S. et al., 2024).

Proper diet and supplementation can significantly improve tear production and alleviate dry eye symptoms.

## 6. Age-related changes in tear film and ocular health in DED

Aging is a major contributor to DED, as tear production and composition decline over time (Gipson, 2013).

### 6.1. Age-related factors affecting DED

- **Lacrimal Gland Dysfunction:** Reduced efficiency leads to aqueous tear deficiency (Wang et al., 2020).
- **Hormonal Changes:** Estrogen and testosterone decline, affecting tear production and lipid stability (Gorimanipalli et al., 2023).
- **Meibomian Gland Dysfunction:** Atrophy and blockage lead to increased tear evaporation (Lin et al., 2020).
- **Ocular Surface Aging:** Decreased cell turnover and regenerative capacity impair tear film stability (Barabino, 2022).

## 7. Systemic diseases and medications impacting DED

Several systemic conditions contribute to DED by affecting tear production, inflammation, and ocular surface integrity.

### 7.1. Key systemic conditions linked to DED

- **Autoimmune Disorders:** Sjogren's syndrome, rheumatoid arthritis, lupus (Wu et al., 2023; Lai et al., 2023; Tseng et al., 2023).
- **Diabetes:** Neuropathy affects lacrimal gland function, reducing tear production (Yu et al., 2021).
- **Thyroid Disorders:** Hyperthyroidism & hypothyroidism disrupt ocular surface health (Naderan, 2018; Stella and Udeh, 2019).
- **Chronic Kidney Disease:** Uremia affects tear secretion (Kalantar-Zadeh et al., 2021).
- **Neurological Disorders:** Parkinson's disease reduces blinking frequency, contributing to ocular dryness (Nagino et al., 2022; Ungureanu et al., 2023).
- **HIV/AIDS & Graft-Versus-Host Disease:** Immunosuppression increases ocular inflammation and dry eye symptoms (Sharma et al., 2021; Roca et al., 2023).

## 8. Hormonal fluctuations and DED

### 8.1. Hormonal imbalances significantly influence tear production and ocular health

- **Menopause:** Reduced estrogen and androgen levels impair lacrimal and meibomian gland function (Gorimanipalli et al., 2023).
- **Andropause:** Declining testosterone levels increase tear evaporation.
- **Pregnancy & Menstrual Cycle:** Fluctuations in progesterone and estrogen can alter tear composition (Zacur, 2006; Kelly et al., 2023).
- **Hormonal Medications:** Oral contraceptives and Hormone Replacement Therapy (HRT) can impact tear production (Tomlinson et al., 2001; Schaumberg et al., 2001).

## 9. Inflammatory pathways in DED

Inflammation is a key driver in the pathogenesis and progression of Dry Eye Disease (DED), with multiple interconnected inflammatory pathways contributing to disease initiation, chronicity, and severity. Understanding these pathways is essential for developing targeted therapies that mitigate the impact of DED.

### 9.1. Cytokine release and inflammatory mediators

In DED, ocular surface epithelial cells respond to environmental stressors such as low humidity and prolonged screen exposure by releasing pro-inflammatory cytokines, including Tumor Necrosis Factor-alpha (TNF-α), Interleukin-1 (IL-1), Interleukin-6 (IL-6), and Interleukin-8 (IL-8) (Mehra and Galor, 2020; Harvanová et al., 2023). These cytokines promote inflammatory cell recruitment, particularly neutrophils and T-cells, exacerbating tissue damage. Additionally, IL-8 functions as a chemoattractant, facilitating inflammatory cell infiltration. Matrix Metalloproteinases (MMPs), particularly MMP-9, are upregulated in DED, leading to collagen degradation and epithelial barrier disruption, further propagating inflammation (Roda et al., 2020; Chu et al., 2024; Ullah et al., 2024).

### 9.2. Activation of the innate immune system

The innate immune response is a crucial early event in DED pathogenesis (Taketani et al., 2020). Toll-like Receptors (TLRs) on corneal epithelial cells recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), activating intracellular signaling pathways that amplify cytokine and chemokine production. Dendritic cells, which process and present antigens, further activate T-cells, intensify chronic inflammation (Tajbakhsh et al., 2023; Lai et al., 2023).

### 9.3. Adaptive immune response

The adaptive immune system plays a central role in sustaining chronic inflammation in DED. Persistent ocular surface irritation triggers the activation of $CD4^+$ T-helper (Th) cells and $CD8^+$ cytotoxic T-cells, leading to prolonged inflammatory cytokine release (Li et al., 2022). In some cases, B-cells contribute to autoimmunity by producing autoantibodies against ocular surface antigens, further exacerbating inflammation and tissue destruction (Wu et al., 2023).

### 9.4. Neurogenic inflammation

Neurogenic inflammation is an essential yet underappreciated contributor to DED pathogenesis (Wu et al., 2023). Corneal sensory nerves detect irritation and initiate inflammatory responses by releasing neuropeptides, such as Substance P and Calcitonin Gene-Related Peptide (CGRP) (Russell et al., 2014). These neuropeptides amplify inflammatory pathways and heighten pain perception. A feedback loop emerges, where nerve damage perpetuates inflammation and pain, complicating disease management (Petersen et al., 2024).

