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# **Cataract Surgery and Dry Eye**

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# 1. Introduction

The World Health Organization (WHO) estimated the presence of approximately 37 million blind people in the world in 2002 (Resnikoff et al., 2004). This awful figure was expected to double by the year 2020 if appropriate preventive measures were not administered (Frick and Foster, 2003). Cataract, the opacification of the crystalline lens, is the single most important cause of blindness in the world. It is estimated that nearly 18 million people are bilaterally blind from cataract, representing almost 48% of all causes of blindness due to eye disease (Resnikoff et al., 2004). Age related cataract cannot usually be prevented; however, cataract surgery is one of the most cost-effective interventions in the field of medicine, resulting in almost immediate visual rehabilitation (Lansingh et al., 2007). Particularly, phacoemulsification is increasingly applied in the management of cataract patients because of its earlier refractive stabilization, reduced induced astigmatism, and milder postoperative inflammation, all resulting in faster visual rehabilitation. It has been shown that improvement in visual acuity following cataract surgery is accompanied by considerable gains in real life activities, emotional and social life components (Lamoureux et al., 2010). Cataract surgery is comparable in terms of cost-effectiveness to hip arthroplasty, and is generally more cost-effective than either knee arthroplasty or cardiac defibrillator implantation, and is cost-effective when considered in absolute terms (Agarwal and Kumar, 2010).

On the other hand, dry eye is estimated to have a prevalence of 11% to 33% depending on population and parameters studied and its prevalence increases with increasing age (Brewitt and Sistani, 2001; Lee et al., 2002; Moss et al., 2000; Schein et al., 1997a; Shimmura et al., 1999). Current evidence clearly demonstrates that dry eye, as a chronic disease, has significant impacts on quality of life and specifically, dry eye is one of the most important factors influencing quality of life in elderly populations. Reduction in quality of life is inevitable when symptoms of dry eye occur. These symptoms range from mild transient irritation to persistent dryness, burning, itchiness, redness, pain, ocular fatigue and visual disturbance. In the United States alone, approximately 7–10 million Americans require artificial tear preparations, with consumers spending over \$100 million/year (Lee et al., 2002). In moderate and severe cases, dry eye can impair the ability of patients to perform activities of daily living, impact work productivity, and influence mood and confidence (Friedman, 2010).

Obviously, a high proportion of cataract patients who are candidates for cataract surgery have dry eye; furthermore, there are overwhelming evidences suggesting aggravation or

initiation of dry eye following cataract surgery (Cohen, 1982; Gharaee et al., 2009; Hardten, 2008; Insler et al., 1985; Jones and Maguire, 1992; Khanal et al., 2008; Ram et al., 2002; Ram et al., 1998; Roberts and Elie, 2007). So even following uneventful cataract extraction and vision improvement the patient could be unsatisfied. A main cause of dissatisfaction in such cases has been shown to be eye fatigue and foreign body sensation due to dry eye syndrome. With these figures in mind, in this chapter, associations between cataract surgery and dry eye are discussed and probable pathogenic factors are highlighted.

# 2. The healthy tear film: Anatomy and physiology

A healthy tear film plays four major functions in the human eye, namely washing, lubricating, protecting, and forming a smooth optical surface on the cornea. Tear film constituents (the mucin, aqueous, and lipid components) work in concert to provide these functions and any alterations to the quality or quantity of the tear film threaten this fragile homeostasis.

Detailed discussion of the lacrimal system is out of scope of this chapter; however in brief, goblet cells in the conjunctiva are responsible for the production of the mucin layer, while the aqueous layer is secreted by the main and accessory lacrimal glands. The mucin layer plays a role in producing an even distribution of aqueous layer on the ocular surface. The lipids of the tear film generally originate at the meibomian glands, but also from other sources in the conjunctiva, cornea, and lacrimal glands (Butovich, 2008), and compose an interface between the underlying aqueous and mucin and the external environment. Alterations to the quality or quantity of the lipids in the human tear film may especially affect tear film evaporation. Regulation of tear secretion is through a complex neurohormonal system.

# 2.1 Sensory innervation of the cornea

Corneal sensation is a function of the long ciliary nerves of the ophthalmic division of the fifth (trigeminal) cranial nerve. It is estimated that there are approximately 7000 sensory receptors per square millimeter in the human corneal epithelium, implying that injuries to individual epithelial cells may be adequate to give a sensation (Muller et al., 2003). Traditionally, it was believed that most sensory nerves enter into the cornea along a transverse meridian (3- and 9-o'clock); this was in accordance with the clinical findings of better corneal sensation and less dry eye symptoms in patients undergoing laser in situ keratomileusis (LASIK) with a nasal hinge (Donnenfeld et al., 2003; Kohlhaas, 1998; Lee and Joo, 2003). However, the current description is that nerve bundles enter the peripheral mid-stromal cornea in a radial fashion, along different meridians and parallel to the corneal surface. Most stromal nerve fibers are located in the anterior third of the stroma; however, thick stromal nerve trunks move from the periphery toward the center below the anterior third of the stroma due to the organization of the collagen lamellae (Muller et al., 2003). Soon after entering the cornea, the main stromal bundles branch repeatedly and dichotomously into smaller fascicles that ascended into progressively more superficial layers of the stroma. Eventually, the stromal nerve fibers abruptly turn 90 degrees, penetrate Bowman's layer, and proceed toward the corneal surface. The nerves penetrate Bowman's layer throughout the peripheral and central cornea (Muller et al., 1996). After penetrating Bowman's layer, the large nerve bundles divide into

