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Tear Dysfunction and the Cornea: LXVII Edward Jackson Memorial Lecture

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Abstract

Purpose—To describe the cause and consequence of tear dysfunction related corneal disease.

Design—Perspective on effects of tear dysfunction on the cornea

Methods—Evidence is presented on the effects of tear dysfunction on corneal morphology, function and health, as well as efficacy of therapies for tear dysfunction related corneal disease.

Results—Tear dysfunction is a prevalent eye disease and the most frequent cause for superficial corneal epithelial disease that results in corneal barrier disruption, an irregular optical surface, light scattering, optical aberrations and exposure and sensitization of pain sensing nerve endings (nociceptors). Tear dysfunction related corneal disease causes irritation and visual symptoms, such as photophobia, blurred and fluctuating vision that may decrease quality of life. Dysfunction of one or more components of the lacrimal functional unit results in changes in tear composition, including elevated osmolarity and increased concentrations of matrix metalloproteinases, inflammatory cytokines and chemokines. These tear compositional changes promote disruption of tight junctions, alter differentiation and accelerate death of corneal epithelial cells.

Conclusions—Corneal epithelial disease resulting from tear dysfunction causes eye irritation and decreases visual function. Clinical and basic research has improved understanding of the pathogenesis of tear dysfunction related corneal epithelial disease, as well as treatment outcomes.

Introduction

The cornea is a truly unique optically clear tissue, devoid of blood vessels that relies on tears to maintain a moist, smooth and lubricated surface in the face of near constant exposure to ambient environmental conditions during waking hours. Additionally, the tears provide a myriad of factors that protect the cornea from microbial infection and the sight threatening effects of excessive inflammation or prolonged wound healing. To maintain corneal clarity and quality vision, humans have a complex and highly regulated system to produce and distribute tears.

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Tear dysfunction is one of the most prevalent medical conditions, affecting tens of millions of patients worldwide. Tear dysfunction is a more encompassing term than dry eye for tear associated disorders of the ocular surface and cornea because it encompasses changes in tear composition rather than tear volume.¹ Tear dysfunction has long been recognized to cause corneal epithelial disease that can decrease visual performance and cause ocular irritation. Mechanisms responsible for these pathological changes were poorly understood until evidence from recent clinical studies and animal models indicates that altered tear composition causes dysfunction, accelerated death and detachment of the superficial epithelium leading to an irregular corneal surface, an unstable tear layer and hyperesthesia of the corneal nerve endings. These changes in the superficial cornea can significantly impact quality of life and productivity in patients suffering from tear dysfunction. I have provided my perspective on the function of tears on maintaining corneal health, the impact of tear dysfunction on the cornea and consequences of tear dysfunction related corneal disease on patient well-being based on published evidence and research I've performed over the past 25 years.

Vision starts at the Tear Layer

The tear/corneal epithelial complex is the major light refracting surface of the eye, accounting for approximately 65% of the optical power of the eye.² A smooth and stable tear layer is essential for maintaining high quality vision between blinks. Ultra structural, biochemical and functional studies show the precorneal tear layer is a gel composed of soluble mucus secreted by the conjunctival goblet cells and fluid and proteins secreted by the lacrimal glands.³⁻⁶ This hydrophilic gel moves over the membrane mucins (glycocalyx) on the superficial corneal epithelial cells and serves as a medium to refresh the tear components and clear debris. The precorneal tear layer provides a smooth coating over the irregular microvilli on apical corneal epithelial cells. The normal tear film remains stable for the entire interblink interval, although the precorneal layer has been observed by optical coherence tomography (OCT), to gradually thin at a rate of 4µm/minute due to evaporation and the pull of gravity toward the inferior meniscus.⁷ The precorneal tear layer is replenished from the reservoir of tears in the inferior tear meniscus by blinking. This meniscus contains 75-90% of the tear volume (Figure 1).^{7,8}

