

From Cornea to Macula: The Potential Role of Dry Eye–Related Ocular Surface Inflammation in Macular Degeneration

Huini Zhang

Sun Yat-Sen University, Guangzhou, 510000, China

ABSTRACT

Dry eye is a chronic inflammatory disease of the ocular surface caused by shortened tear film rupture time and high osmotic pressure. Macular degeneration, especially AMD, is one of the main causes of blindness worldwide, traditionally believed to be mainly caused by RPE aging, oxidative damage, and choroidal circulation disorders. In recent years, epidemiological and basic research has also suggested that chronic inflammatory reactions on the ocular surface can participate in the occurrence and development of macular degeneration through common inflammatory pathways, oxidative stress amplification effects, and immune regulation disorders. In summary, this article mainly elaborates on the inflammatory pathway from the cornea to the macular area and the possible ways in which inflammatory mediators extend from the ocular surface to the posterior part of the eye. It also provides new ideas for the involvement of ocular surface inflammation caused by dry eye in the treatment of AMD, hoping to help achieve a multi site integrated diagnosis and treatment model for the eye.

KEYWORDS

Dry eyes; Ocular surface inflammation; Macular degeneration; Age-related macular degeneration

1. INTRODUCTION

Dry Eye Disease (DED) is one of the most common diseases in clinic, with a worldwide incidence rate of about 5% -50%, which increases significantly with age. The main pathological basis is the imbalance of tear film homeostasis and the activation of ocular epithelial cells and immune cells by hypertonic tears, which release a large amount of inflammatory factors, causing sustained and low-level chronic ocular inflammatory reactions [1]. Macular degeneration, especially age-related macular degeneration (AMD), is the leading cause of irreversible blindness in the elderly population in developed countries and China. The classic pathological changes of AMD include the formation of choroidal warts, dysfunction of retinal pigment epithelium (RPE) cells, degeneration of photoreceptors, and choroidal neovascularization. The traditional view is that the risk factors for AMD include advanced age, genetic susceptibility, smoking, hypertension, and high-fat diet. However, in recent years, the role of inflammation theory in the pathogenesis of AMD has become increasingly prominent. Dry eye and AMD are both age-related diseases that often coexist in the same elderly patient. In previous clinical practice of ophthalmology, anterior segment diseases and posterior segment diseases were often treated separately. However, the ocular surface is not a closed system, and there are potential biological molecular exchange pathways between tears, cornea, aqueous humor, and vitreous body. Whether sustained ocular surface inflammatory factors will spread to the macula and affect the occurrence and development of AMD is currently one of the hot topics of concern in the ophthalmology community. Here, the author reviews the importance of dry

eye associated ocular surface inflammation in AMD, its possible pathways of action, and prevention and treatment measures [2].

2. CLINICAL SIGNIFICANCE OF OCULAR SURFACE INFLAMMATION AS A POTENTIAL DRIVING FACTOR FOR MACULAR DEGENERATION

For many years, the clinical evaluation and treatment of AMD have focused on the fundus and overlooked the inflammatory damage to the anterior segment, especially the ocular surface. However, in recent years, dry eyes discovered in bed may have a significant correlation with AMD. Firstly, epidemiological investigations have shown that the spectrum of common risk factors for dry eye and AMD is similar [3]. Aging is the strongest independent risk factor for dry eye and AMD. In addition, estrogen, ultraviolet radiation, and mild chronic systemic inflammatory disease (mild elevation of CRP) are all promoting factors for both. A cross-sectional study has found that the detection rate of early AMD (especially a large number of vitreous membrane warts) in patients with moderate to severe dry eye is higher than that in the control group without dry eye, suggesting that ocular surface inflammation may be associated with the formation of subretinal deposits. Secondly, the systemic and local transmission effects of inflammatory burden. Dry eye is not only a local disease, but the inflammatory mediators produced by dry eye (IL-1 β , IL-6, TNF - α , MMP-9) can enter tears, some of which can enter the nasal cavity and systemic circulation through the nasolacrimal duct, and some can diffuse to the posterior segment through the corneal limbal vascular network and aqueous humor circulation. The above-mentioned inflammatory factors were also found to be significantly elevated in the vitreous and retina of AMD patients [4]. Therefore, chronic inflammation originating from ocular surface may promote the occurrence and development of AMD by exacerbating or maintaining a low degree of inflammation in the macular area through the "inflammation spillover" effect. Thirdly, from the perspective of counterevidence in treatment, there is no systematic report on whether some anti-inflammatory drugs used for dry eye treatment (such as cyclosporine A eye drops and levonorgestrel eye drops) will have long-term effects on macular health while relieving ocular surface symptoms. However, there have been case reports indicating that the activity of choroidal neovascularization in AMD patients seems to be lower after long-term control of ocular surface inflammation. Although it cannot explain a causal relationship, it indirectly confirms the existence of the "ocular surface macular inflammation axis" hypothesis. Therefore, recognizing that dry eye related ocular surface inflammation may be a potential pathogenic factor for AMD is of great significance for clinical practice. Firstly, it reminds ophthalmologists to pay attention to evaluating the ocular surface status of AMD patients; Secondly, it provides a new intervention target for early prevention of AMD: starting from ocular surface inflammation to slow down the progression of macular degeneration.