several smaller ones. Each small nerve bundle then turns abruptly once more at 90 degrees and continues parallel to the corneal surface, between Bowman's layer and the basal epithelial cell layer, forming the sub-basal nerve plexus. Sub-basal fibers subsequently form branches that turn upward and enter the corneal epithelium between the basal cells to reach the wing cells, where they terminate (Muller et al., 1996; Ueda et al., 1989). The exact orientation and the depth of nerve fiber bundles are not known and may vary between patients (Kim and Foulks, 1999; Muller et al., 2003; Muller et al., 1996; Muller et al., 1997).

Intact corneal innervation is mandatory for normal blinking and tearing reflexes, which in turn is essential to maintaining the integrity of the ocular surface. Under normal physiologic conditions, sensory nerves in the cornea transmit an afferent stimulation signal through the ophthalmic division of the trigeminal nerve to the brain stem and then, after a series of interneurons, the efferent signal is transmitted to the lacrimal gland through the parasympathetic and sympathetic nerves that innervate the gland and drive tear production and secretion (Dartt, 2004). Damage to this neural circuit interrupts the normal regulation of lacrimal gland secretion and influences both basal and stimulated tear production. This is one of the major pathogenic pathways in induction of postoperative dry eye in patients undergoing ophthalmic surgeries.

Most surgical procedures that cause denervation of the cornea result in impaired epithelial wound healing, increased epithelial permeability, decreased epithelial metabolic activity and loss of cytoskeletal structures associated with cellular adhesion (Donnenfeld et al., 2003; Kohlhaas, 1998). As mentioned earlier, the normal corneal epithelium has the highest density of sensory nerve endings throughout the human body. These receptors are located between the wing cell layers of the corneal epithelium and are protected from direct environmental stimulation by the overlying tear film and the intact surface epithelial cells. In early stages of dry eye, and in the presence of an unstable tear film and superficial punctate keratopathy, the environmental stimuli have greater access to the sensory nerve endings and this may be a key cause for the marked symptoms of ocular irritation experienced by dry eye patients, even in mild cases.

On the other hand, it has been demonstrated that hyposecretion of tears may lead to pathologic alterations in corneal nerves and a decline in corneal sensitivity which subsequently perpetuate the dry eye state in these patients (Xu et al., 1996). The exposure of nerve endings, in conjunction with tear hyperosmolarity and increased expression of a number of inflammatory cytokines, including interleukin (IL)-1alpha and IL-1beta, IL-6, and tumor necrosis factor-alpha may cause injury to the corneal nerves and incite neural degeneration (Barton et al., 1997; Solomon et al., 2001; Yoon et al., 2007). Meanwhile, many of these inflammatory cytokines can induce synthesis of a number of neurotrophic factors, including nerve growth factors, which stimulate the regeneration of corneal nerves (Dastjerdi and Dana, 2009). Changes in corneal nerves in patients with dry eye encompass a wide range of morphologic changes (such as presence of nerve sprouts, abnormal tortuosity, increased bead-like formation and thinning of nerve fiber bundles) to decreased, or paradoxically increased, number of nerve fibers depending on the stage of dry eye (Benitez del Castillo et al., 2004; Erdelyi et al., 2007; Hosal et al., 2005; Tuominen et al., 2003; Villani et al., 2007; Zhang et al., 2005). This could be an explanation for the discrepancy between dry eye signs and symptoms observed in many patients (Dastjerdi and Dana, 2009; Hay et al., 1998).

In addition, the presence of nerve fibers invaginating corneal epithelial cells and keratocytes suggests that both cell types are directly innervated. Immunocytochemical staining indicates the presence of different neuropeptides within the cell soma and peripheral axonal fibers of corneal neurons, suggesting that they are functionally heterogeneous. Until now, at least 17 different neuropeptides and neurotransmitters have been described in the corneal nerves (Dastjerdi and Dana, 2009). There are evidences that intact corneal nerve fibers exert trophic influences on the corneal epithelium and neuroregulation is responsible for maintenance of the integrity and repair of the ocular surface (Donnenfeld et al., 2003).

