Inflammation in dry eye disease: From pathogenesis to promising therapeutic avenues

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Abstract

Tear film dysfunction is a unifying characteristic of dry eye disease (DED), propelled by an intricate interplay of intrinsic and extrinsic drivers. This article explores the complex pathophysiology of tear film instability, including abnormalities in the lipid, aqueous, and mucin layers. The involvement of inflammation and neurosensory changes in disease pathology is also discussed. Current and future therapeutic modalities are addressed, emphasizing targeted therapies designed to restore tear film homeostasis and enhance patient outcomes in managing DED.

Keywords: Tear film dysfunction, ocular inflammation, pro-inflammatory cytokines, dry eye disease

1. Introduction

Dry Eye Disease (DED) is a common, multifactorial illness characterised by tear film instability leading to visual disturbances and eye discomfort, and largely affecting quality of life. Initially considered trivial, DED today is recognized as a condition entailing hyperosmolarity, inflammation, and neurosensory abnormality. The tear film is the eye's vital environmental interface, maintaining corneal lubrication, clarity, and immunological protection. The increasing worldwide prevalence of DED is attributed to aging, environmental stress, and the use of digital devices. This review discusses the pathophysiology, triggering factors, and treatment options for DED and emphasizes the latest research breakthroughs and new strategies to enhance patient outcomes.

2. Pathophysiology of DED

The progression and severity of DED are greatly affected by the inflammation that is a component of the pathophysiology of this condition. Either decreased tear secretion (aqueous-deficient dry eye) or elevated tear evaporation (evaporative dry eye) is the typical etiology of dry eye, and results in hyperosmolarity and instability of the tear film (1). These ocular surface epithelial cells are under stress due to tear hyperosmolarity, which leads them to produce pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6). Dendritic cells and CD4+ T lymphocytes, particularly the Th1 and Th17 subsets, are some of the immune cells that are attracted and activated by the inflammatory cascade initiated by these cytokines. These activated T cells secrete more pro-inflammatory cytokines, such as interleukin-17 (IL-17) and interferon-gamma (IFN-γ), that reduce tear film stability, inhibit mucin formation, and further damage the ocular surface by inducing loss of goblet cells (2). The underlying immunoinflammatory mechanisms in the pathophysiology of the eye are illustrated in Figure 1.

In addition, the barrier function of the cornea is disrupted, epithelial tight junction proteins are degraded, and further damage to the epithelium is induced by inflammatory mediator-induced upregulation of enzymes like matrix metalloproteinase-9 (MMP-9). The outcome is a cycle of escalating inflammation, unstable tear film, and ocular surface injury. The injured sensory nerves release neuropeptides like substance P and calcitonin gene-related peptide (CGRP), which induce vasodilation, recruitment of immune cells, and cytokine release (2,3). Inflammation eventually extends to the lacrimal glands, impairing their ability to produce tears. The chronic inflammation ultimately leads to a self-perpetuating cycle in which immunological activation, damage to the epithelium, and tear deficiency reinforce each other. This cycle explains the progressive and chronic nature of DED and highlights the importance of anti-inflammatory therapies such as lifitegrast, corticosteroids, and cyclosporine in managing the disease and restoring ocular surface homeostasis (3).