### 9.5. Tear film instability and inflammation

Tear film instability is both a cause and consequence of inflammation in DED. Reduced tear secretion leads to an unstable tear film, exposing the ocular surface to environmental stressors that drive inflammation. Increased tear osmolarity, a hallmark of DED, induces osmotic stress, triggering epithelial cell apoptosis and inflammatory cytokine release. The imbalance of tear film components, including lipids, proteins, and mucins, exacerbates instability, perpetuating inflammation (Rao et al., 2022; Zhao et al., 2024).

### 9.6. Oxidative stress

Oxidative stress is a significant contributor to the inflammatory cycle in DED. Environmental factors and chronic inflammation lead to the excessive production of reactive oxygen species (ROS), including superoxide, hydrogen peroxide, and hydroxyl radicals. These molecules cause oxidative damage to ocular surface cells, further activating inflammatory pathways. Endogenous antioxidants, such as glutathione, are often insufficient to counteract this stress, leading to impaired repair mechanisms and prolonged inflammation (Bu et al., 2024).

### 9.7. Corneal nerve dysfunction

Corneal nerve dysfunction is a critical factor in both sensory abnormalities and inflammation in DED (Maity et al., 2024). This dysfunction worsens symptoms and accelerates disease progression, highlighting the need for targeted therapeutic interventions.

#### 9.7.1. Role of corneal nerves

Corneal nerves are essential for detecting mechanical, thermal, and chemical stimuli, regulating the blink reflex and tear secretion. Additionally, these nerves release neuropeptides that modulate tear production and inflammation. Disruptions in corneal nerve function contribute to tear film instability, epithelial damage, and chronic pain (Maity et al., 2024).

#### 9.7.2. Mechanisms of nerve dysfunction

Corneal nerve damage in DED arises from environmental stressors, persistent inflammation, and mechanical trauma. Reduced corneal nerve density correlates with disease severity, contributing to neuropathic pain and altered sensory responses (Uchino et al., 2023). Patients may experience hyperalgesia (increased pain sensitivity), spontaneous pain, or dysesthesia (abnormal sensations) even without direct stimuli. Chronic inflammation and oxidative stress impair nerve regeneration, prolonging symptoms and disease burden.

Patients with corneal nerve dysfunction exhibit diminished corneal sensitivity, leading to reduced blink reflex and tear secretion. Sensory abnormalities, including burning, itching, and discomfort, occur even in the absence of visible ocular surface damage. Blink rate alterations further compromise tear film stability, exacerbating DED symptoms (Leonardi et al., 2024).

DED involves a complex interplay of inflammatory pathways, including cytokine release, innate and adaptive immune responses, neurogenic inflammation, oxidative stress, and corneal nerve dysfunction. These interconnected mechanisms perpetuate chronic inflammation, tear film instability, and ocular surface damage. Understanding these molecular and immunological pathways is crucial for developing targeted, multi-faceted therapeutic strategies to manage and treat DED effectively.

## 10. Symptoms of DED

### 10.1. Ocular discomfort

Persistent burning, stinging, itching, or a foreign body sensation in the eyes.

### 10.2. Dryness and sensitivity

A constant dry feeling, often worsened by wind, air conditioning, or prolonged screen use; increased sensitivity to light (photophobia) (Fig. 1).

### 10.3. Visual disturbances

Blurred vision that fluctuates with blinking, visual fatigue, and difficulty focusing on tasks like reading or driving (Fig. 1).

### 10.4. Excessive tearing (Epiphora)

Reflexive overproduction of tears in response to ocular irritation (Fig. 1).

### 10.5. Eye redness and inflammation

Conjunctival redness and eyelid inflammation, often associated with meibomian gland dysfunction (Fig. 1).

### 10.6. Contact lens discomfort

Increased irritation, dryness, and difficulty tolerating contact lenses.