To maintain continuous unobstructed vision, the eye is open ninety-two percent of the time with a blink rate of 15 times per minute. This renders the cornea the most exposed mucosal surface in the body. Thus, the corneal surface is presented with the challenge of resisting desiccation and maintaining a smooth optical surface during inter-blink intervals. It must also be capable of surviving environmental, occupational and recreational desiccating stress. To maintain clarity, the cornea must be resistant to microbial invasion and be capable of initiating rapid, scar-free healing after wounding. Because the cornea lacks blood vessels to supply the anti-microbial defense and wound healing factors necessary to combat these challenges, it depends on the tears to deliver them. Humans have highly complex tear secreting apparatus that we have termed the *Lacrimal Functional Unit* (LFU), to maintain a stable pre corneal tear film (Figure 2).⁹ The LFU consists of an afferent component of trigeminal nociceptors in the cornea and ocular surface that synapse in the brainstem with autonomic and motor efferent nerves, as well as higher order sensory neurons. Autonomic nerve fibers, primarily cholinergic, have been found to innervate the meibomian glands, conjunctival goblet cells and main and accessory lacrimal glands.¹⁰⁻¹² Motor efferent fibers stimulate the orbicularis oculi muscle to initiate blinking to express lipid secretions from the meibomian glands, spread tears over the corneal surface and direct them into the lacrimal puncta.

Tears contain a biochemically complex mixture of factors (Table 1) that are produced by the lacrimal glands and ocular surface epithelium to lubricate, support, protect and heal the cornea (Figure 3). Reflex tear secretion and blinking clear proteases and inflammatory mediators produced by the surface epithelium and resident immune cells that are capable of causing corneal epithelial disease through dilution and removal through the nasolacrimal duct system. Lipids secreted by the meibomian glands retard tear evaporation.

Tear Dysfunction – A Major Clinical Problem

Tear dysfunction occurs when the lacrimal functional unit is no longer able to maintain a stable precorneal tear layer. It may develop from dysfunction or disease of one or more components of the lacrimal functional unit. Tear dysfunction is one of the most prevalent eye conditions. Epidemiological studies performed worldwide on different populations and using a variety of diagnostic criteria have reported the prevalence to range from 2-14.4% depending on the study population and diagnostic criteria.¹³⁻¹⁹ This translates to a prevalence of tear dysfunction between 6 and 43.2 million people in the United States. A number of risk factors for dry eye have been identified. Age is perhaps the biggest risk factor with the prevalence increasing in both men and woman with every decade of life over the age of 40, with a greater prevalence in women than men at every age.^{18,19} Other risk factors identified include contact lenses^{20,21}, higher dietary consumption of n-6 to n-3 essential fatty acids²², diabetes mellitus^{16,17}, cigarette smoking^{16,23}, prolonged video display viewing²¹ and low humidity environments.²⁴ Patients with tear dysfunction typically report irritation symptoms including foreign body sensation, burning and dryness, as well as vision related symptoms such as photophobia and blurred and fluctuating vision. These symptoms may decrease quality of life in afflicted patients. In fact, the impact of tear dysfunction on quality of life was rated to be equivalent to unstable angina using utility assessments.²⁵ In some cases, the consequences of tear dysfunction can be devastating and result in functional and occupational disability.

The majority of the symptoms of tear dysfunction result from corneal epithelial disease. Tear dysfunction has been recognized for over a century as the major cause of superficial corneal epithelial disease.²⁶ It is now recognized this epitheliopathy reduces corneal barrier function, causes an irregular optical surface, light scattering, optical aberrations and exposure and sensitization of corneal nociceptors.