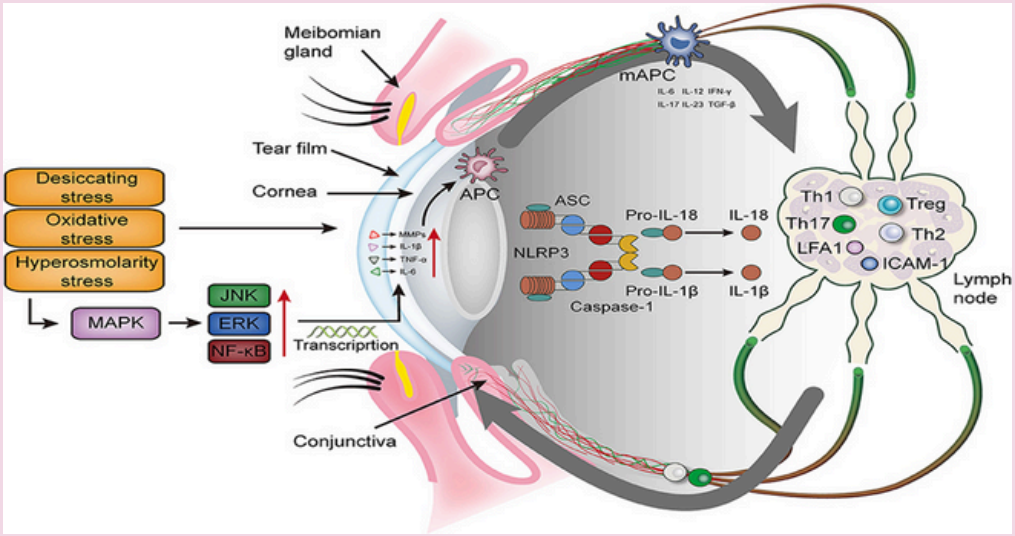

Figure 1. Immunoinflammatory mechanisms in dry eye disease (4)

3. Triggers of tear film dysfunction

The tear film, crucial for healthy eyes, can be compromised by a variety of influences, leading to dry eye (5) (Table 1). Systemic diseases like Sjögren's syndrome, rheumatoid arthritis, and lupus are known conditions, as are specific drugs like antihistamines and diuretics. Environmental factors like low humidity and prolonged screen time can also contribute in tear film failure (6).

Table 1. Triggers of tear film dysfunction

S. No.	Risk factors for dry eye disease	Description	Ref
1.	Meibomian gland dysfunction (MGD)	MGD is a prevalent cause of dry eye and results from the meibomian glands (located in the eyelids) secreting too little or altered oil, which is critical for the tear film's lipid layer.	(7)
2.	Autoimmune diseases	Rheumatoid arthritis, lupus, sarcoidosis, and Sjögren's syndrome are autoimmune diseases that can harm the tear glands and decrease their ability to produce tears.	(8)
3.	Medications	Several drugs, including diuretics, antihistamines, and antidepressants, can decrease tear production.	(9)

4.	Environmental factors	Dry or windy conditions may cause more tears to evaporate. Smoky atmospheres: Irritants may lead to dry eye by damaging the surface of the eyes.	(10)
5.	Aging	The tear ducts may constrict or obstruct as people age, resulting in excessive tears.	(11)
6.	Hormonal changes	Tear production may be affected by hormonal changes that occur during menopause, pregnancy, or thyroid disorders.	(12)
7.	Contact lens wear	Contact lenses can damage the tear film.	(13)
8.	Infrequent blinking	Blinking infrequently, such as while looking at displays, causes evaporation to rise and tear film stability to decrease, leading to tear film dysfunction.	(14)
9.	Eye surgery	A specific kind of eye surgery may impact tear film stability.	(15)
10.	Neurologic conditions	Tear film dysfunction or dry eye can result from neurological disorders that interfere with the tear film.	(16)

4. Therapeutic strategies for dry eye disease

Therapeutic approaches to DED focus on restoring tear film stability, diminishing inflammation, and alleviating symptoms (17). Therapy involves artificial tears, punctal occlusion, anti-inflammatory medications such as cyclosporine, and treatment of meibomian gland disease. New therapies include autologous serum, platelet-rich plasma, and surgery, with new biologics and gene therapies representing potential for the future (18). Some of the current therapeutic approaches are presented in Table 2.