### 10.7. Eyelid issues

Crustiness, sticky secretions, or blepharitis, particularly upon

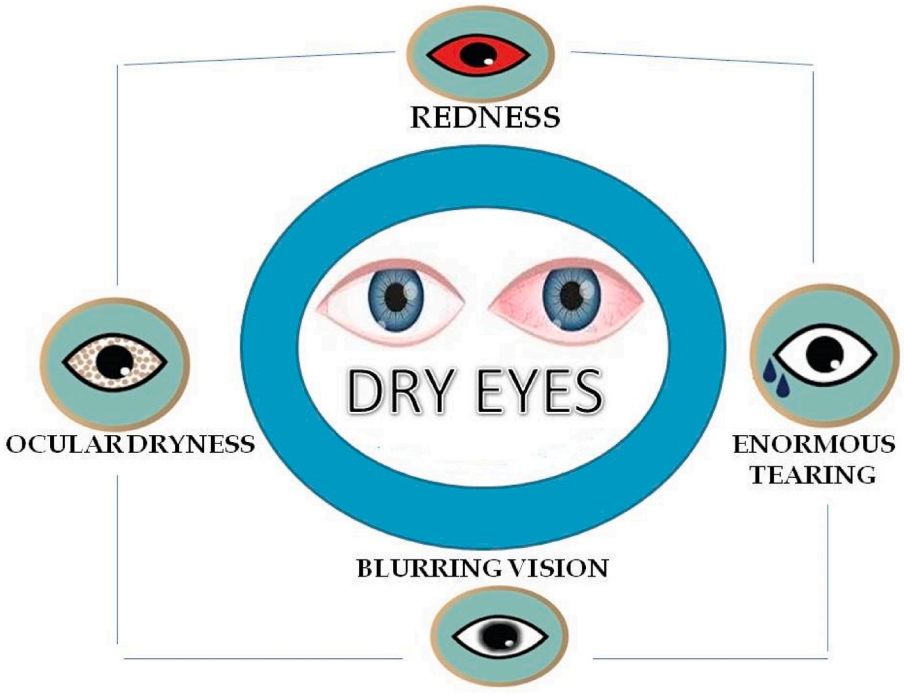


**Fig. 1.** Key symptoms and clinical manifestations of dry eye syndrome (DES).

waking.

### 10.8. Fluctuating symptoms

Symptoms worsening with prolonged visual tasks, such as reading or screen use.

This figure illustrates the typical symptoms associated with dry eyes, which may include sensations of stinging, burning, or itching. Patients often report feeling like there is a foreign object in the eye, accompanied by redness, light sensitivity, blurred vision, and excessive tearing. Additionally, dry eyes can cause discomfort when wearing contact lenses and lead to eye fatigue, particularly after extended periods of reading or using digital devices.

## 11. Clinical signs of DED

Objective clinical signs provide crucial insights into tear film dysfunction and ocular surface damage. These include.

### 11.1. Conjunctival hyperemia

Redness of the conjunctiva, indicating ocular inflammation (Tawfik et al., 2024).

### 11.2. Corneal staining

Fluorescein or lissamine green staining reveals punctate epithelial erosions, signifying corneal surface damage (Li et al., 2022).

### 11.3. Tear film instability

A reduced tear break-up time (TBUT) (<5 s) signifies rapid tear film evaporation (Wu et al., 2023).

### 11.4. Meibomian gland dysfunction (MGD)

Gland obstruction, abnormal lipid secretion, and meibography-confirmed gland dropout contribute to evaporative DED (Maity et al., 2024).

### 11.5. Elevated tear osmolarity

Increased tear osmolarity (>300 mOsm/L) reflects tear hyperosmolarity, leading to epithelial damage (Bu et al., 2024).

### 11.6. Eyelid margin changes

Inflammation, crusting, and scaling, often linked to blepharitis, exacerbate symptoms (Leonardi et al., 2024).

### 11.7. Punctate epithelial erosions

Small corneal epithelial defects visible with fluorescein staining, indicative of chronic dryness (Uchino et al., 2023).

### 11.8. Corneal dellen

Localized thinning of the corneal stroma in severe cases of DED (Petersen et al., 2024).

### 11.9. Abnormal blink patterns

Increased or incomplete blinking, reducing tear film replenishment, worsening ocular surface dryness (Vidal-Rohr et al., 2024).

## 12. Clinical evaluation

To accurately diagnose and assess the severity of DED, clinicians typically use a combination of these signs along with patient-reported symptoms and various diagnostic tests, including Muñoz-Villegas, P. et al., 2024.

- **Slit-Lamp Examination:** To visualize conjunctival and corneal changes.
- **Tear Break-Up Time (TBUT):** To assess tear film stability.
- **Tear Osmolarity Testing:** To measure tear osmolarity levels.
- **Meibography:** To evaluate meibomian gland structure and function.
- **Fluorescein Staining:** To identify corneal and conjunctival damage.

## 13. Dry eye disease (DED) scoring questionnaire

A scoring questionnaire for Dry Eye Disease (DED) typically assesses the frequency, severity, and impact of dry eye symptoms on daily life. Here's a sample questionnaire based on commonly used tools like the Ocular Surface Disease Index (OSDI), the Dry Eye Questionnaire (DEQ), and other validated scales (Table 1)

### 13.1. Scoring and grading of dry eye disease (DED)

Scoring and grading systems for Dry Eye Disease (DED) are essential for assessing the severity of the condition and guiding treatment decisions. Here's a detailed overview of how DED is typically scored and graded.

#### 13.1.1. Ocular Surface Disease Index (OSDI)

- **Description:** A questionnaire evaluating the frequency, severity, and impact of dry eye symptoms.
- **Scoring:**
  - o **0–12:** Mild Dry Eye
  - o **13–22:** Moderate Dry Eye
  - o **23–100:** Severe Dry Eye

#### 13.1.2. Tear break-up time (TBUT)

- **Description:** Measures the time in seconds until dry spots appear on the corneal surface after blinking.
- **Grading:**
  - o **Normal:** TBUT >10 s
  - o **Mild DED:** TBUT 6–10 s
  - o **Moderate DED:** TBUT 2–5 s
  - o **Severe DED:** TBUT <2 s