The mechanism underlying corneal damage in patients with reduced corneal sensation and dry eye –for instance, following surgery – is thought to be related to reduced levels of neurotransmitters. Peptidergic transmitters in nerve fibers may be involved in neuroimmunomodulation of the cornea (Muller et al., 1996). Enhanced epithelial cell proliferation is strongly believed to be mediated by neurotransmitters and nerve growth factors released from corneal nerve endings (Cavanagh and Colley, 1989). For example, it has been reported that acetylcholine derived from the corneal sensory nerve endings, increases intracellular levels of cyclic guanosine monophosphate (cGMP), which is associated with epithelial mitosis in the cornea and therefore enhances epithelial cell growth (Cavanagh and Colley, 1989). Substance P is a neuropeptide present in corneal nerves and has been found to stimulate DNA synthesis and promote corneal epithelial cell growth; it may also play a role in corneal epithelial wound healing. Calcitonin gene related peptide (CGRP), which often colocalizes with substance P in most ocular nerve fibers, also plays important roles in epithelial renewal and wound repair (Dastjerdi and Dana, 2009; Muller et al., 2003).

# 3. Dry eye syndrome

In a restructured definition of dry eye and its classifications by the International Dry Eye Workshop, dry eye is defined as a disorder of the lacrimal functional unit (LFU), an integrated system comprising the lacrimal glands, ocular surface (cornea, conjunctiva, and meibomian glands) and lids, and the sensory and motor nerves that connect them (2007). Disease or damage to any component of the LFU (the afferent sensory nerves, the efferent autonomic and motor nerves, and the tear-secreting glands) can destabilize the tear film and lead to ocular surface condition that expresses itself as dry eye.

A vital portion of the LFU is the part played by sensory impulses, which arise from the ocular surface and this is thought to be the main area of possible damage in ophthalmic surgeries involving the cornea.

As discussed earlier, disruption of a sufficient sensory drive from the ocular surface is strongly believed to be associated with the occurrence of dry eye by two exclusive and functionally diverse mechanisms: by decreasing reflex-induced lacrimal secretion (tear deficient dry eye) and by reducing the blink rate and, consequently, increasing evaporative loss (evaporative dry eye) (Bron, 1997; Lemp, 1995).

Corneal nerve alterations, either as a primary reason for tear hyposecretion or just the outcome of dryness of the ocular surface, have crucial effects on the integrated system of the LCU and can compromise various aspects of it, such as blinking, the tear reflex, and trophism of the epithelial cells, thus neatly contributing to the increase of the vicious circle of hypo-tearing leading to inflammation causing cell/nerve damage (Dastjerdi and Dana, 2009).

Different risk factors for dry eye have been identified, including increasing age, various systemic diseases (including diabetes, arthritis, allergy, and so), systemic medications, hormonal changes (menopause), neural alterations, ocular conditions (glaucoma, pterygium, meibomian gland dysfunction, lacrimal duct obstruction, contact lens wear) or environmental influences (climate, cigarette smoking) and many others (Manaviat et al., 2008; Moss et al., 2000; Ousler et al., 2005; Stern et al., 1998; Wolfe and Michaud, 2008).

Most dry-eye symptoms result from an abnormal, nonlubricative ocular surface that increases shear forces under the eyelids and diminishes the ability of the ocular surface to respond to environmental challenges. Dry eye manifestations could be described as visual fatigue, secretion, foreign body sensation, eyelids heaviness, dryness, uncomfortable eyes, pain, tears, blurred vision, itchiness, photophobia, and eye redness.

#### 3.1 Dry eye diagnosis

Dry eye signs tend to agree poorly with patient-reported symptoms (Hay et al., 1998; McCarty et al., 1998; Moss et al., 2000; Schein et al., 1997b; Shimmura et al., 1999). As alleviation of dry eye symptoms is of primary importance in dry eye treatment, identification of dry eye symptoms can be regarded as important as objective dry eye tests are (Bandeen-Roche et al., 1997; Lemp, 1995; Nichols et al., 2000). More recently, the impact of dry eye on quality of life parameters has been suggested as a more valuable tool for assessing the burden of disease as well as response to treatment (Friedman, 2010).

Currently, the majority of clinicians probe into the patient's symptomatology regularly and the clinical tests most routinely used to evaluate severity of dry eye are tear break up time and corneal staining (Smith et al., 2008).

Finally, it is important to remember that diurnal variation is known to occur in symptomatology and clinical signs, and to affect the visual function capabilities of dry eye patients (Abelson et al., 2009; Walker et al., 2010).

## 3.1.1 Ocular Surface Disease Index (OSDI)

The Ocular Surface Disease Index (OSDI) was developed by the Outcomes Research Group (OSDI®, Allergan, Inc., Irvine, CA, USA) and consists of a 12-item questionnaire designed to provide a rapid assessment of the symptoms of ocular irritation consistent with dry eye disease and their impact on vision-related functioning. The questions are subscaled in three major categories: vision-related function, ocular symptoms, and environmental triggers. The total score of the OSDI ranges from zero to 100, where the higher scores represent a greater disability (Li et al., 2007; Vroman et al., 2005).