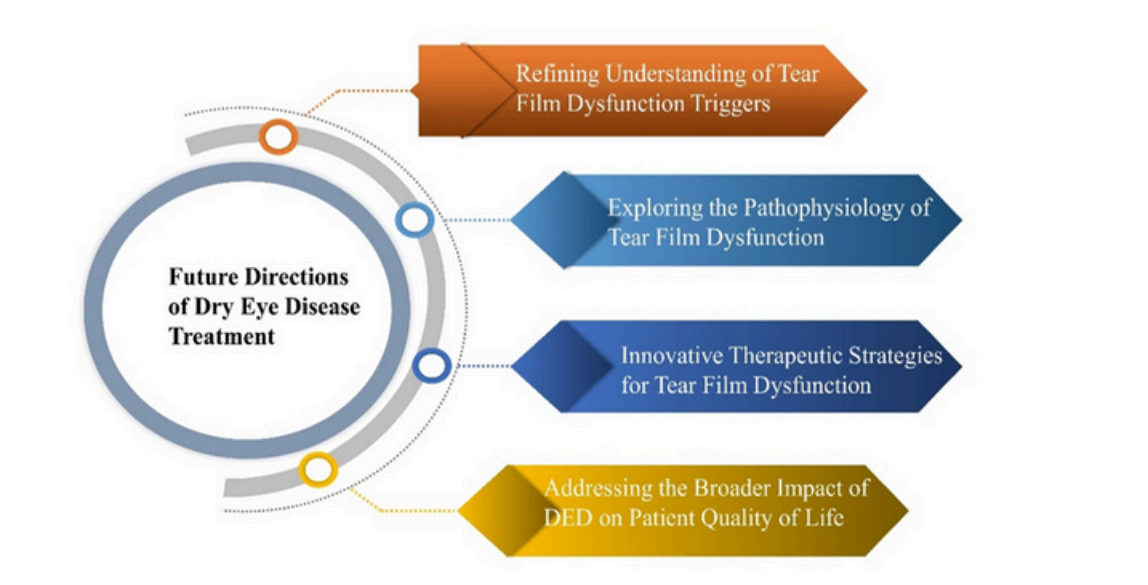

Figure 2. Future direction and research gaps of dry eye disease treatment

Table 2. An overview of therapeutic strategies for dry eye disease

S. No.	Therapy Class	Examples	Mechanism of Action	Ref
1.	Anti-inflammatory agents	Cyclosporine A, Lifitegrast, Corticosteroids	Suppress T-cell activation, prevent the production of cytokines, and stop the interaction between LFA-1 and ICAM-1	(19)
2.	Immunomodulatory agents	Tacrolimus, Anakinra	Calcineurin inhibitor (Tacrolimus); IL-1 receptor antagonist (Anakinra)	(20)
3.	Lubricants (Artificial tears)	Carboxymethyl-cellulose, Hyaluronic acid	Stabilization of tear films; mechanical protection	(21)
4.	Secretagogues	Diquafosol,Pilocarpine	Stimulate aqueous and mucin secretion via P2Y2 receptors (Diquafosol)	(22)
5.	MMP inhibitors	Doxycycline (low-dose oral)	MMP-9 inhibition and anti-inflammatory properties	(23)
6.	Biologic agents	Autologous serum, Platelet-rich plasma	Provide growth factors and mediators that reduce inflammation	(24)
7.	Punctal occlusion	Plastic plugs/Silicone	Decrease tear leakage and improve tear retention	(25)
8.	Thermal pulsation / Lid hygiene	Lipi Flow, Warm compresses	Boost meibomian gland activity and lower evaporative DED	(26)
9.	Novel therapies	RGN-259 (Thymosin β4), Mesenchymal stem cells	Promote the repair of epithelium; reduce inflammation	(27)
10.	Adjunctive measures	Omega-3 supplements, Environmental modifications	Anti-inflammatory dietary support; reduce evaporative stress	(28)

5. Conclusion

In recent years, the understanding of DED has evolved beyond the traditional view of DED as merely a deficiency in tear production, and studies have established that inflammation is a central component in its pathogenesis. Elucidating the initiating factors, developing further understanding of mechanisms underlying inflammation and tear film dysfunction, and formulating novel treatment strategies that specifically address the fundamental causes of the disease should remain the primary research objectives. From identifying triggers and clarifying the pathophysiological mechanisms to designing

more specialized and effective treatment strategies, future research on DED is to bridge the gaps in tear film failure knowledge (Figure 2). In moving the field forward, a multidisciplinary approach involving immunology, regenerative medicine, molecular biology, and personalization of therapy will be necessary. Additionally, improving diagnostic procedures and expanding investigations into the extended impact of DED will ultimately lead to better patient outcomes, improved quality of life, and more effective management of this incapacitating condition.