3. POSSIBLE MECHANISMS LINKING DRY EYE RELATED OCULAR SURFACE INFLAMMATION AND MACULAR DEGENERATION

3.1. Transmission Pathways of Inflammatory Signals Between Cornea and Ocular Surface

The cornea is the transparent structure at the forefront of the ocular surface, serving not only as an important optical pathway but also as a crucial gateway for immune inflammatory responses [5]. In dry eye conditions, high tear film osmotic pressure first damages the corneal epithelial barrier function, leading to downregulation of tight junction protein expression in corneal epithelial cells. Damaged corneal epithelial cells can produce DAMPs (damage associated molecular patterns), such as high mobility group protein B1 (HMGB1) and adenosine triphosphate (ATP), to activate

endogenous immune cells (dendritic cells, macrophages) in the corneal margin and central cornea. These activated cells also produce a large amount of chemokines (CCL2 or CCL5) to attract some inflammatory cells in the circulation to the surface of the eye. In addition, more importantly, there are abundant sensory nerves (mainly the ophthalmic branches of the trigeminal nerve) in the cornea. Inflammatory mediators related to dry eyes can stimulate sensory nerve endings to release substance P and calcitonin gene-related peptide (CGRP), causing axonal reflex and exacerbating focal neurogenic inflammatory reactions. The above inflammatory factors can be transmitted to the posterior segment through three pathways: ① through aqueous humor; ② Through the vitreous body; ③ Circulating through the bloodstream to the choroid.

3.2. Diffusion and Action of Inflammatory Mediators in the Posterior Segment of the Eye

Inflammatory factors mainly rely on the convection and diffusion of intraocular fluid from the ocular surface to the macular area. The aqueous humor is secreted by the ciliary body, produced in the posterior chamber, flows into the anterior chamber through the pupil, and then exits from the anterior chamber angle. Inflammatory factors on the surface of the cornea and iris can enter the aqueous humor and circulate with it to the anterior vitreous membrane [6]. Although the blood eye barrier (blood aqueous barrier and blood retinal barrier) can prevent the passive diffusion of large molecules under physiological conditions, chronic ocular surface inflammation can lead to a decrease in the function of the blood aqueous barrier, an increase in permeability, and the entry of small molecule inflammatory factors such as IL-1 β , IL-6, TNF - α into the posterior segment. Previous studies have shown that an increase in inflammatory factors from the ocular surface can be detected in the vitreous of experimental dry eye animals, and after reaching the macular area, the following effects are produced: ① activation of retinal M \ddot{u} ller cells and microglia, leading to their transformation into M1 pro-inflammatory phenotype; ② Inducing the expression of VEGF in RPE and inducing the formation of choroidal neovascularization; ③ Reducing the phagocytic ability of RPE cells leads to increased deposition of debris in the outer segments of photoreceptors and accelerates the formation of vitreous membrane warts.