#### 13.1.3. Fluorescein staining

- **Description:** Uses fluorescein dye to assess damage to the corneal and conjunctival epithelium.
- **Grading (Oxford Scale):**
  - o **Grade 0:** No staining
  - o **Grade 1:** Mild staining (few small spots)
  - o **Grade 2:** Moderate staining (multiple spots or patches)
  - o **Grade 3:** Severe staining (extensive areas of damage)

#### 13.1.4. Tear Osmolarity Testing

- **Description:** Measures the concentration of osmotic solutes in the tears.
- **Grading:**
  - o **Normal:** Osmolarity <308 mOsm/L
  - o **Mild DED:** Osmolarity 308–312 mOsm/L
  - o **Moderate DED:** Osmolarity 313–317 mOsm/L

**Table 1**
Questionnaire to the Suspected Patients Possibly Suffering from Dry Eye Disease This table presents a structured set of questions aimed at identifying and assessing potential symptoms of Dry Eye Disease in patients. The questionnaire includes inquiries related to the frequency and severity of discomfort, visual disturbances, environmental factors, and lifestyle habits that may contribute to the condition, helping clinicians better diagnose and manage DED.

| | None of the time | Some of the time | Frequently (after 4-5 hours) | Very Frequently (1/2hour to 1 hour) | All the time |
|---|---|---|---|---|---|
| **1. Do you feel difficulty in seeing bright light?** | 0 | 1 | 2 | 3 | 4 |
| **2.Do you feel foreign Body sensation?** | 0 | 1 | 2 | 3 | 4 |
| **3. Do you feel your vision get masked during reading and Writing?** | 0 | 1 | 2 | 3 | 4 |
| **4. Are your eyes painful?** | 0 | 1 | 2 | 3 | 4 |
| **5. Do you have any Difficulty in reading?** | 0 | 1 | 2 | 3 | 4 |
| **6.Do you have any difficulty in watching TV and mobiles?** | 0 | 1 | 2 | 3 | 4 |
| **7. Do you have difficulty working with a Computer?** | 0 | 1 | 2 | 3 | 4 |
| **8.Do you find any difficulty in windy Conditions?** | 0 | 1 | 2 | 3 | 4 |
| **9. Difficulty in hot air Rooms?** | 0 | 1 | 2 | 3 | 4 |
| **10. Difficulty in Air-conditioned rooms?** | 0 | 1 | 2 | 3 | 4 |
| **11. Poor vision during long term work and all Activities?** | 0 | 1 | 2 | 3 | 4 |
| **12. Do you have blurred vision which has Affected your work?** | 0 | 1 | 2 | 3 | 4 |

- **Severe DED:** Osmolarity >317 mOsm/L

#### 13.1.5. Schirmer test

- **Description:** Measures tear production by evaluating the amount of wetting of filter paper placed in the lower conjunctival sac.
- **Grading:**
  - **Normal:** ≥ 15 mm in 5 min
  - **Mild DED:** 10–14 mm in 5 min
  - **Moderate DED:** 5–9 mm in 5 min
  - **Severe DED:** < 5 mm in 5 min

#### 13.1.6. Meibomian gland dysfunction (MGD) grading

- **Description:** Assesses the function and appearance of meibomian glands.
- **Grading:**
  - **Grade 0:** Normal meibomian glands
  - **Grade 1:** Mild obstruction with some reduced quality of secretions
  - **Grade 2:** Moderate obstruction with significant reduction in secretion quality
  - **Grade 3:** Severe obstruction with extensive gland atrophy and very poor secretion quality

#### 13.1.7. Corneal dellen and epithelial damage

- **Description:** Assessed through slit-lamp examination to detect corneal thinning or epithelial erosions.
- **Grading:**
  - **Normal:** No corneal dellen or epithelial damage
  - **Mild DED:** Minor dellen or scattered epithelial erosions
  - **Moderate DED:** More pronounced dellen or larger areas of epithelial damage
  - **Severe DED:** Extensive dellen or significant corneal damage

## 14. Combined scoring and grading approach

In clinical practice, a comprehensive assessment of DED often combines various scoring and grading methods to provide a complete picture of the condition. For example.

### 14.1. Initial evaluation

- **Symptom Assessment:** Use questionnaires like OSDI to evaluate symptom severity.
- **Clinical Tests:** Perform TBUT, Schirmer test, and fluorescein staining to assess tear film stability and ocular surface damage.

### 14.2. Grading and interpretation

- **Symptom Severity:** Based on questionnaire scores.
- **Clinical Findings:** Combine results from TBUT, tear osmolarity, staining, and other tests to grade the severity.

### 14.3. Treatment planning

- **Mild DED:** Typically involves artificial tears and lifestyle modifications.
- **Moderate DED:** May include more advanced treatments such as prescription eye drops or punctal plugs.
- **Severe DED:** Often requires aggressive management, including possible surgical interventions or biologic therapies.

By integrating symptom questionnaires with objective clinical assessments, healthcare providers can more accurately diagnose the severity of DED and develop a personalized treatment plan.

## 15. Occular surface scoring index (OSDI) for dry eyes

Give or ask the following questionnaire to the suspected patients depending upon the score helps in judging the patients with the severity of dry eyes, higher the score severity is more, lower the score severity is manageable (Table 1).