Changes in Tear Composition and Corneal Epithelial Disease

Lacrimal gland disease, meibomian gland disease and reduced tear clearance from ocular surface diseases such as conjunctivochalasis have been reported to alter tear composition (Table 2). Conditions causing dysfunction of the lacrimal gland, such as Sjögren Syndrome (SS), result in significantly decreased concentrations of certain proteins and growth factors that are secreted by lacrimal acinar cells into tears, including lactoferrin and epidermal growth factor (EGF).^{27,28} Reduced tear EGF concentration was found to correlate with severity of corneal fluorescein staining in patients with tear dysfunction.²⁸ Exposure of the corneal epithelium to increased osmolarity or to certain inflammatory/immune cytokines has been found to promote inflammation, abnormal differentiation, accelerated detachment and programmed death (apoptosis) of the corneal epithelium (Figure 4). Elevated tear osmolarity, primarily attributed to increased Na⁺ ion concentration is a common feature of tear dysfunction caused by lacrimal and meibomian gland disease.²⁹ The mean osmolarity measured in tears - collected from the inferior meniscus in eyes with tear dysfunction - has been found to be about 20-40 mOsm greater than the normal tear film, ranging from 314-365mOsm/L²⁹; however, osmolarity in areas of break-up of the precorneal tear layer has been calculated to be much higher and consistent with values of 560 mOsm/L measured

in tear samples collected from the entire ocular surface of mice with experimentally induced dry eye.³⁰⁻³² Exposure to a high osmolality environment has been identified as a considerable stress to the corneal epithelium, resulting in activation of the mitogen activated protein kinase (MAPK) and NFkB stress signaling pathways in these cells (Figure 4). These pathways initiate a cascade of events, including transcriptional activation of genes encoding inflammatory, matrix metalloproteinases (particularly MMP-9) and pro-apoptotic factors.^{33,34}

MMP-9 has been found to regulate physiological shedding of the corneal epithelium through lysis of the membrane spanning tight junction protein occludin.^{35,36} In eyes with normal tear production, MMP-9 exists predominantly in a latent inactive form and the low levels of mature MMP-9 are bound to its physiological inhibitor, tissue inhibitor of matrix metalloproteinase 1 (TIMP1).^{37,38} MMP-9 activity increases in the closed eye during sleep when tear production and clearance decrease.³⁹ A diurnal increase in MMP-9 expression was found to contribute to controlled extracellular cleavage of junctional complexes in the apical corneal epithelium in the *Xenopus* cornea and it may make a similar contribution to physiological turnover in the human cornea (Weichmann AF, Pflugfelder SC, Howard E. 2011 ARVO Abstract). MMP-9 activity on the ocular surface increases in eyes with tear dysfunction due to increased production by stressed epithelial cells and infiltrating leukocytes, as well as increased activity of its physiological activators (e.g MMP-3) and reduced tear concentrations of TIMPs.⁴⁰⁻⁴³ Increased MMP-9 activity accelerates detachment of apical corneal epithelium, exposing less mature subapical epithelial cells and nociceptors, as shown in Figure 5. Furthermore, loose epithelium, decreased surface lubrication and friction from blinking exacerbates the problem and may promote development of filamentary keratitis.⁴⁴⁻⁴⁶ Disruption of the apical barrier can cause irritation and reduce visual performance, as discussed below. Pathways mediated by the stress kinase JNK 2 were found to be primarily responsible for the MMP mediated corneal barrier disruption in experimental dry eye.⁴⁷ JNK2 has been reported to have a similar function in osmotically induced barrier disruption in the colonic epithelium.⁴⁸

In addition to the ocular surface epithelium, inflammatory mediators produced by inflammatory/immune cells that reside on the ocular surface or that are recruited to the conjunctival epithelium, particularly CD4+ T cells were found to participate in the development of corneal epithelial disease in dry eye. Our group has found that exposure to desiccating stress recruits activated CD4+ T cells of the Th1 and Th17 lineages to the ocular surface.^{49,50} IFN- γ , the signature cytokine produced by Th1 cells was found to induce apoptosis of the cornea and conjunctival epithelia, while IL-17 produced by Th17 cells stimulated production of MMPs 3 and 9 by the corneal epithelium.⁵⁰⁻⁵² The corneal epithelium has been found to express receptors for both IFN- γ and IL-17.^{50,52}