3.3. Potential Bridging Effect of Oxidative Stress and Immune Regulation

Dry eye and AMD both undergo significant oxidative damage processes and have potential common foundations at the molecular level, indicating a possible connection between the two. In dry eyes, the increased osmotic pressure of tears can directly cause an increase in ROS in the corneal epithelium, leading to the activation of NF-kappa-B and stimulating the secretion of inflammatory cytokines; In addition, the antioxidant substances in the tear film, including vitamin C, transferrin, and SOD, are reduced, resulting in an oxidative antioxidant imbalance. The ROS and oxidative lipid mediators (such as 4-hydroxynonenal, 4-HNE) generated by the ocular surface can reach the retina through the diffusion pathways mentioned above [7]. As one of the cells with the most vigorous metabolism and highest oxidative load in the retina, RPE cells can produce a large amount of ROS through the process of phagocytosis and digestion of photoreceptor outer segments. In addition, exogenous oxidative load from the ocular surface will far exceed the antioxidant reserve capacity of RPE, causing mitochondrial DNA damage and excessive accumulation of lipofuscin, thereby inducing RPE cell apoptosis, which is an important early event in AMD. In addition, chronic ocular surface inflammation can induce systemic and local Treg dysfunction, disrupting the Th17/Treg balance. The Th17 cell-mediated inflammatory process exacerbates immune inflammatory damage in the macular area; On the other hand, due to the weakened immunosuppressive effect of Treg, immune inflammation cannot self repair. These immune abnormalities may be one of the key factors contributing to the sustained development of AMD.

3.4. Multifactor Interaction: Age, Chronic Inflammation, And Retinal Injury

As a form of chronic ocular surface inflammation, dry eye is closely related to systemic diseases associated with aging. Aging itself is a form of immune aging and inflammatory aging, characterized by systemic low-grade inflammation and weakened immune surveillance function [8]. As a local chronic inflammatory burden, it is more likely to cross the fragile blood eye barrier of the elderly body and affect the posterior segment, and elderly AMD patients often have complement system disorders. Complement factor H (CFH) gene polymorphism is one of the strongest genetic risk factors for AMD. Interestingly, the complement system is also abnormally activated in dry eyes. The levels of C3a, C5a and other complement fragments in dry tears are significantly increased. These complement activation products can reach the choroid through aqueous humor and interact with complement regulatory proteins that are excessively deposited on the surface of RPE, further exacerbating the deposition of complement attack complexes (MAC) in the macular region, promoting RPE injury and choroidal neovascularization. In summary, dry eye related ocular surface inflammation does not directly "cause" AMD, but rather acts as a chronic, persistent low-grade inflammatory stimulus that synergistically promotes the occurrence and progression of macular degeneration with factors such as age, genetic susceptibility, and oxidative stress.

4. POTENTIAL INTERVENTION STRATEGIES FOR DRY EYE RELATED OCULAR SURFACE INFLAMMATION IN THE PREVENTION AND TREATMENT OF MACULAR DEGENERATION

Based on the hypothesis that ocular surface inflammation may be involved in the progression of macular degeneration, anti-inflammatory treatment for dry eyes may provide new ideas for the prevention and adjuvant treatment of AMD. Potential strategies are proposed from four levels: assessment, treatment, management, and emergency response.

4.1. Clinical Grading and Evaluation Indicators of Dry Eye Inflammation Status

At present, clinical evaluation of dry eye mainly focuses on symptoms (such as dry eye and foreign body sensation) and signs (tear film rupture time, corneal fluorescein staining), and the quantitative assessment of inflammatory status is not sufficient [9]. To explore the association between ocular surface inflammation and AMD, it is recommended to include the following indicators in routine examinations of AMD patients: collection of trace tears (capillary or Schirmer test strips can be used), detection of MMP-9, IL-6, TNF - α , etc. MMP-9 testing has been approved by the FDA for dry eye auxiliary diagnosis, with low cost and suitable for promotion. Evaluate the expression level of HLA DR in conjunctival epithelial cells to reflect the immune activation status of the ocular surface. Observe the density and morphology of corneal dendritic cells, which are closely related to the degree of ocular surface inflammation. It is recommended to classify dry eye related ocular surface inflammation into three levels: mild (only symptoms or unstable tear film), moderate (MMP-9 positive or mild corneal staining), and severe (corneal epithelial erosion, extensive infiltration of dendritic cells). For AMD patients with moderate to severe inflammation, consideration should be given to initiating ocular anti-inflammatory interventions.

