Special Issue

Age-Related Changes and Diseases of the Ocular Surface and Cornea

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Aging of the ocular surface and corneal tissues, major components of the visual system, causes major eye disease and results in substantial cost in medical and social terms. These diseases include the highly prevalent dry eye disease that affects the ocular surface and its glands, leading to tear film alterations, discomfort, and decreased vision. Studies show that 14.4% of the population in the United States older than 50 years have dry eye disease and demonstrate that it is particularly prevalent among women. Annual medical costs per patient with dry eye in the United States are estimated at $783 per year, with an overall medical cost adjusted to prevalence of $3.84 billion per year. Societal costs, which include loss of productivity, are estimated per patient at $11,302 per year, with overall costs adjusted to prevalence of $55.4 billion per year. Because there are few effective treatments for the disease, more research on its etiology and mechanisms is warranted and needed. Increased public education about risk factors for the disease is also required. Another major age-related eye disease of the cornea that leads to vision impairment and potentially blindness if left untreated is Fuchs' endothelial corneal dystrophy. This disease leads to loss of the endothelial cells on the internal side of the cornea that are responsible for keeping the cornea in the proper hydration state to ensure its transparency to light. The mechanism of cell loss is unknown, and the only treatment available to date is surgical transplantation of the cornea or inner part of the cornea. These medically costly procedures require donor corneas, eye banking, and medical follow-up, with accrued costs. Fuchs' endothelial corneal dystrophy is a major cause of corneal transplantation in the United States; therefore, research support is needed to determine the mechanism of this age-related disease, to develop medical, nonsurgical methods for treatment.

Keywords: age-related diseases of cornea, dry eye, Fuchs' endothelial corneal dystrophy, cornea, ocular surface

Age-related changes in the cornea and ocular surface tissues have a major effect on vision. The diseases that affect these vital components of the eye cause major vision loss and place a sizable medical and socioeconomic burden on society. Left untreated, more severe age-related disease can cause loss of transparency and then blindness. The objectives of this article are (1) to summarize major age-related changes that occur in the tissues and functions of the ocular surface and cornea, (2) to point out the major age-related diseases that affect these vital ocular components, and (3) to suggest several pathways toward slowing or treating the age-related changes and diseases of the ocular surface and cornea.

The two major functions of the cornea are (1) to support the tear film at the apical surface, which provides the major refractive surface of the eye, and (2) to transmit light through its extraordinarily translucent tissue to the lens and then to the retina. The tissues at the ocular surface support the cornea in its vital functions. To characterize the age-related changes and diseases relevant to these two major functions and their diseases, the ocular surface and cornea will be considered separately.

Age-Related Changes and Diseases of the Ocular Surface

Age-Related Changes in the Ocular Surface

Tears, which form the refractive surface on the cornea, are produced and maintained by the ocular surface system (Fig. 1).[1,2] This system is composed of the continuous surface epithelium lining the lids, conjunctiva, and cornea and the epithelial-derived glands, including the meibomian, lacrimal, and accessory glands, as well as the connective tissues underlying these epithelia and the lids, which exquisitely fit over the cornea and move tear components over the surface of the eye to clean and maintain the tear film and protect the ocular surface. This entire system, comprising the epithelial component with its various specialized areas (glands plus surface epithelium), their underlying matrices, and the lids, is integrated functionally by nerves, the immune system, the vascular system, and hormones (Fig. 1).

The epithelial components and specializations within this system produce different components of the tears (i.e., meibomian glands produce the surface lipid layer, the lacrimal