Desiccation, osmotic stress and the inflammatory cytokines IL-1 and IFN- γ can promote skin epidermal like differentiation in the corneal epithelium with increased production of cornified envelope precursors that are absent or produced at low levels in unstressed corneal epithelial cells.^{49,53} Furthermore, exposure to high osmolality activates intrinsic apoptotic pathways in corneal epithelial cells that can lead to accelerated turnover of the apical epithelium.⁵⁴ Increased numbers of cornifying, dead and detaching epithelial cells may be responsible for the increased number of opaque corneal epithelial cells that have been observed by confocal microscopy and metaplastic cells noted in conjunctival impression cytology of patients with tear dysfunction.⁵⁵⁻⁵⁷

Clinical Consequences of Tear Dysfunction on the Superficial Cornea

The principal clinical manifestation of tear dysfunction related superficial corneal epithelial disease is eye irritation. Typical symptoms consist of dryness, foreign body sensation and burning. Patients often complain of exquisite sensitivity to wind or drafts from air conditioning vents. While the mechanisms responsible for these Irritation symptoms is not fully understood, it appears they are due in large part to greater exposure of corneal nociceptors to environmental stimuli, as well as sensitization of these nerve endings by inflammatory mediators. Rosenthal has proposed the term “corneal neuralgia” to describe the heightened corneal sensitivity associated with tear dysfunction.⁵⁸ Transient receptor potential cation channel subfamily member 8 (TRPM8) ion channels in cold receptors in the corneal epithelium that increase firing as the temperature decreases from 34 to 24°C have been shown to regulate basal tear flow by the lacrimal gland.⁵⁹ More rapid corneal cooling in eyes with tear dysfunction and accelerated tear break up likely results in increased nerve firing that may be interpreted as eye discomfort.^{60,61} Studies evaluating corneal sensitivity in dry eye have reported conflicting results of either heightened or reduced sensitivity. Hyperesthesia has been observed in several studies using a gas esthesiometer,^{62,63} while studies testing mechanical sensitivity with a nylon monofilament have generally found reduced sensitivity to this mechanical stimulus.^{64,65} The conflicting findings of hyper or hypoesthesia in eyes with tear dysfunction may be attributed to the type of test stimulus applied or corneal nerve degeneration that may develop in eyes with longstanding tear dysfunction, particularly Sjögren’s syndrome.^{66,67}

Many patients with corneal epitheliopathy complain of photosensitivity that in some cases can be severe and disabling, forcing them to wear tinted glasses and avoid bright lights. This symptom may be attributed in part to light scattering from the irregular tear film and superficial corneal epithelium. Videokeratoscopic surface regularity indices have found greater surface irregularity in eyes with tear dysfunction that correlated with the severity of corneal fluorescein staining.⁶⁸ Serial corneal topographic measurements taken of the open eye after a blink have observed a more rapid increase of corneal surface irregularity than eyes with normal tear function and the rate of change corresponded to the severity of corneal epithelial disease.^{69,70}

Corneal epithelial disease may also reduce optical performance. Many patients with tear dysfunction complain of fluctuating vision that may improve following instillation of artificial tears. Often patients with tear dysfunction have normal visual acuity measured by conventional methods; however, reduced visual performance has been found with more sophisticated measures of visual function. Patients with corneal epithelial disease were noted to have greater reduction in contrast sensitivity and low contrast visual acuity than eyes with normal tear function.^{40, 71-74} A number of studies have reported increased levels of higher order aberrations, particularly coma, in eyes with tear dysfunction.^{75,76} These alterations in visual quality lead to a reduction in functional visual acuity.^{77,78}

Tear dysfunction can directly or indirectly increase the risk for developing microbial keratitis. Tear fluid contains factors that inhibit microbial attachment and invasion into the corneal epithelium.⁷⁹ Corneal epitheliopathy from severe tear dysfunction has also been identified as a risk factor for microbial keratitis.^{80,81}

Eyes with reduced tear clearance associated with meibomian gland disease have been reported to have increased levels of tear EGF and VEGF that has been found to be associated with subepithelial fibrosis and peripheral vascularization.^{82,83}