#### 3.1.2 Tear Break-up Time (TBUT)

A commercially available fluorescein-impregnated strip wet with non-preserved saline is used in this test and placed in the inferior fornix. Alternatively, sodium fluorescein can be instilled; however, the first method seems to disturb the natural condition of the ocular surface less. The patient is then asked to blink 3 times, and then to look straight ahead without any blink. The tear film is observed using a cobalt blue filter under wide beam illumination at the slit-lamp. The interval between the last blink and the appearance of the first randomly appeared corneal dry spot is measured as TBUT. A value less than 10 seconds is regarded as abnormal (Gharaee et al., 2009; Liu et al., 2008).

Patients with a tear break up time of less than 10 seconds before surgery have been shown to be at significant risk of experiencing tear film instability following phacoemulsification (Liu et al., 2002).

However, there are some concerns that fluorescein itself can reduce the break up time of tear film (Taylor, 1980).

# 3.1.3 Schirmer's 1 test (S1T)

The test is performed under natural lighting conditions without topical anesthesia. One of several types of commercially available filter paper, standardized for the Schirmer's test, is placed in the lower fornix, over the junction of the middle and lateral thirds of the lower eyelid, and left in place for 5 minutes while the eyes are closed. The distance moistened is directly read off the scale on the paper itself. A reading of less than 10 mm is considered abnormal (Cho and Kim, 2009; Gharaee et al., 2009; Liu et al., 2008). Noticeably, it has been suggested that in patients who are candidates for LASIK surgery, those with S1T less than 20 mm/ 5 min may be more likely to develop chronic dry eye after surgery (Konomi et al., 2008). However, there may be many differences between the incision of LASIK and that of cataract surgery with respect to incision width, depth, and location (Cho and Kim, 2009).

#### 3.1.4 Tear Meniscus Height (TMH)

This value is evaluated by measuring the height of the lacrimal river (tear film meniscus) and reading the scale on slit lamp microscopy without fluorescein. In dry eye patients, the lacrimal river may disappear.

#### 3.1.5 Corneal staining

The cornea fluorescein staining is evaluated by using fluorescein test paper to contact the lower fornix of the eye. After 3 blinks, the subjects are asked to look straight ahead without any blink. The cornea is assessed under the wide beam cobalt blue light of the biomicroscope. Staining in any part of the cornea is considered abnormal. There are various classification schemes for grading the severity of staining.

#### 3.1.6 Ocular surface stress test

Hardten introduced the "ocular surface stress test" as a tool to detect patients most at risk of developing initial or worsening manifestations of dry eye following phacoemulsification. In this test, ophthalmic examinations are performed in the usual manner and after instillation of dilating and anesthetic eye drops, the patient is instructed to sit in the waiting room for 30 – 60 minutes. The patient is then re-examined and the presence of epithelial irregularity or punctate keratopathy after fluorescein staining is regarded as an alarming sign of an ocular surface problem (Hardten, 2008).

#### 3.1.7 Ocular Protection Index (OPI)

The OPI is a binomial parameter incorporating TBUT and blink rate to decipher the level of ocular surface protection provided by the tear film between blinks. The OPI is calculated by dividing TBUT (in seconds) by inter-blink interval (or number of seconds between blinks) (Ousler, III et al., 2008).

# 4. Dry eye in cataract patients

Multiple studies have demonstrated somewhat less favorable outcomes of cataract surgery in patients with dry eye, especially in those with associated connective tissue disorders (Adenis et al., 1996; Cohen, 1982; Gharaee et al., 2009; Golubovic and Parunovic, 1987; Hirsch, 2003; Insler et al., 1985; Krachmer and Laibson, 1974; Mehra and Elaraoud, 1992; Pfister and Murphy, 1980; Radtke et al., 1978; Ram et al., 2002; Ram et al., 1998; Zabel et al., 1989). In addition, there are several studies, investigating dry eye in healthy patients undergoing cataract surgery and there are evidences that dry eye manifestations such as red eye, foreign body sensation and fatigue will inevitably emerge in most patients after cataract surgery (Cho and Kim, 2009; Gharaee et al., 2009; Li et al., 2007).

Various complications including punctuate epithelial erosions, persistent or recurrent epithelial defects, filamentary keratitis, secondary infections, corneal ulceration, and keratolysis have been reported after cataract surgery in patients with dry eye. Patients with Sjögren's syndrome are predisposed to complications such as suture abscesses, infectious keratitis, peripheral keratolysis, filamentary keratitis, and endophthalmitis following conventional extracapsular cataract extraction (Cohen, 1982; Insler et al., 1985; Jones and Maguire, 1992; Krachmer and Laibson, 1974; Mehra and Elaraoud, 1992; Ormerod et al., 1988; Pfister and Murphy, 1980; Radtke et al., 1978; Ram et al., 2002; Ram et al., 1998). In addition, dry eyes are more susceptible to infection especially with Staphylococci and Streptococci (Dohlman et al., 1970; Jain et al., 1983; Ram et al., 1998; Scott et al., 1996). This could be due to decreased quantities of various protective enzymes such as lysozymes, lactoferrins, beta-lysins, and immunoglobulins in the tear film. (Dohlman et al., 1970; Holly and Lemp, 1977; Scott et al., 1996; Seal et al., 1986).