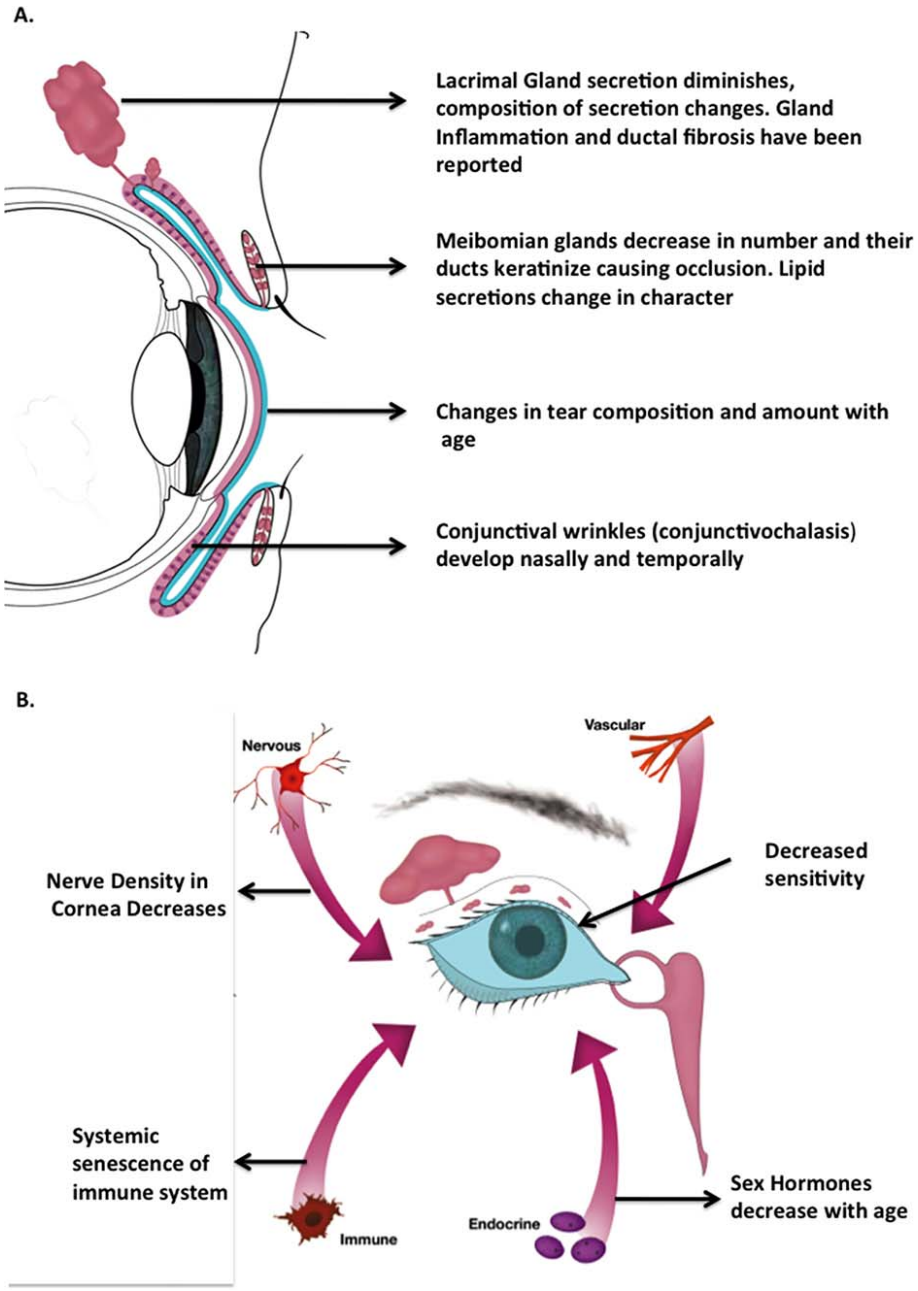

FIGURE 1. Major age-related changes in the ocular surface system components (**A**) and in the components that integrate the functions of the ocular surface system (**B**).

gland produces and secretes water and a myriad of other protective proteins, and the conjunctival goblet cells and the corneal epithelium secrete mucins and release membrane mucins into the tear fluid, respectively). The age-related changes that have been documented occur in most components of the ocular surface system. Examples of these changes within the meibomian gland include keratinization of the gland ducts, gland dropout, and alteration in lipids of meibum. For an excellent review of meibomian gland development, anatomy, physiology, and changes in age and disease, see the 2011 article by Knop et al.[3] The lacrimal gland shows diminished levels and composition of secretion with age, and gland inflammation and ductal fibrosis (especially in women) have been reported.[4] As a result of glandular changes with age, the tear film composition changes; for a review, see the 2007 article by the Research Subcommittee of the International Dry Eye WorkShop.[1] Findings by McGill et al.[5] indicate that the levels of lactoferrin and lysozyme decrease with age. However, it is unknown to date whether age affects the myriad of other important tear proteins or whether tear osmolarity, an increase of which occurs in dry eye, changes with age.

Age-related alterations also occur in the integrating components of the ocular surface system. First, there is a well-known diminution of sex hormones that occurs with age in both sexes that affects glandular functions of the ocular surface system.[3] Second, the number of nerves in the corneal epithelial subbasal plexus decreases with age,[6] leading perhaps to the loss of sensitivity observed with age.[7] Third, although not specifically demonstrated in the eye, there is a systemic loss of immune

function with age.[8] Major age-related changes in the ocular surface system are summarized in Figures 1A and 1B.