### 15.1. Evaluating the OSDI score

The OSDI is assessed on a scale of 0–100, with higher scores representing greater disability. The index demonstrates sensitivity and specificity in distinguishing between normal subjects and patients with dry eye disease. The OSDI is a valuable and reliable instrument for measuring dry eye disease severity and helps in grading normal mild dry eyes, moderate and severe dry eyes and the need for interventions.

## 16. Diagnostic approaches

In DED Corneal nerve dysfunction can be diagnosed using techniques such as corneal confocal microscopy, which allows for the visualization of corneal nerves, assessing their density, morphology, and potential damage. Findings typically include reduced nerve density or abnormal nerve morphology, indicative of dysfunction. Sensory testing, which evaluates the cornea's response to mechanical or chemical stimuli, can also help identify altered sensory responses and contribute to the overall assessment of nerve dysfunction in DED (Liu et al., 2024).

### *16.1. Investigating Dry Eye Disease (DED)*

Investigating Dry Eye Disease (DED) involves a comprehensive approach to accurately diagnose the condition, assess its severity, and determine the underlying causes. Various diagnostic tests and evaluations are used to gather information about tear production, ocular surface health, and the presence of inflammation. Here's an overview of the key investigations used in DED.

### *16.2. Tear film assessment*

#### *16.2.1. Tear break-up time (TBUT)*

- **Purpose:** Measures the stability of the tear film by assessing the time it takes for dry spots to appear after a blink.
- **Procedure:** Fluorescein dye is applied to the eye, and the time until the first dry spot appears is recorded.

#### *16.2.2. Tear Osmolarity Testing*

- **Purpose:** Measures the concentration of solutes in tears to assess tear film stability and dehydration.
- **Procedure:** A small sample of tear fluid is collected and analyzed using an osmometer.

#### *16.2.3. Schirmer's test*

- **Purpose:** Measures tear production by assessing the wetting of a standardized strip of paper placed in the lower conjunctival sac.
- **Procedure:** Paper strips are placed in the lower eyelid, and the amount of moisture absorbed over a set time is measured.

### *16.3. Ocular surface evaluation*

#### *16.3.1. Slit lamp examination*

- **Purpose:** Provides a detailed view of the ocular surface, including the cornea, conjunctiva, and lids, to identify signs of dryness and damage.
- **Procedure:** A specialized microscope is used to examine the eye with and without the use of dye.

#### *16.3.2. Corneal staining*

- **Purpose:** Detects damage to the corneal epithelium and evaluates the extent of dryness.
- **Procedure:** Fluorescein dye is applied to the eye, and the staining patterns are observed using a slit lamp.

#### *16.3.3. Lissamine green and rose Bengal staining*

- **Purpose:** Assesses damage to the conjunctival and corneal epithelium.
- **Procedure:** These dyes stain damaged or devitalized cells, highlighting areas of ocular surface damage.

### *16.4. Meibomian gland evaluation*

#### *16.4.1. Meibography*

- **Purpose:** Visualizes the structure and function of meibomian glands to assess for meibomian gland dysfunction (MGD).
- **Procedure:** Imaging techniques such as infrared meibography are used to view the meibomian glands.

#### *16.4.2. Meibomian gland expression*

- **Purpose:** Assesses the quality and quantity of meibomian gland secretions.
- **Procedure:** Gentle pressure is applied to the eyelid to express meibomian gland secretions, which are then analyzed for consistency and quantity.

### *16.5. Inflammatory marker testing*

#### *16.5.1. Tear fluid analysis for inflammatory markers*

- **Purpose:** Detects the presence of inflammatory mediators in tear fluid, such as matrix metalloproteinase-9 (MMP-9).
- **Procedure:** Tear samples are analyzed for inflammatory markers using various assays.

#### *16.5.2. Conjunctival Biopsy*

- **Purpose:** Provides a histological examination of the conjunctival tissue to identify chronic inflammation or other pathological changes.
- **Procedure:** A small sample of conjunctival tissue is collected and analyzed microscopically.

### *16.6. Advanced imaging techniques*

#### *16.6.1. Corneal confocal microscopy*

- **Purpose:** Provides high-resolution images of corneal nerves and other corneal structures to assess nerve density and integrity.
- **Procedure:** A confocal microscope is used to capture detailed images of the cornea.

#### *16.6.2. Ocular surface thermography*

- **Purpose:** Measures the temperature of the ocular surface to evaluate tear film stability and detect abnormalities.
- **Procedure:** Infrared thermography is used to record temperature variations across the ocular surface.

### *16.7. Genetic and biomarker analysis*

Genetic and biomarker analysis helps identify risk factors, diagnose DED, and guide personalized treatments.

#### *16.7.1. Genetic analysis*

- **HLA Genes:** Linked to autoimmune-related DED (e.g., Sjögren's syndrome).
- **Inflammatory Genes (TNF-α, IL-6, IL-17):** Variants increase susceptibility to chronic inflammation.
- **Aquaporin (AQP5) Genes:** Affect tear secretion and tear film stability.
- **Meibomian Gland Function Genes:** Influence lipid metabolism, impacting evaporative DED.