References

1. Harrell CR, Feulner L, Djonov V, Pavlovic D, Volarevic V. The Molecular Mechanisms Responsible for Tear Hyperosmolarity-Induced Pathological Changes in the Eyes of Dry Eye Disease Patients. Cells. 2023 Dec 1;12(23):2755.
2. Periman LM, Perez VL, Saban DR, Lin MC, Neri P. The immunological basis of dry eye disease and current topical treatment options. Journal of ocular pharmacology and therapeutics. 2020 Apr 1;36(3):137-46.
3. Bhujel B, Oh SH, Kim CM, Yoon YJ, Chung HS, Ye EA, Lee H, Kim JY. Current Advances in Regenerative Strategies for Dry Eye Diseases: A Comprehensive Review. Bioengineering. 2023 Dec 29;11(1):39.
4. Ling J, Chan BC, Tsang MS, Gao X, Leung PC, Lam CW, Hu JM, Wong CK. Current advances in mechanisms and treatment of dry eye disease: toward anti-inflammatory and immunomodulatory therapy and traditional Chinese medicine. Frontiers in Medicine. 2022 Jan 17;8:815075
5. Abed EK, Abbood AA. Risk Factors and Management Strategies for Dry Eye Syndrome: A Comparative Study. Sriwijaya Journal of Ophthalmology. 2024 Jul 29;7(2):333-44.
6. Kwon J, Moghtader A, Kang C, Bibak Bejandi Z, Shahjahan S, Alzein A, Djalilian AR. Overview of Dry Eye Disease for Primary Care Physicians. Medicina. 2025 Mar 6;61(3):460.
7. Sheppard JD, Nichols KK. Dry eye disease associated with meibomian gland dysfunction: focus on tear film characteristics and the therapeutic landscape. Ophthalmology and therapy. 2023 Jun;12(3):1397-418.
8. Shan H, Liu W, Li Y, Pang K. The autoimmune rheumatic disease related dry eye and its association with retinopathy. Biomolecules. 2023 Apr 23;13(5):724.
9. Guo M, Diaz GM, Yu Y, Patel CA, Farrar JT, Asbell PA, Ying GS, Assessment DE, Management Study Research Group. Association between systemic medication use and severity of dry eye signs and symptoms in the DRy eye assessment and management (DREAM) study. The Ocular Surface. 2024 Apr 1;32:112-9.
10. Patel S, Mittal R, Kumar N, Galor A. The environment and dry eye manifestations, mechanisms, and more. Frontiers in toxicology. 2023 Aug 23;5:1173683.
11. Fan M, Hung JL, Hung SH, Chen LC, Horng CT. Improvement of Presbyopia, Dry Eye, Intraocular Pressure, and Near Vision Through Cassiae Tea Consumption. Medicina. 2024 Dec 29;61(1):35.
12. Kaštelan S, Hat K, Tomić Z, Matejić T, Gotovac N. Sex Differences in the Lacrimal Gland: Implications for Dry Eye Disease. International Journal of Molecular Sciences. 2025 Apr 18;26(8):3833.
13. Kareem M, Agbaje T, Alam F, Butt H. A review of thin films used in smart contact lenses. Advanced Engineering Materials. 2024 Feb;26(4):2300363.
14. Romeo MA, Coco G, Taloni A, Carnovale-Scalzo G, Scorcia V, Giannaccare G. Digital Applications for Videoterminal-Associated Dry Eye Disease. Vision. 2024 Nov 28;8(4):67.
15. Pac CP, Munteanu M, Sánchez-González JM, Rocha-de-Lossada C, Mercea N, Ferrari F, Stanca HT, Cosnita DA, Ionica M, Boruga O, Danielescu C. Long-Term Impacts of Intense Pulsed Light Therapy on Ocular Surface Health and Tear Film Dynamics in Patients with Dry Eye Disease: Detailed Analysis and Observations Over a 1-Year Follow-Up Period. Ophthalmology and Therapy. 2024 Oct;13(10):2715-30.