Dry Eye Disease, the Major Age-Related Disease of the Ocular Surface

Because various functions of the ocular surface system are integrated and because epithelial specializations provide different products for the tear film, it is not surprising that alterations in any one or more functions of the ocular surface system components with age will cause a disruption of the tear film. This will lead to drying of the ocular surface, which in turn leads to a decrease in visual acuity and subjacent epithelial injury with ensuing inflammation. Therefore, dry eye is a multifactorial disease of the ocular surface that results in symptoms of discomfort, visual disturbance, tear alterations, and tear film instability with damage to the ocular surface. It is accompanied by increased osmolarity of the tears and inflammation of the ocular surface. Mild to severe forms of the disease are noted.[1]

Dry eye disease has multiple etiologies, all of which may be derived from alterations in one or more components of the ocular surface system. The majority of patients with dry eye have meibomian gland disease (MGD); for a review, see the article by Knop et al.[3] Dry eye can be secondary to Sjögren's syndrome, rosacea, or systemic or topical medication use, to name a few. In fact, patients show a wide variety of presentations and symptoms, and the lack of definitive diagnosis and etiology frustrates ophthalmologists and patients. Thus, because of the multifactorial and elusive etiology of dry eye, effective treatments are often unavailable.

Risk factors for dry eye disease have been summarized.[9] Those that have been most consistently described include older age, female sex, postmenopausal estrogen therapy, imbalanced ratios of omega-3 to omega-6 fatty acids, antihistamine use, other medication use, connective tissue disease, LASIK and refractive laser surgical procedures, radiation therapy, hematopoietic stem cell transplantation, vitamin A deficiency, hepatitis C infection, and androgen deficiency.

While major progress has been made recently in developing hypotheses for the mechanism of dry eye disease, proof of the mechanism remains elusive because of its multifactorial nature. Several hypotheses have been advanced. One hypothesis, based on extensive studies in mice,[10,11] is that defects in tear amounts or composition lead to epithelial surface injury and stress, which in turn lead to an immune-mediated inflammatory response. Having autoimmune characteristics, the inflammatory response becomes chronic. This hypothesis relates to the common postinjury pathway of the disease but does not identify the source of the injury, which is or can be multifactorial. Although the autoimmune designation has been proven for mice, data from human studies are at best suggestive. Another hypothesis, one particularly relative to the prevalence of dry eye in women, is that hormonal changes with age drive alterations in ocular surface epithelial functions, which in turn promote epithelial injury and dry eye; these data are supported by the appearance of dry eye in patients with androgen deficiency (for a review, see the 2004 article by Sullivan[12]).

Prevalence of Dry Eye Disease. Estimates of the prevalence of dry eye in the worldwide population older than 50 years range from 5% to 30% depending on the study (the range is accounted for by variable definitions of dry eye disease).[9] In the United States, studies[13,14] indicate that at least 14% of the population older than 50 years have dry eye, indicating that it is one of the major eye diseases in the country. Moreover, the disease in the United States is prevalent among women. While 3.23 million women are reported to have moderate to severe dry eye, only 1.68 million men are estimated to do so.[15]

Economic Burden of Dry Eye in the United States. A recent, first estimate of the economic burden of dry eye in the United States indicates that the average annual cost of managing dry eye is $783 per patient, with an overall cost adjusted to prevalence of $3.84 billion.[16] From a societal perspective, the cost of lost productivity is estimated to be $11,302 per patient per year, with overall costs adjusted to prevalence of $55.4 billion per year. These data indicate that dry eye disease is an enormous economic burden to individuals and society.

Age-Related Infections of the Ocular Surface

Infections of the ocular surface can cause corneal blindness and until recently were second only to cataract as the major cause of blindness worldwide.[17] With improved hygiene and economic status in developing countries, there has been great progress in reducing the burden of blindness from these diseases, particularly from trachoma. Moreover, these diseases occur mostly in younger people and are therefore not considered age related. However, one infection that often occurs at the ocular surface and cornea and is age related is herpes zoster ophthalmicus (HZO). This disease, also known as shingles, is a painful rash that occurs mostly in tissues innervated by the trigeminal nerves shared by the skin around the eye, as well as the ocular surface and its adnexa.[2] Caused by reactivation of the varicella-zoster virus that lies dormant in nerve ganglia, HZO occurs typically in older adults. Progress in treating the disease has been made with the development of antiviral medications and a vaccine against the virus. While the vaccine has helped prevent the disease, it is not a cure; recurrences occur following vaccination, albeit with decreased severity. Thus, work to improve the efficacy of the vaccine is needed to eradicate this painful debilitating disease. Estimates of the prevalence of HZO indicate that 20% of the US population have had herpes zoster and that 10% to 20% of those affected have ocular zoster.[18]

Age-Related Changes and Diseases of the Cornea

Age-Related Changes in the Cornea

Major changes in the cornea with age include thickening of both the epithelial and endothelial basement membranes, the latter known as Descemet's membrane. As stated above, nerve density in the subbasal plexus, below the epithelium, decreases. Moreover, a decrease in the number of conjunctival keratocytes has been reported.[19]

However, the most important and clinically relevant change in the cornea with age is the well-documented loss of corneal endothelial cells. Continual loss of these nonmitotic cells can lead to disease, as described below. Figure 2 shows the major age-related changes in the cornea.