#### 16.7.2. Biomarker analysis

- **Inflammatory Markers:** Elevated MMP-9, IL-6, TNF-α indicate ocular surface inflammation.
- **Oxidative Stress Markers:** High ROS, low SOD/GPx suggest oxidative damage.
- **Tear Film Proteins:** Lactoferrin, lysozyme, lipocalin-1 changes reflect tear instability.
- **Neuropathic Pain Markers:** Substance P, CGRP linked to ocular discomfort.

#### 16.7.3. Clinical relevance

- **Early Diagnosis:** Biomarkers detect DED before severe damage occurs.
- **Personalized Treatment:** Genetic profiling aids targeted therapies.
- **Monitoring Progression:** Biomarker tracking optimizes treatment efficacy.

## 17. Novel investigation technologies

Innovative technologies in the investigation of Dry Eye Disease (DED) have significantly advanced the ability to diagnose and understand the condition. Here are some cutting-edge technologies and methods that are shaping the future of DED diagnosis.

### 17.1. Advanced imaging techniques

#### 17.1.1. Optical coherence tomography (OCT)

- **Innovation: Enhanced** with swept-source OCT and anterior segment OCT, these technologies offer high-resolution cross-sectional images of the cornea, tear meniscus, and conjunctiva. They allow detailed assessment of tear film dynamics, corneal structure, and changes in the ocular surface.

#### 17.1.2. Confocal microscopy

- **Innovation:** In vivo confocal microscopy provides high-resolution images of corneal nerves and epithelial cells. Recent advancements enable detailed visualization of nerve density, which helps in assessing neuropathic pain and corneal damage.

#### 17.1.3. Ocular surface thermography

- **Innovation:** This non-invasive technique uses infrared imaging to measure temperature variations across the ocular surface, identifying areas of inflammation and assessing tear film stability.

### 17.2. Tear film analysis

#### 17.2.1. Tear Osmolarity Testing

- **Innovation:** New tear osmometer devices offer rapid and precise measurements of tear osmolarity, providing critical information on tear film stability and diagnosing dry eye more accurately.
- **Advanced Tear break-up Time (TBUT) Devices:**
  - **Innovation:** Modern TBUT devices use high-speed video and digital imaging to measure tear break-up time with greater precision, offering a clearer picture of tear film stability.

### 17.3. Biomarker and genetic analysis

#### 17.3.1. Molecular biomarkers

- **Innovation:** Advanced assays and multiplexed biomarker tests detect specific inflammatory mediators and proteins, such as matrix metalloproteinase-9 (MMP-9), in tear fluid. These biomarkers help gauge the level of inflammation and disease severity.

#### 17.3.2. Genomic and epigenetic profiling

- **Innovation:** High-throughput sequencing and epigenetic technologies analyze genetic and epigenetic factors influencing dry eye susceptibility. These tools identify genetic predispositions and epigenetic modifications that contribute to the disease.

### 17.4. Artificial intelligence (AI) and machine learning

#### 17.4.1. AI-enhanced diagnostics

- **Innovation:** AI algorithms analyze imaging data from optical coherence tomography (OCT), confocal microscopy, and other sources to detect patterns and anomalies associated with DED. Machine learning models predict disease progression and tailor personalized treatment strategies.

#### 17.4.2. Automated tear film analysis

- **Innovation:** AI-driven platforms provide automated and objective measurements of tear film parameters, such as break-up time and osmolarity, ensuring consistent and accurate diagnostics.

### 17.5. Wearable technologies

#### 17.5.1. Smart contact lenses

- **Innovation:** Contact lenses equipped with embedded sensors monitor tear film properties, temperature, and other metrics in real-time (Midhila. et al., 2023). They offer continuous data on ocular surface health and tear production.

#### 17.5.2. Wearable ocular monitors

- **Innovation:** Devices that track environmental factors, blinking patterns, and tear production provide comprehensive data on how lifestyle and environment impact dry eye symptoms.

### 17.6. Integrated diagnostic platforms

#### 17.6.1. Multi-modal diagnostic systems

- **Innovation:** Integrated systems combine various diagnostic tests, such as tear film analysis, imaging, and inflammatory marker testing, into a single platform. These systems streamline the diagnostic process and provide a holistic view of DED.

### 17.7. Novel functional tests

#### 17.7.1. Blink rate and pattern analysis

- **Innovation:** New technologies analyze blinking patterns and frequency using digital imaging and sensors. This helps assess how blinking behaviour affects tear film stability and ocular surface health.

#### 17.7.2. Non-invasive tear break-up time (NIBUT) devices

- **Innovation:** Advanced non-invasive methods measure the tear break-up time without using dyes, providing a more comfortable and objective assessment of tear film stability.

These innovative technologies enhance the precision of DED diagnosis, improve the understanding of its underlying mechanisms, and facilitate personalized treatment approaches. By incorporating these advancements into clinical practice, healthcare providers can better manage dry eye symptoms and improve patient outcomes.

## 18. Treatment modalities for dry eye disease (DED)

### 18.1. Pharmacological therapies

#### 18.1.1. Anti-inflammatory medications

- **Usage:** These medications are used to reduce inflammation on the ocular surface. They can be used for both short-term and long-term treatment, depending on the severity of the condition.