16. Luib E, Demleitner AF, Cordts I, Westenberg E, Rau P, Pürner D, Haller B, Lingor P. Reduced tear fluid production in neurological diseases: A cohort study in 708 patients. Journal of neurology. 2024 Apr;271(4):1824-36.
17. Sheppard J, Shen Lee B, Periman LM. Dry eye disease: identification and therapeutic strategies for primary care clinicians and clinical specialists. Annals of medicine. 2023 Dec 31;55(1):241-52.
18. Suleman A, Aluyi-Osa G, Ashipa F, Spadea L, Gagliano C, D'Esposito F, Zeppieri M, Musa M. Autologous blood in the management of ocular surface disorders. World Journal of Experimental Medicine. 2024 Dec 20;14(4):96412.
19. Huang D, Li Z. Multidimensional immunotherapy for dry eye disease: current status and future directions. Frontiers in Ophthalmology. 2024 Nov 1;4:1449283.
20. Sahay P, Kumawat D. An Overview of Topical Immunomodulators used in Ophthalmology. Delhi Journal of Ophthalmology. 2022 Jan 1;32(3):104-10.
21. Aragona P, Benítez-del-Castillo JM, Coroneo MT, Mukherji S, Tan J, Vandewalle E, Vingrys A, Liu H, Carlisle-Wilcox C, Vehige J, Simmons PA. Safety and efficacy of a preservative-free artificial tear containing carboxymethylcellulose and hyaluronic acid for dry eye disease: a randomized, controlled, multicenter 3-month study. Clinical Ophthalmology. 2020 Oct 1:2951-63.
22. Tan CQ, Wu D, Toh XY, Lim BX, Shih KC, Tong L, Lim CH. Applications of Diquafosol Sodium in Ophthalmology: A Comprehensive Review of Therapeutic Utility. Life. 2025 Mar 17;15(3):484.
23. Perez VL, Mah FS, Willcox M, Pflugfelder S. Anti-inflammatories in the treatment of dry eye disease: a review. Journal of ocular pharmacology and therapeutics. 2023 Mar 1;39(2):89-101.
24. Metheetrairut C, Ngowyutagon P, Tunganuntarat A, Khowawisetsut L, Kittisares K, Prabhasawat P. Comparison of epitheliotrophic factors in platelet-rich plasma versus autologous serum and their treatment efficacy in dry eye disease. Scientific reports. 2022 May 26;12(1):8906.
25. Singh RB, Yung A, Coco G, Sinha S, Dohlman TH, Yin J, Dana R. Efficacy and retention of silicone punctal plugs for treatment of dry eye in patients with and without ocular graft-versus-host-disease. The ocular surface. 2020 Oct 1;18(4):731-5.
26. Blackie CA, Murakami D, Donnenfeld E, Oliff HS. Vectored thermal pulsation as a treatment for meibomian gland dysfunction: a review spanning 15 years. Ophthalmology and Therapy. 2024 Aug;13(8):2083-123.
27. Sosne G, Kleinman HK, Springs C, Gross RH, Sung J, Kang S. 0.1% RGN-259 (thymosin ß4) ophthalmic solution promotes healing and improves comfort in neurotrophic keratopathy patients in a randomized, placebo-controlled, double-masked phase III clinical trial. International Journal of Molecular Sciences. 2022 Dec 29;24(1):554.
28. Cong Y, Zhang Y, Han Y, Wu Y, Wang D, Zhang B. Recommendations for nutritional supplements for dry eye disease: current advances. Frontiers in Pharmacology. 2024 May 30;15:1388787.