Various factors play a role in outcomes in the patients with or without dry eye that have surgery. Most important is postoperative corneal desensitization (Lyne, 1982). Conventional extracapsular cataract extraction requires an incision that involves at least 4 to 5 clock hours of the limbus, denervating the superior half of the cornea. Lyne reported that the loss of corneal sensitivity after cataract surgery often persists for more than 2 years and can be permanent (Lyne, 1982). Corneal sensitivity impairment after ocular surface surgery is dependent on the extent of the corneal incision (Lyne, 1982). As mentioned earlier, the sensory denervation interferes with the normal physiology of the corneal epithelium and decreases epithelial cell mitosis, delaying wound healing.

In addition, topical anesthesia and eye drops containing preservatives like benzalkonium chloride are well known to have effects on the corneal epithelium (Walker, 2004). Exposure to light from the operating microscope might also be associated with postoperative dry eye (Cho and Kim, 2009). Furthermore, the use of ultrasound in cataract surgery may damage corneal structures such as the epithelium, stroma, keratocyte, endothelium, and nerve plexuses (Mencucci et al., 2005).

Ocular surface complications are much rarer following small incision phacoemulsification. Phacoemulsification has several advantages compared with extracapsular cataract extraction in patients with dry eye, including a much smaller incision with less corneal denervation, minimal tear-film surfacing problems (Khanal et al., 2008), and absence of sutures and so, smaller risk of infections (Ram et al., 2002). In addition, the shorter duration of phacoemulsification is accompanied by shorter microscope light exposure and the faster visual rehabilitation permits rapid tapering of topical medications.

In a study on dry eye following cataract surgery, my colleagues and I focused on tear film changes after phacoemulsification and the effect of clear corneal incision location on tear film (Gharaee et al., 2009). We enrolled 68 eyes of 68 patients without preoperative dry eye and with senile cataract requiring phacoemulsification in a prospective, cohort study. Basic Tear Secretion Test (BTST), Tear Meniscus Height (TMH) measurement, Tear Break Up Time Test (TBUT) and Schirmer's 1 Test (S1T) were performed in all participants before and three months after surgery. Preoperative keratometry was used to determine the steepest meridian and corresponding location of the clear corneal incision. The cohort included 46 men (67.6%) and 22 women (32.3%), with an age range of 48 to 82 years (mean, 66.9±9.4 years). Phacoemulsification was performed with a temporal clear corneal incision in 36 eyes (52.9%) and with a superotemporal clear corneal incision in 32 eyes (47.1%). All incisions were made using a 3.2mm, single-use surgical knife (MSL 32, Mani Ophthalmic Knife, Japan) and left un-sutured at the conclusion of surgery. Topical chloramphenicol and betamethasone eye drops were administered on a tapering dose for one month postoperatively. There was no statistically significant difference between the results of preand post- operative S1T, TMH and BTST. These latter tests were not statistically different between incisions at different locations. However, TBUT results differed significantly in preand post-operative examination in both incision location groups (P<0.001) - though there was no statistically significant difference in TBUT results comparing incision locations (Gharaee et al., 2009). We had speculated that cutting more sensory nerves on the rich temporal meridians would have more effect on the tear film properties. However, this hypothesis was not confirmed in our study and this is in accordance with the newer description of the corneal nerve distribution described in this chapter (Muller et al, 1996; Ueda et al, 1989). Interestingly, Vroman and colleagues investigated the effect of hinge location on corneal sensation and dry eye after LASIK in a cohort of 47 myopic patients. In their series patient with a nasal hinge had significantly better corneal sensation than those with a superior hinge; however, dry eye occurred with the same frequency in both groups (Vroman et al., 2005).

Cho and associates investigated the effect of incision location and shape on postoperative dry eye in patients undergoing phacoemulsification. Their results suggested that incision location has no effect on dry eye signs in either patients with or without preoperative dry eye; however, with regard to incision shape, a grooved incision was associated with more dry eye signs than single plane incisions in those patients without preoperative dry eye. In addition, there was significant correlation between microscopic light exposure time and dry eye test values. Moreover, corneal suture removal was associated with aggravation of dry eye symptoms in patients with preoperative dry eye (Cho and Kim, 2009).