Age-Related Diseases of the Cornea

Corneal endothelial cells are vital for maintaining corneal transparency to light because they provide a barrier function and pump water, which can accumulate in the corneal stoma from the anterior chamber. People are born with a fixed number of corneal endothelial cells, and that number gradually declines with age. Because the endothelial cells do not divide, cell loss induced by age or disease cannot be reversed, and the relative state of cornea dehydration cannot be maintained. As a

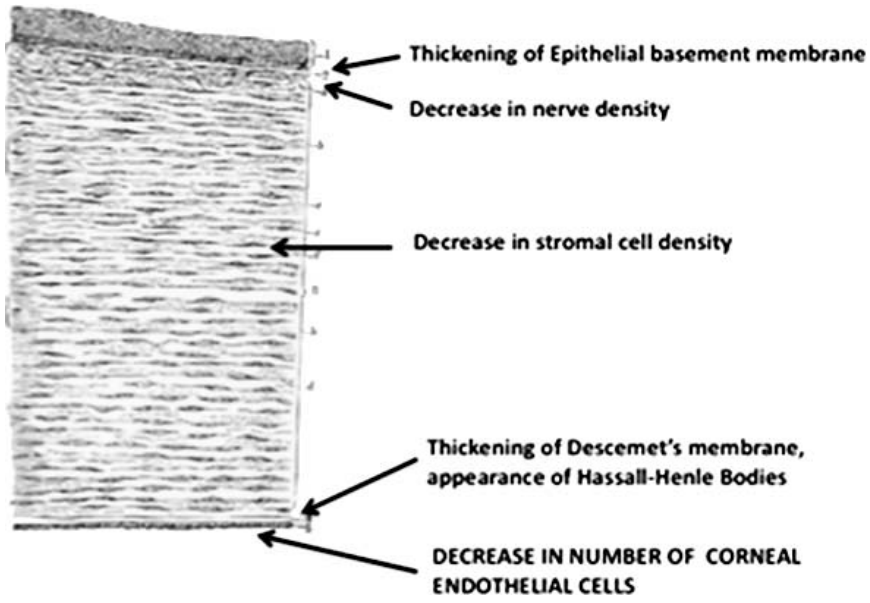

FIGURE 2. Age-related changes in the cornea.

result, fluid accumulation leads to corneal edema and loss of corneal transparency. This condition, termed bullous keratopathy, is characterized not only by opaque corneas but also by separation of the corneal epithelium from its underlying matrix in small blister-like elevations known as bullae. The following two major causes of bullous keratopathy are both age related: (1) Fuchs' endothelial corneal dystrophy (FECD) and (2) iatrogenic endothelial damage due to cataract or other surgery. Left untreated, bullous keratopathy represents a serious sight-threatening corneal disease, the only current treatment for which is corneal transplantation or endothelial keratoplasty such as Descemet's stripping endothelial keratoplasy or Descemet's membrane endothelial keratoplasty, in which only the posterior portion of the cornea is replaced. These two diseases are the major causes of corneal transplantation, approximately 40,000 of which occur annually in the United States.[20] The incidence of iatrogenically induced bullous keratopathy is decreasing with the improvement in cataract and other corneal surgical methodologies[21] and will not be discussed herein.