Approaches to treat Tear Dysfunction Related Corneal Disease

Increased knowledge regarding the cellular and molecular mechanisms of tear dysfunction mediated corneal epithelial disease has prompted use of therapies that target disease related factors and has generated buzz in the pharmaceutical industry about topical use of targeted immunomodulators. Over the past decade there has been a trend toward increased use of anti-inflammatory therapies to improve comfort, corneal smoothness and barrier function. Cyclosporin A (CsA), the only FDA approved therapy for tear dysfunction, inhibits T cell activation and production of the Th cytokines IFN- γ and IL-17.^{84,85} Topical CsA significantly reduced severity of corneal fluorescein staining after 4 and 6 months of use.⁸⁶ Corticosteroids, tetracyclines and n-3/n-6 essential fatty acids have also been found to decrease production of a variety of inflammatory mediators and improve corneal epithelial disease.⁸⁹⁻⁹² The efficacy of corticosteroids and tetracyclines on corneal barrier function may be due to their ability to inhibit MMP hypoesthesia in eyes with tear dysfunction may be attributed to the type of test stimulus applied or corneal nerve degeneration that may develop in eyes with longstanding tear dysfunction, particularly Sjögren's syndrome.^{66,67}

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For severe corneal epitheliopathy from tear dysfunction, the prosthetic replacement of the ocular surface ecosystem (PROSE), a specially designed scleral bearing contact lens with a fluid filled reservoir over the cornea, has proven to be an excellent option for improving irritation symptoms and visual acuity.^{96,97} The fluid filled reservoir shields the cornea from blink trauma, noxious environmental stimuli and inflammatory mediators in the tears. The body temperature saline reservoir also prevents corneal cooling and nerve firing that occurs in the inter blink intervals. Patients may experience almost immediate relief in photophobia and irritation symptoms after placing the device on the cornea. Compared to artificial tears, autologous serum (20%) was found to significantly improve corneal epithelial disease in patients with severe dry eye.⁹⁸ Injection of Botulinum toxin A in the lid has been found to decrease blink force and to improve superior limbic keratoconjunctivitis and filamentary keratitis.^{99,100}

Discussion

This perspective has described the effects of tear dysfunction on the cornea. Corneal disease resulting from tear dysfunction is one of the most common eye conditions and a major cause for patients seeking eye care. Irritation and visual disturbance from superficial corneal epithelial disease can greatly impact productivity and quality of life in afflicted patients. Changes in tear composition appear to be primarily responsible for the corneal epithelial barrier disruption and activation of stress pathways in the corneal epithelium that lead to an irregular and poorly lubricated corneal surface. Greater understanding of the mechanisms responsible for these pathological changes has led to new treatment options and improved outcomes.

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Biography

Stephen C. Pflugfelder, M.D. graduated from Colgate University summa cum laude and SUNY Upstate Medical University Syracuse where he was elected to AOA. He did his Ophthalmology residency at Baylor College of Medicine where he served as Chief Resident in 1984. He performed a Cornea fellowship at the Bascom Palmer Eye Institute of the University of Miami School of Medicine. He was appointed to the faculty of the Bascom Palmer Eye Institute in 1985 and was promoted to Professor in 1998. He joined the faculty of the Cullen Eye Institute of Baylor College of Medicine as a Professor and Director of the Ocular Surface Center in July 2000. He was awarded the James and Margaret Elkins Chair in Ophthalmology at the Baylor College of Medicine in 2001. He has published over 190 peer-reviewed articles and over 45 book chapters and monographs, primarily in the field of cornea diseases and surgery. He served as a co-editor for "Dry Eye and Ocular Surface Disorders" a comprehensive textbook on the subject that was published in 2004. He was included in the last five editions of "Best Doctors in America". He received the American Academy of Ophthalmology Senior Achievement Award in 2000 and a Research to Prevent Blindness Senior Investigator Award in 2002. He served as Chairman of the American Academy of Ophthalmology Lifelong Education for Ophthalmologists Committee and as a member of the American Academy of Ophthalmology Preferred Practice Pattern Committee on Corneal and Ocular Surface diseases. He serves on the Editorial Boards of the journals *American Journal of Ophthalmology*, *Cornea*, *Investigative Ophthalmology and Visual Science* and *The Ocular Surface*. He will present the Edward Jackson Memorial Lecture at the 2011 American Academy of Ophthalmology. His research interests include the role of inflammation in dry eye and corneal bioengineering.

