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Exploring the Correlation Between Corneal Endothelial Cell Density, Morphology, and Dry Eye Disease: A Narrative Review

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ABSTRACT

Dry eye disease (DED) is a multifactorial disorder of the ocular surface characterized by tear film instability, hyperosmolarity, inflammation, and neurosensory abnormalities. While the pathological effects of DED on the corneal epithelium and ocular surface have been extensively investigated, increasing evidence suggests that chronic ocular surface inflammation may also influence deeper corneal structures, including the corneal endothelium. The corneal endothelium plays a critical role in maintaining corneal transparency through regulation of stromal hydration. Alterations in endothelial cell density (ECD), coefficient of variation (CV), hexagonality (HEX), and central corneal thickness (CCT) have been reported in patients with varying severities of DED. This narrative review summarizes current evidence regarding the relationship between corneal endothelial cell characteristics and DED, explores potential pathophysiological mechanisms linking ocular surface inflammation to endothelial dysfunction, and discusses the clinical implications of these findings. Although available evidence remains limited and sometimes conflicting, chronic inflammation, oxidative stress, tear film instability, and neuroimmune interactions appear to contribute to subtle endothelial alterations in patients with moderate-to-severe DED. Further longitudinal studies are required to establish causality and determine the clinical significance of endothelial changes in DED management.

Keywords

Dry eye disease, Corneal endothelium, Endothelial cell density, Specular microscopy, Ocular surface disease, Inflammation.

Introduction

Dry eye disease (DED) is among the most common ocular disorders worldwide, affecting millions of individuals and significantly impairing visual function and quality of life. The Tear Film and Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) defines DED as a multifactorial disease of the ocular surface characterized by loss of tear film homeostasis accompanied by ocular symptoms, in which tear film instability, hyperosmolarity, inflammation, and neurosensory abnormalities play etiological roles [1].

Historically, research in DED has focused primarily on the tear film, conjunctiva, corneal epithelium, meibomian glands, and lacrimal functional unit [2]. However, advances in ocular imaging technologies such as specular microscopy, confocal microscopy, and anterior segment optical coherence tomography (AS-OCT) have facilitated evaluation of deeper corneal layers, raising questions regarding the potential impact of chronic ocular surface disease on the corneal endothelium [3].

The corneal endothelium consists of a monolayer of hexagonal cells lining the posterior corneal surface. These cells maintain corneal transparency through active regulation of stromal hydration via barrier and pump functions [4]. Human corneal endothelial cells possess limited regenerative capacity; therefore, progressive endothelial cell loss may compromise corneal clarity and visual function [5].

Emerging studies suggest that chronic inflammatory processes associated with DED may extend beyond the ocular surface and

induce measurable changes in endothelial cell morphology and density [6]. Understanding this relationship may provide additional insight into disease severity, chronicity, and the broader impact of ocular surface inflammation on corneal health.

Pathophysiological Basis Linking Dry Eye Disease and Corneal Endothelial Alterations

DED is increasingly recognized as an inflammatory disease involving complex interactions between tear film instability, immune activation, oxidative stress, and neurosensory dysfunction [7]. Hyperosmolar tears stimulate production of inflammatory mediators including interleukin (IL)-1β, IL-6, IL-17, tumor necrosis factor-alpha (TNF-α), and matrix metalloproteinases (MMPs), leading to ocular surface damage and chronic inflammation [8].

Persistent inflammation may influence deeper corneal layers through several mechanisms:

1. **Inflammatory Cytokine Diffusion**: Inflammatory mediators generated at the ocular surface may penetrate the corneal stroma and affect endothelial cell metabolism. Experimental studies have demonstrated that pro-inflammatory cytokines can alter endothelial barrier function and cellular morphology [9].
2. **Oxidative Stress**: Oxidative stress is a hallmark of DED. Elevated reactive oxygen species (ROS) levels have been identified in tears and ocular surface tissues of patients with severe disease [10]. Corneal endothelial cells are particularly susceptible to oxidative injury due to their high metabolic activity and limited proliferative capacity.
3. **Neuroimmune Interactions:** Corneal nerves contribute significantly to ocular surface homeostasis. Chronic DED is associated with nerve damage and neurosensory abnormalities that may influence endothelial health through altered trophic support and inflammatory signaling pathways [11].
4. **Tear Film Instability and Corneal Hypoxia:** Prolonged tear film instability may alter oxygen exchange and metabolic homeostasis across the cornea. Chronic environmental stress may contribute indirectly to endothelial dysfunction in susceptible individuals [12].

These mechanisms provide biological plausibility for the association between DED and endothelial alterations reported in clinical studies.