#### 18.1.2. Secretagogues

- **Usage:** These agents stimulate the production of natural tears to help maintain moisture on the eye surface.

#### 18.1.3. Autologous serum eye drops

- **Usage:** Created from a patient's own blood, these drops contain essential growth factors and nutrients that aid in healing and increasing tear production.

### 18.2. Innovative devices and procedures

#### 18.2.1. Punctal plugs

- **Usage:** Small devices inserted into the tear ducts to block drainage and help retain tears on the eye surface. They can be temporary or permanent.

#### 18.2.2. Thermal pulsation devices

- **Usage:** These devices apply controlled heat and pressure to the eyelids to treat meibomian gland dysfunction, which is a common cause of dry eye.

#### 18.2.3. Meibomian gland expression

- **Usage:** This procedure involves manually or mechanically expressing the meibomian glands to release clogged secretions, improving the quality of the tear film.

### 18.3. Lifestyle and environmental modifications

#### 18.3.1. Use of humidifiers

- **Usage:** Adding moisture to the air can help reduce tear evaporation and maintain eye hydration.

#### 18.3.2. Blinking exercises

- **Usage:** Encouraging regular, complete blinking helps spread tears evenly across the ocular surface, reducing dryness.

#### 18.3.3. Screen break strategies

- **Usage:** Implementing regular breaks from screen time can reduce eye strain and encourage more frequent blinking.

### 18.4. Nutritional supplements

#### 18.4.1. Omega-3 fatty acids

- **Usage:** These supplements can help reduce inflammation and support tear production, contributing to better eye health.

#### 18.4.2. Antioxidants

- **Usage:** Consuming antioxidants helps protect ocular surface cells from oxidative stress and supports overall eye health.

### 18.5. Innovative treatment modalities

#### 18.5.1. New pharmacological agents

- **Development:** Research is focused on developing new drugs that target novel pathways involved in DED. These agents aim to provide more effective and targeted treatment options.

#### 18.5.2. Regenerative medicine

- **Stem Cell Therapy:**
  - **Usage:** This approach uses stem cells to regenerate damaged cells on the ocular surface, offering a potential long-term solution for severe cases of dry eye.

#### 18.5.3. Biologic treatments

- **Usage:** These treatments involve using biologic agents to inhibit specific inflammatory pathways, reducing inflammation and promoting healing.

### 18.6. Emerging research and future directions

#### 18.6.1. Gene therapy

- **Potential:** Aimed at targeting genetic causes of DED, gene therapy could offer long-term solutions by addressing the root causes at the genetic level.

#### 18.6.2. Microbiome studies

- **Impact:** Research into the ocular surface microbiome is providing new insights into how microbial balance affects dry eye, leading to potential microbiome-targeted therapies.

#### 18.6.3. AI and machine learning

- **Usage:** AI is advanced technologies (Kuppan et al., 2024), that can enhance diagnostic accuracy and enable personalized treatment plans through the analysis of large datasets and predictive modeling.

### 18.7. Clinical implications

- **Integration of New Treatments:** Adapting advanced therapies into everyday clinical practice to improve patient outcomes.
- **Personalized Medicine:** Customizing treatment plans based on individual patient profiles, including genetic and biomarker information.

- **Patient Education:** Stressing the importance of lifestyle modifications and adherence to prescribed treatments to manage symptoms effectively.

## 19. Pediatric Dry Eye Disease (DED) and treatment

Pediatric Dry Eye Disease (DED) presents unique challenges compared to its manifestation in adults, necessitating a tailored approach to care that takes into account the distinct developmental needs of children. Although less prevalent in the pediatric population, DED can arise from a variety of factors including environmental influences, prolonged exposure to screens, underlying systemic diseases, and congenital anomalies. Effective management of pediatric DED requires a multifaceted treatment strategy encompassing pharmacological therapies, innovative interventions, lifestyle adjustments, providing good nutritive supplements rich in vitamin, antioxidants (Srinivasan et al., 2024), minerals, fatty acids and ongoing monitoring (Rojas-Carabali et al., 2024).

### *19.1. Pharmacological therapies*

The cornerstone of pediatric DED treatment often involves the use of anti-inflammatory medications and lubricating eye drops designed to reduce inflammation and maintain adequate ocular moisture and suitable nutritional supplements. Given the sensitive nature of treating children, it is crucial that pediatric-specific formulations and dosages be administered under the close supervision of a healthcare professional. In cases where bacterial infections or blepharitis are contributing factors, antibiotic ointments may be prescribed to target the underlying infection and alleviate associated symptoms.

### *19.2. Innovative devices and procedures*

In more persistent cases of DED, specialized devices and procedures may be employed. Punctal plugs, for instance, can be temporarily inserted to block tear drainage, thereby enhancing tear retention on the ocular surface. Another procedural option is meibomian gland expression, which involves manually clearing obstructions in the glands to improve the quality of the tear film and reduce symptoms of dryness.