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Figure 1. Inferior tear meniscus measured by optical coherence tomography (OCT) just before (left) and 1 second after (right) a blink. Blinking decreased the tear meniscus area by two-thirds through upward pull over the cornea and lacrimal drainage.

Figure 2.

Integrated Lacrimal Functional Unit (LFU) that regulates secretion and delivery of tears to the cornea and ocular surface. Nociceptors in the cornea (yellow) synapse with autonomic, motor and higher sensory neurons in the brainstem that innervate the tear-producing glands and orbicularis muscle to initiate blinking. Reprinted with permission from: Beuerman R, Stern ME, Mircheff A, Pflugfelder SC. The Lacrimal Functional Unit in **Dry Eye and the Ocular Surface**, SC Pflugfelder, ME Stern and R Beuerman editors, Marcel Dekker, New York, 2004, pp 11-40.

Figure 3.

The precorneal tear layer contains factors produced by the lacrimal glands, conjunctival goblet cells and surface epithelium that lubricate (mucins), heal (epidermal growth factor - EGF) and protect the cornea from infection (lactoferrin, defensins, IgA) and excessive inflammation (interleukin 1 receptor antagonist – IL-1RA, transforming growth factor beta - TGF-β and tissue inhibitor of matrix metalloproteinase 1 – TIMP1). MMP-9 = matrix metalloproteinase 9.

Figure 4.

Tear dysfunction related alterations in tear composition, including increased osmolarity and inflammatory cytokines produced by epithelial cells (IL-1 and TNF- α) and activated CD4+ T cells (IFN- γ and IL-17) activate the c-jun n-terminal kinase (JNK) and nuclear factor kappa B (NF κ B) stress signaling pathways leading to transcription of stress genes such as inflammatory cytokines and chemokines, matrix metalloproteinases (MMPs), pro-apoptotic factors and cornified envelop precursor proteins. (IFN- γ = interferon gamma)

Figure 5.

Reduced tear production and desiccation in experimental dry eye in mice leads to proteolytic dissolution of tight junction protein occludin and accelerated desquamation in the apical epithelial cells (upper) resulting in exposure of less differentiated subapical epithelia and activated nociceptors that signal discomfort from the ocular surface (lower).

Table 1

Role of Tear Components on Corneal Health

Role	Component	References
Lubrication	MUC1, MUC4, MUC16, MUC5AC	101-103
Wound healing	EGF, Substance P, TGF- β	104-106
Antimicrobial defense	Lactoferrin, Lysozyme, Defensins (α and β), IgA	107-111
Anti-inflammatory	IL-1RA, TGF- β 2	37, 106,112
Protease inhibitors	TIMP1, SLPI	43,113

MUC= mucin gene, EGF= epidermal growth factor, TGF= transforming growth factor, IL-1RA= interleukin 1 receptor antagonist, TIMP1= tissue inhibitor of matrix metalloproteinase 1, SLPI= secretory leukocyte peptidase inhibitor

Table 2

Tear Composition changes associated with corneal epithelial disease

Tear Component	Change	Reference
Sodium ion	↑ osmolarity	114
Growth Factor	↓ EGF	28,83
Cytokine/chemokine	↑ IFN- γ , IL-1, IL-6, IL-8, MIP-1 α	28,83
Protease	MMP-9	40, 93, 115

EGF-epidermal growth factor, IFN- γ = interferon gamma, MIP-1 α = macrophage inflammatory protein 1 alpha, MMP-9 = matrix metalloproteinase

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