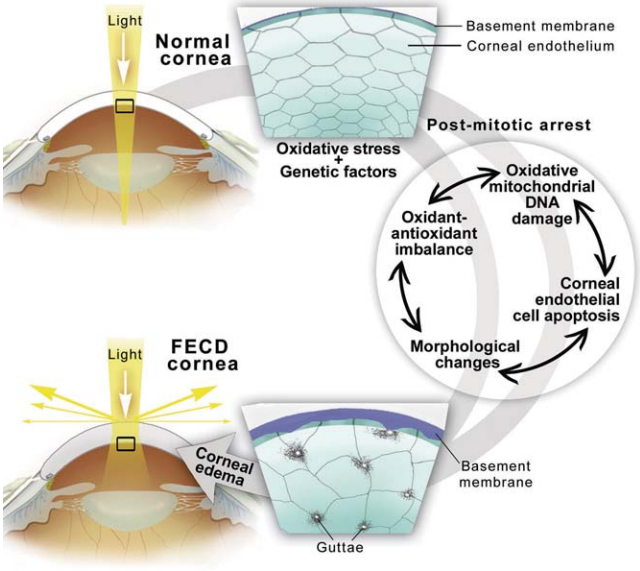

FIGURE 3. Hypothesis of the role of oxidative stress as the mechanism of disease in FECD. The hypothesis is based on studies of human corneas ex vivo and in vitro. Reprinted from Jurkunas UV, Bitar MS, Funaki T, Azizi B. Evidence of oxidative stress in the pathogenesis of Fuchs endothelial corneal dystrophy. *Am J Pathol.* 2010;177:2278–2289. Copyright 2010, with permission from the American Society for Investigative Pathology.

Fuchs' Endothelial Cell Dystrophy. Fuchs' endothelial corneal dystrophy is characterized not only by loss of endothelial cells but also by the development of mounds of extracellular material on Descemet's membrane, under discrete regions of endothelium, termed guttae. Cells on these mounds, or guttae, are attenuated and have an aberrant structure.[22] Fuchs' endothelial corneal dystrophy is primarily a late-onset genetic disorder. The genetic basis of FECD is complex and heterogeneous, demonstrating variable expressivity and incomplete penetrance. To date, several causal genes (*ZEB1*, *SLC4A11*, *TCF4*, and *LOXHD1*) have been identified, representing a small proportion of the total genetic load of FECD. Another gene, *col8A2*, has been identified in early-onset FECD (1% of the population with FECD).[23]

Risk factors for FECD include family history, female sex, and age. It is unknown whether environmental or lifestyle factors influence progression of the disease.

Because the genetic basis of FECD is complex, the search for a common pathophysiologic mechanism of the disease has led to the hypotheses that endothelial cells of patients with FECD have an alteration in their antioxidant system that results in diminished capacity to prevent cell damage due to oxidative stress, which can lead to apoptosis and endothelial cell loss.[24] The hypothesis (Fig. 3) is based on the demonstration of decreased antioxidant gene expression and increased oxidative DNA damage in endothelium of corneas from patients with FECD compared with that of age-matched control subjects.

Prevalence of FECD. A recent study[25] of 8 million enrollees in a national managed care network throughout the United States estimated the overall prevalence of corneal dystrophies to be 0.13% of the population, with the specific prevalence of FECD at 0.078%. Based on a population of 310 million, it is estimated that approximately 166,800 people in the United States carry the disease.[25] Older studies have found

higher prevalences of FECD. In 1980, Rosemblum et al.[26] reported a prevalence of 4%, and Waring et al.[27] in 1978 reported that guttae occur in 5% to 70% of patients and that their numbers increase with age. Variations in the results of these studies are because of differences in study methods.

The economic burden, both medical and social, from this age-related corneal dystrophy has not been assessed to date. However, along with iatrogenic bullous keratopathy, FECD represents the leading cause of corneal transplantation and Descemet's stripping endothelial keratoplasy. Considering that the medical costs per patient per transplantation may approach $5500 (provided in the public domain at http://www.healthcarebluebook.com/page_Results.aspx?id=280&dataset=MD), the annual costs per 20,000 corneal transplantations would approach $110 million.

What Can Be Done to Slow or Prevent Corneal and Ocular Surface Aging and Disease?

The enormous and growing effects of age-related diseases of the ocular surface and cornea are recognized as both social and medical burdens. The following recommendations are made to governmental agencies that control federal support for research and public education, as well as to professionals treating patients and to academicians doing research.

Aging

- Improve normative age-related data on changes in the ocular surface, cornea, and tears in humans with no apparent clinical disease;
- Enhance data on the effects of environmental stress, the microbiome, and lifestyle on the ocular surface, cornea, and tears in humans; and
- Educate the public on prevention, emphasizing risk factors that predispose to ocular surface or corneal stress.

Corneal and Ocular Surface Disease

Dry eye. Because it is highly prevalent and costly to treat, increase funding for research on dry eye, specifically the following:

- Identify biomarkers that distinguish the etiology of this multifactorial disease (e.g., MGD and lacrimal gland insufficiency),
- Verify the autoimmune hypothesis of the mechanism of this chronic disease in humans and thereby identify possible targets for immune-based therapy,
- Determine the basis of sex differences in dry eye disease, and
- Develop treatments specific to the various etiologies of dry eye disease.

Fuchs' endothelial corneal dystrophy.

- Fund research to determine the mechanism of FECD, to develop early, nonsurgical therapies; and
- Determine if lifestyle or environmental factors influence disease progression in FECD.

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