### *19.3. Lifestyle and environmental modifications*

Environmental control plays a significant role in managing pediatric DED. The use of humidifiers in living spaces can help maintain ambient moisture levels, reducing tear evaporation. Additionally, managing screen time is critical; adhering to the 20-20-20 rule encouraging children to look at something 20 feet away for 20 s every 20 min can significantly mitigate eye strain and prevent dryness. Maintaining proper eyelid hygiene, particularly in cases of blepharitis, is also essential. Gentle cleaning of the eyelids can prevent the buildup of debris and reduce the risk of infection-related dry eye symptoms.

### *19.4. Nutritional supplements*

Nutrition is another important aspect of DED management. Omega-3 fatty acids, either through diet or supplements, have been shown to reduce inflammation and support tear production. Pediatric patients should receive appropriate doses tailored to their age and nutritional needs, ensuring safe and effective supplementation.

### *19.5. Educational and behavioral interventions*

Education is a vital component of managing pediatric DED. Parents and caregivers should be well-informed about the condition, the importance of treatment adherence, and how to recognize symptom triggers. Teaching children to blink fully and regularly, for instance, can help distribute the tear film more evenly across the ocular surface, thereby reducing dryness and discomfort.

### *19.6. Monitoring and follow-up*

Continuous monitoring by an ophthalmologist is crucial in managing pediatric DED. Regular follow-up appointments allow for the assessment of treatment efficacy, adjustment of therapeutic strategies, and the early detection of any changes in the condition. This proactive approach ensures that children receive the best possible care, promoting long-term eye health and overall well-being.

In summary, the treatment of Pediatric DED requires a comprehensive approach that integrates pharmacological therapies, innovative devices and procedures, lifestyle and environmental modifications, nutritional support, and continuous education and follow-up. By addressing the multifactorial nature of DED in children, healthcare providers can effectively alleviate symptoms, improve ocular health, and enhance the quality of life for pediatric patients.

## 20. Conclusion

Dry Eye Disease (DED) is a complex condition affecting individuals of all ages, with advancements in understanding its mechanisms, diagnostic innovations, and treatment modalities offering hope for improved management. The condition involves tear film instability, inflammatory pathways, neuropathic pain, meibomian gland dysfunction, and the ocular surface microbiome, necessitating a multifactorial approach to treatment.

Diagnostic innovations such as ocular surface thermography, meibography, corneal confocal microscopy, and tear film analysis, along with genetic and biomarker studies, provide detailed insights and enable early detection. Integrating artificial intelligence and machine learning enhances diagnostic accuracy and facilitates personalized treatment strategies.

Current treatments include pharmacological therapies, innovative devices, lifestyle modifications, and nutritional supplements. Anti-inflammatory medications, secretagogues, and autologous serum eye drops address symptoms, while devices like punctal plugs, thermal pulsation devices, and meibomian gland expression provide targeted relief. Lifestyle changes and supplements, particularly omega-3 fatty acids and antioxidants, support ocular health and reduce inflammation. Emerging treatments such as new pharmacological agents, regenerative medicine, and biologic therapies show significant promise.

Looking ahead, research holds promise for breakthroughs in gene therapy and microbiome-targeted treatments. Advances in AI and machine learning will continue to refine diagnostics and personalized care. Additionally, exploring systemic disease links and assessing long-term outcomes will be crucial. A holistic, personalized approach will be essential for improving patient outcomes. Continued innovation and research are expected to yield more effective therapies, enhancing the management of this chronic condition.

### *20.1. Future directions*

Future research should focus on elucidating the precise mechanisms underlying corneal nerve damage in DED and exploring innovative treatments that target nerve regeneration and pain modulation. A deeper understanding of these processes is essential for developing targeted therapies that address both the sensory and inflammatory aspects of DED, ultimately improving patient outcomes (Lv, Z. et al., 2024). Artificial intelligence (AI), Internet of things (IOT) (Midhila et al., 2023 ),Nanotechnology (Adur, A. J. et al., 2025) based medications and Telemedicine would further benefit the patient and these can be explored.

## CRediT authorship contribution statement

**K. Narendra:** Writing – original draft, Investigation, Conceptualization. **Sonali K. Singh:** Writing – review & editing, Software, Resources, Methodology, Investigation, Formal analysis, Data curation. **C. K. Deepa:** Writing – review & editing, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation. **S. Meghana:** Writing – review & editing, Visualization, Validation, Supervision, Investigation, Conceptualization. **K.R. Akanth:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Investigation, Formal analysis, Data curation. **M. Manjushree:** Writing – original draft, Conceptualization. **D. Raajasubramaniyan:** Visualization, Validation, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis. **S. Srinivasan:** Software, Resources, Investigation, Funding acquisition, Formal analysis, Data curation. **R. Murali:** Visualization, Validation, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. **H.N. Sowbhagya:** Writing – review & editing, Visualization, Validation, Supervision, Data curation, Conceptualization.

## Ethical approval

All authors have read, understood, and have complied as applicable with the statement on "Ethical responsibilities of Authors" as found in the Instructions for Authors.

## Availability of data and materials

All data generated or analyzed during this study are included in this published article. Furthermore, the data supporting this study's findings are available on request with the **H.N.Sowbhagya.** Email Id: drsowbhagyaaooaji@gmail.com.

## Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used Chatgpt in order to restructure certain sentences for better articulation. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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