Khanal and associates investigated post-phacoemulsification changes in corneal sensitivity and tear physiology in a longitudinal, randomized trial on 18 patients (Khanal et al., 2008). They found that deterioration in corneal sensitivity and tear physiology is seen immediately after phacoemulsification. Despite a trend toward full-recovery, corneal sensitivity does not return to preoperative levels until 3 months postoperatively, whereas the tear functions recover within 1 month. In addition, postoperative treatment with tear lubricant was not found to have any effect on the improvement of tear physiology and corneal sensitivity post-surgically. In our study, we evaluated tear film properties 3 months after surgery and similarly we did not found statistically significant changes in tear tests (Gharaee et al., 2009). In another study, Ram and associates evaluated the outcome of phacoemulsification in 23 patients with dry eye (Ram et al., 2002). Although all patients with dry eye reported more

discomfort and irritation for 3 to 4 weeks following cataract surgery compared to preoperatively, and a minimal detrimental effect on Schirmer's and TBUT tests was also found, they concluded that phacoemulsification was safe and led to minimal complications in patients with age-related dry eye with or without associated systemic disorders.

It is estimated that up to 20% of all cataract surgeries are performed on diabetic patients (Liu et al., 2008) and nearly half of diabetic patients had dry eye in some reports (Manaviat et al., 2008). Liu and coworkers compared 25 diabetic cataract patients with 20 age-matched non-diabetic cataract patients (Liu et al., 2008). They found that tear secretion was reduced in diabetic cataract patients after phacoemulsification, which worsened dry eye symptoms and predisposed those patients to ocular damage. However, in non-diabetics there was no significant, persistent change in tear film. As we found in our study, they also observed a transient increase in S1T in the early postoperative period, which returned to preoperative levels in 180 days.

Li and colleagues investigated pathogenic factors responsible for dry eye in patients after cataract surgery (Li et al., 2007). In their study impression cytology demonstrated that, even 3 months following cataract surgery, goblet cells were reduced in the bulbar conjunctiva along with changes of squamous metaplasia, and this was most marked in the regions covered by the lower lid; these findings suggest that dry eye might be induced by eye drops (Li et al., 2007). The authors stated that dry eye could develop or deteriorate dramatically after cataract surgery if not treated timely and this could happen as early as one week postoperatively and peaks at about one month. Furthermore, misuse of eye drops is one of the major pathogenic factors that causes dry eye after cataract surgery. Other authors had similar findings previously (Lyne, 1982; Zabel et al., 1989); however, the role of eye drops in postoperative dry eye has not been confirmed in all studies (Khanal et al., 2008; Ram et al., 2002).

## 5. Treatment

Due to the many different causes and pathophysiologies, dry eye treatment continues to present a substantial challenge to the clinician. Dry eye aggravation following cataract surgery, especially with modern microincision phacoemulsification techniques, seems to be self-limited. In patients with preoperative dry eye, augmentation of dry eye treatment may be necessary; however, in those with normal tear status prior to surgery, temporary measures may be adequate. Over-the-counter ocular lubricants remain the mainstay of treatment, and a formulation of cyclosporine A is the only Food and Drug Administration (FDA)-approved ophthalmic solution for dry eye, but its indication is limited to patients who experience inflammation associated with dry eye. Punctal plugs and dissolving inserts placed in the subconjunctival sacs are other treatment options. Nutritional influences on dry eye are well-known and omega-3 and omega-6 fatty acid intake could have beneficial effects on dry eye.

#### 6. Conclusion

Dry eye manifestations appear or are aggravated following cataract surgery in most patients. Before surgery, patients should be informed about the presence of dry eye manifestations and the possible increase in dry eye symptoms. This would decrease the likelihood that patients will blame the cataract surgery per se for "tired eyes" or "fluctuation of vision," which are often signs of ocular surface disease. Increasing awareness helps the patient separate those dry eye symptoms from those of the surgery and makes postoperative care and counseling easier for the staff and physician (Hardten, 2008).

Intraoperative exposure to the operating microscope light should be minimized. The clinician should also be cognizant of the fact that grooved incisions, despite their advantages in other respects, can aggravate dry eye symptoms and signs in eyes that were healthy preoperatively (Cho and Kim, 2009). In addition, it is advised that eye drops should be carefully administered before and after cataract surgery to avoid or reduce the occurrence of dry eye postoperatively.

The use of artificial tears was found not to facilitate recovery of tear physiology following phacoemulsification in all studies. Nevertheless, based on the findings of some studies (Foulks, 2003; Tomlinson et al., 1998; Yazdani et al., 2001), it may still be advisable for patients experiencing postoperative dry eye symptoms to use artificial tears to alleviate the symptoms. In patients with postoperative dry eye, timely effective treatment such as with artificial tears or lacrimal plugs is necessary (Li et al., 2007).

Future research should focus on realistic modifications to the phacoemulsification procedure to achieve a safer approach in patients with ocular surface problems.