4.2. Potential Impact of Anti-Inflammatory Treatment on the Risk of Macular Degeneration

At present, first-line anti-inflammatory agents used for the treatment of dry eye include cyclosporine A eye drops, tacrolimus eye drops, levonorgestrel eye drops, and short-term use of glucocorticoids. They can reduce the inflammatory response on the ocular surface by inhibiting T cell activation or interfering with the chemokine pathway. In theory, reducing ocular surface inflammation can limit

the backward spread of inflammatory mediators (IL-6, TNF- α , and MMP-9) through aqueous humor or blood, thereby reducing chronic inflammatory burden in the macular area, slowing down RPE damage and vitreous membrane wart formation. In addition, omega-3 fatty acid supplements have dual effects of anti-inflammatory and regulating lipid metabolism. Multiple clinical studies have shown that oral administration of omega-3 fatty acids can alleviate dry eye discomfort and help reduce tear fluid osmotic pressure and levels of various inflammatory factors; In addition, large-scale epidemiological investigations have also found that individuals who consume a higher amount of omega-3 fatty acids in their diet have a significantly reduced risk of developing advanced AMD (especially choroidal neovascularization). For early AMD patients with combined dry eye syndrome, omega-3 fatty acid supplementation may achieve the benefit of killing two birds with one stone. Although there is no prospective randomized controlled trial evidence to suggest that controlling inflammation in dry eyes can slow down the progression of AMD, based on current research mechanisms, epidemiological clues, and clinical practice experience, in high-risk AMD patients (such as those with neovascularization in the contralateral eye or with more vitreous or reticular pseudovitreous warts), inflammation in dry eyes should be taken seriously and controlled, such as using appropriate eye drops for anti-inflammatory treatment and taking omega-3 fatty acids orally. It should be part of the comprehensive prevention and control plan.

4.3. Long Term Follow-Up and Management Optimization Based on Ocular Surface Regulation

Eye surface inflammation in AMD patients should be managed as part of their long-term follow-up, and a multi-faceted and individualized approach should be adopted. In AMD examinations, for patients with dry eye risk factors, regular assessments of ocular surface inflammation, such as OSDI scores, can be considered every 6-12 months; TBUT; Corneal fluorescein staining; Rapid testing of MMP-9 in tears. Meanwhile, MMP-9 can serve as an objective inflammatory indicator for detecting subclinical levels of ocular surface inflammation, and targeted treatment is needed for different grades of ocular surface inflammation in terms of treatment. Mild dry eyes are mainly cleaned by artificial tears combined with eyelid hot compress; Moderate dry eye syndrome can be treated with cyclosporine A or rituximab eye drops in addition to artificial tears [10]. These drugs can be used for a long time and have good safety; Severe dry eye with corneal epithelial erosion can be treated with short-term combination therapy of low concentration glucocorticoids (such as 0.1% fluorometholone), with a general course of treatment not exceeding 2-4 weeks. During this period, regular monitoring of intraocular pressure and changes in lens opacity is necessary. Increasing the humidity of the surrounding air (such as using humidifiers), reducing the time spent watching screens continuously, ensuring sufficient sleep, and consuming foods containing omega-3 fatty acids (such as deep-sea fish and flaxseed) can all help maintain tear film stability and reduce the burden of eye surface inflammation; Some anti-inflammatory eye drops contain the preservative benzalkonium chloride, and long-term use can cause damage to the corneal endothelium and epithelial barrier. For dry eye AMD patients who require long-term medication treatment, single use formulations without preservatives should be selected as much as possible to reduce further damage to the ocular surface and minimize the increase in inflammatory reactions caused by iatrogenic ocular surface damage.

4.4. Emergency Response Related to Inflammation and Key Points for Retinal Protection

In some cases, dry eye inflammation may suddenly worsen, such as bacterial infection secondary to corneal epithelial damage, acute onset of meibomian gland inflammation, etc. At this time, the inflammatory load on the ocular surface suddenly increases, theoretically affecting the macula as well. The principle for handling this situation is to add high-dose corticosteroid eye drops (such as 1% prednisolone) in the short term and cover them with antibiotics; Use the patient's own serum or recombinant human epidermal growth factor eye drops to assist in epithelial repair and inhibit the

release of DAMPs. When the ocular surface is in the acute inflammation stage, AMD patients can strengthen their retinal nerve protection measures appropriately according to their condition, such as continuous use of AREDS2 formula (including lutein, zeaxanthin, vitamin C, vitamin E, and zinc) or addition of preparations such as phosphatidylcholine. 2-4 weeks after the control of acute inflammation, repeat the fundus optical coherence tomography (OCT) scan to observe whether new vitreous membrane warts, retinal fluid or pigment epithelium detachment appear in the macular area.