Corneal Endothelial Cell Parameters Evaluated in Dry Eye Disease

Specular microscopy remains the gold standard for noninvasive assessment of corneal endothelial morphology. The most reported parameters include:

Endothelial Cell Density (ECD): represents the number of endothelial cells per square millimeter. Normal adult values typically range from 2500 to 3000 cells/mm² and gradually decline with age [13].

Coefficient of Variation (CV): reflects variability in endothelial cell size (polymegathism). Increased CV indicates cellular stress and endothelial dysfunction [14].

Hexagonality (HEX): represents the percentage of endothelial cells with six-sided morphology. Reduced HEX reflects pleomorphism and endothelial instability [14].

Central Corneal Thickness (CCT): CCT is indirectly influenced by endothelial pump function. Endothelial dysfunction may result in increased stromal hydration and corneal thickening [15].

Evidence of Endothelial Changes in Dry Eye Disease

Several studies have investigated endothelial characteristics in patients with DED.

In a prospective study utilizing specular microscopy, investigators reported significantly lower endothelial cell density in patients with severe aqueous-deficient DED compared with healthy controls. The reduction was accompanied by increased polymegathism and decreased hexagonality, suggesting chronic endothelial stress [16].

Similarly, research involving patients with Sjögren syndrome-associated DED demonstrated reduced endothelial cell density and increased morphological abnormalities compared with age-matched controls [17]. Since Sjögren syndrome involves systemic autoimmune inflammation, endothelial alterations may reflect both local ocular and systemic immune-mediated mechanisms.

Confocal microscopy studies have also revealed increased inflammatory cell infiltration throughout the cornea in DED patients, supporting the concept that chronic inflammation extends beyond superficial epithelial structures [18].

However, not all investigations have identified significant endothelial differences. Several studies found comparable endothelial cell densities between mild DED patients and controls, suggesting that endothelial involvement may be limited to more advanced or chronic disease [19].

The heterogeneity of findings likely reflects variations in disease severity, diagnostic criteria, imaging modalities, and study populations.

Dry Eye Subtypes and Endothelial Characteristics

Different DED subtypes may influence endothelial morphology differently.

Aqueous-Deficient Dry Eye: particularly in Sjögren syndrome, is characterized by severe ocular surface inflammation. Studies generally report greater endothelial abnormalities in this subgroup [17].

Evaporative Dry Eye: Patients with meibomian gland dysfunction-related evaporative DED may exhibit less pronounced endothelial alterations because inflammation tends to be concentrated at the lid margin and tear film interface [20].

Autoimmune Dry Eye: Autoimmune-mediated DED appears most strongly associated with endothelial changes due to persistent systemic and local inflammatory activity [21].

These observations suggest that endothelial assessment may provide additional information regarding disease severity and inflammatory burden.

Clinical Implications

Although endothelial alterations in DED are generally subtle, several clinical implications warrant consideration.

First, patients with severe chronic DED may possess reduced endothelial reserve, potentially increasing vulnerability to intraocular surgical procedures such as cataract surgery [22].

Second, endothelial assessment may serve as an additional biomarker of disease chronicity and inflammatory burden in selected patients.

Third, identification of endothelial abnormalities may encourage more aggressive treatment of ocular surface inflammation to prevent progression of corneal structural damage.

Finally, understanding the broader corneal effects of DED may improve multidisciplinary management strategies involving cornea specialists, refractive surgeons, rheumatologists, and ocular surface disease experts.

Future Directions

Current evidence remains insufficient to establish a definitive causal relationship between DED and endothelial dysfunction. Future research should focus on large prospective longitudinal studies, standardized DED severity classifications, correlation between inflammatory biomarkers and endothelial parameters, advanced imaging using specular microscopy and in vivo confocal microscopy, evaluation of endothelial changes following DED treatment and investigation of endothelial alterations in specific DED subtypes, particularly autoimmune-associated disease.

Such studies may clarify whether endothelial changes represent a consequence of chronic ocular surface inflammation or simply an associated finding.

Conclusion

Dry eye disease is increasingly recognized as a condition affecting the entire cornea rather than exclusively the ocular surface. Available evidence suggests that chronic inflammation, oxidative stress, and neuroimmune dysregulation associated with DED may contribute to subtle alterations in corneal endothelial cell density and morphology. Reductions in endothelial cell density, increased polymegathism, and decreased hexagonality have been reported, particularly in severe and autoimmune-associated forms of DED.

However, current findings remain inconsistent, and further prospective studies are required to determine the clinical significance of these observations. Assessment of corneal endothelial characteristics may provide valuable complementary information regarding disease severity and long-term corneal health in patients with DED.

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