#### 7. References

- 2007, The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007): Ocul.Surf., v. 5, no. 2, p. 75-92.
- Abelson, M. B., G. W. Ousler, III, and C. Maffei, 2009, Dry eye in 2008: Curr. Opin. Ophthalmol., v. 20, no. 4, p. 282-286.
- Adenis, J. P., J. A. Bernard, A. Ducasse, B. Fayet, and J. L. George, 1996, [Dry syndrome and cataract surgery. A case]: J Fr.Ophtalmol., v. 19, no. 3, p. 222-224.
- Agarwal, A., and D. A. Kumar, 2010, Cost-effectiveness of cataract surgery: Curr. Opin. Ophthalmol..
- Bandeen-Roche, K., B. Munoz, J. M. Tielsch, S. K. West, and O. D. Schein, 1997, Self-reported assessment of dry eye in a population-based setting: Invest Ophthalmol.Vis.Sci., v. 38, no. 12, p. 2469-2475.
- Barton, K., D. C. Monroy, A. Nava, and S. C. Pflugfelder, 1997, Inflammatory cytokines in the tears of patients with ocular rosacea: Ophthalmology, v. 104, no. 11, p. 1868-1874.
- Benitez del Castillo, J. M., M. A. Wasfy, C. Fernandez, and J. Garcia-Sanchez, 2004, An in vivo confocal masked study on corneal epithelium and subbasal nerves in patients with dry eye: Invest Ophthalmol.Vis.Sci., v. 45, no. 9, p. 3030-3035.
- Brewitt, H., and F. Sistani, 2001, Dry eye disease: the scale of the problem: Surv. Ophthalmol., v. 45 Suppl 2, p. S199-S202.
- Bron, A. J., 1997, The Doyne Lecture. Reflections on the tears: Eye (Lond), v. 11 (Pt 5), p. 583-602.
- Butovich, I. A., 2008, On the lipid composition of human meibum and tears: comparative analysis of nonpolar lipids: Invest Ophthalmol.Vis.Sci., v. 49, no. 9, p. 3779-3789.
- Cavanagh, H. D., and A. M. Colley, 1989, The molecular basis of neurotrophic keratitis: Acta Ophthalmol.Suppl, v. 192, p. 115-134.
- Cho, Y. K., and M. S. Kim, 2009, Dry eye after cataract surgery and associated intraoperative risk factors: Korean J.Ophthalmol., v. 23, no. 2, p. 65-73.
- Cohen, K. L., 1982, Sterile corneal perforation after cataract surgery in Sjogren's syndrome: Br.J.Ophthalmol., v. 66, no. 3, p. 179-182.
- Collins, M., R. Seeto, L. Campbell, and M. Ross, 1989, Blinking and corneal sensitivity: Acta Ophthalmol.(Copenh), v. 67, no. 5, p. 525-531.

- Dartt, D. A., 2004, Dysfunctional neural regulation of lacrimal gland secretion and its role in the pathogenesis of dry eye syndromes: Ocul.Surf., v. 2, no. 2, p. 76-91.
- Dastjerdi, M. H., and R. Dana, 2009, Corneal nerve alterations in dry eye-associated ocular surface disease: Int.Ophthalmol.Clin., v. 49, no. 1, p. 11-20.
- Dohlman, C. H., M. A. Lemp, and F. P. English, 1970, Dry eye syndromes: Int. Ophthalmol. Clin., v. 10, no. 2, p. 215-251.
- Donnenfeld, E. D., K. Solomon, H. D. Perry, S. J. Doshi, M. Ehrenhaus, R. Solomon, and S. Biser, 2003, The effect of hinge position on corneal sensation and dry eye after LASIK: Ophthalmology, v. 110, no. 5, p. 1023-1029.
- Erdelyi, B., R. Kraak, A. Zhivov, R. Guthoff, and J. Nemeth, 2007, In vivo confocal laser scanning microscopy of the cornea in dry eye: Graefes Arch.Clin.Exp.Ophthalmol., v. 245, no. 1, p. 39-44.
- Ernest, P., R. Tipperman, R. Eagle, C. Kardasis, K. Lavery, A. Sensoli, and M. Rhem, 1998, Is there a difference in incision healing based on location?: J.Cataract Refract.Surg., v. 24, no. 4, p. 482-486.
- Foulks, G. N., 2003, The evolving treatment of dry eye: Ophthalmol.Clin.North Am., v. 16, no. 1, p. 29-35.
- Frick, K. D., and A. Foster, 2003, The magnitude and cost of global blindness: an increasing problem that can be alleviated: Am.J Ophthalmol., v. 135, no. 4, p. 471-476.
- Friedman, N. J., 2010, Impact of dry eye disease and treatment on quality of life: Curr.Opin.Ophthalmol., v. 21, no. 4, p. 310-316.
- Gharaee, H., M. N. Mousavi, R. Daneshvar, M. Hosseini, and S. Sazande, 2009, Effect of Clear Corneal Incision Location on Tear Film following Phacoemulsification Surgery: Iranian Journal of Ophthalmology, v. 21, no. 3, p. 29-34.
- Golubovic, S., and A. Parunovic, 1987, Corneal perforation in dry eye patients: Fortschr.Ophthalmol., v. 84, no. 1, p. 33-37.
- Hardten, D. R., 2008, Dry eye disease in patients after cataract surgery: Cornea, v. 27, no. 7, p. 855.
- Hay, E. M., E. Thomas, B. Pal, A. Hajeer, H. Chambers, and A. J. Silman, 1998, Weak association between subjective symptoms or and objective testing for dry eyes and dry mouth: results from a population based study: Ann.Rheum.Dis., v. 57, no. 1, p. 20-24.
- Hirsch, J. D., 2003, Considerations in the pharmacoeconomics of dry eye: Manag.Care, v. 12, no. 12 Suppl, p. 33-38.
- Hoffman, R. S., I. H. Fine, and M. Packer, 2005, New phacoemulsification technology: Curr.Opin.Ophthalmol., v. 16, no. 1, p. 38-43.
- Holly, F. J., and M. A. Lemp, 1977, Tear physiology and dry eyes: Surv.Ophthalmol., v. 22, no. 2, p. 69-87.
- Hosal, B. M., N. Ornek, G. Zilelioglu, and A. H. Elhan, 2005, Morphology of corneal nerves and corneal sensation in dry eye: a preliminary study: Eye (Lond), v. 19, no. 12, p. 1276-1279.
- Insler, M. S., G. Boutros, and D. W. Boulware, 1985, Corneal ulceration following cataract surgery in patients with rheumatoid arthritis: J.Am.Intraocul.Implant.Soc., v. 11, no. 6, p. 594-597.
- Jain, I. S., A. Gupta, J. Ram, and Dhir SP., 1983, Mima polymorpha: a dangerous opportunist in ocular infections.: J OcularTher Surg, v. 2, p. 143-145.
- Jones, R. R., and L. J. Maguire, 1992, Corneal complications after cataract surgery in patients with rheumatoid arthritis: Cornea, v. 11, no. 2, p. 148-150.
- Khanal, S., A. Tomlinson, L. Esakowitz, P. Bhatt, D. Jones, S. Nabili, and S. Mukerji, 2008, Changes in corneal sensitivity and tear physiology after phacoemulsification: Ophthalmic Physiol Opt., v. 28, no. 2, p. 127-134.