5. CONCLUSION

In summary, chronic ocular surface inflammation and macular degeneration associated with dry eye have a certain intrinsic correlation in pathology, and can form a potential connection through the local spread of inflammatory factors to the whole body, the chain reaction of oxidative damage, and immune disorders in the body. Although it is not clear whether ocular surface inflammation is one of the culprits causing macular degeneration, sufficient research evidence and clinical manifestations have demonstrated that ocular surface inflammation can be an effective prevention and intervention measure for AMD. In clinical practice, ophthalmologists should break the inherent thinking pattern of "anterior posterior" treatment, routinely evaluate ocular surface inflammation in AMD patients, and actively provide anti-inflammatory interventions for patients with moderate to severe dry eye. In addition, further prospective cohort studies are needed to determine the relationship between dry eye severity and the risk of AMD progression, and to conduct clinical randomized controlled trials to demonstrate whether anti dry eye inflammation treatment can slow down the development of AMD. Furthermore, it is necessary to further explore the molecular mechanisms underlying the ocular choroidal retinal inflammatory axis and identify potential intervention targets. From the cornea to the macula, it is not only a pathway for light, but also a dark river for inflammatory transmission. Paying attention to this channel is conducive to establishing a more comprehensive network for the prevention and control of elderly eye diseases.

REFERENCES

- [1] Magnin S, Figueiredo O D C E, Vermeirsch S, et al. Ultra-high-resolution imaging of acute macular neuroretinopathy: a case report [J]. *American Journal of Ophthalmology Case Reports*, 2026, 42 102564-102564. DOI:10.1016/J.AJOC.2026.102564.
- [2] Alshaikhsalama A, Thompson K, Hashim H, et al. Analyzing the association between age-related macular degeneration, retinal vascular occlusions, and dementia. [J]. *European journal of ophthalmology*, 2026, 11206721261438587. DOI:10.1177/11206721261438587.
- [3] J G M, Shweta J, Akhila S, et al. Macular Telangiectasia Type 2 With Bidirectional Neovascular Network [J]. *RETINAL Cases & Brief Reports*, 2026, DOI:10.1097/ICB.0000000000001919.
- [4] Ninan J, Jay C, Umesh B C, et al. Large and medium choroidal vessel remodelling in progressive age-related macular degeneration and polypoidal choroidal vasculopathy [J]. *RETINAL Cases & Brief Reports*, 2026, DOI:10.1097/ICB.0000000000001925.
- [5] Christina M, Aikaterini G, Asli P, et al. Acute Macular Neuroretinopathy in a 27-year-old male patient following impending central retinal vein occlusion [J]. *RETINAL Cases & Brief Reports*, 2026, DOI:10.1097/ICB.0000000000001921.
- [6] Li S, Xu Y, Xu Y, et al. Remote Management of Patients With Diabetic Macular Edema Receiving Long-Term Intravitreal Anti-Vascular Endothelial Growth Factor Therapy (RE-SHINE Study): Protocol for a Real-World Study. [J]. *JMIR research protocols*, 2026, 15 e85764. DOI:10.2196/85764.
- [7] Krishnan R A, Famiyeh M I, Ahmad A, et al. Macular and retinal manifestations following COVID-19 vaccinations: a 2025 update systematic review and meta-analysis [J]. *Eye*, 2026, (prepublish): 1-9. DOI:10.1038/S41433-026-04324-4.
- [8] Mehta H. Social deprivation in neovascular age-related macular degeneration: when equal treatment does not deliver equal vision [J]. *Eye*, 2026, (prepublish): 1-2. DOI:10.1038/S41433-026-04423-2.

- [9] Bagewadi S, Parameswaran S, Sethuraman S, et al. Hyaluronic acid-poly (vinyl alcohol) composite hydrogels with self-assembled peptide nanofibers as Bruch's membrane mimics for age-related macular degeneration treatment. [J]. International journal of biological macromolecules, 2026, 151748. DOI:10.1016/J.IJBIOMAC.2026.151748.
- [10] Shi N X, Zhang Y Q, Ju J C, et al. Efficacy of Anti-VEGF therapy for different OCT Patterns in diabetic macular edema and the correlation between ellipsoid zone integrity and visual acuity. [J]. Scientific reports, 2026, DOI:10.1038/S41598-026-47416-7.