Kim, J., and G. N. Foulks, 1999, Evaluation of the effect of lissamine green and rose bengal on human corneal epithelial cells: Cornea, v. 18, no. 3, p. 328-332.

- Kohlhaas, M., 1998, Corneal sensation after cataract and refractive surgery: J Cataract Refract.Surg, v. 24, no. 10, p. 1399-1409.
- Konomi, K., L. L. Chen, R. S. Tarko, A. Scally, D. A. Schaumberg, D. Azar, and D. A. Dartt, 2008, Preoperative characteristics and a potential mechanism of chronic dry eye after LASIK: Invest Ophthalmol.Vis.Sci., v. 49, no. 1, p. 168-174.
- Krachmer, J. H., and P. R. Laibson, 1974, Corneal thinning and perforation in Sjogren's syndrome: Am.J.Ophthalmol., v. 78, no. 6, p. 917-920.
- Lamoureux, E. L., E. Fenwick, K. Pesudovs, and D. Tan, 2010, The impact of cataract surgery on quality of life: Curr.Opin.Ophthalmol..
- Lansingh, V. C., M. J. Carter, and M. Martens, 2007, Global cost-effectiveness of cataract surgery: Ophthalmology, v. 114, no. 9, p. 1670-1678.
- Lawrenson, J. G., 1997, Corneal sensitivity in health and disease: Ophthalmic Physiol Opt., v. 17 Suppl 1, p. S17-S22.
- Lee, A. J., J. Lee, S. M. Saw, G. Gazzard, D. Koh, D. Widjaja, and D. T. Tan, 2002, Prevalence and risk factors associated with dry eye symptoms: a population based study in Indonesia: Br.J.Ophthalmol., v. 86, no. 12, p. 1347-1351.
- Lee, K. W., and C. K. Joo, 2003, Clinical results of laser in situ keratomileusis with superior and nasal hinges: J Cataract Refract.Surg, v. 29, no. 3, p. 457-461.
- Lemp, M. A., 1995, Report of the National Eye Institute/Industry workshop on Clinical Trials in Dry Eyes: CLAO J, v. 21, no. 4, p. 221-232.
- Li, X. M., L. Hu, J. Hu, and W. Wang, 2007, Investigation of dry eye disease and analysis of the pathogenic factors in patients after cataract surgery: Cornea, v. 26, no. 9 Suppl 1, p. S16-S20.
- Liu, X., Y. S. Gu, and Y. S. Xu, 2008, Changes of tear film and tear secretion after phacoemulsification in diabetic patients: J.Zhejiang.Univ Sci.B, v. 9, no. 4, p. 324-328.
- Liu, Z. et al., 2002, [Tear film changes after phacoemulsification]: Zhonghua Yan.Ke.Za Zhi., v. 38, no. 5, p. 274-277.
- Lyne, A., 1982, Corneal sensitivity after surgery: Trans.Ophthalmol.Soc.U.K., v. 102 (pt 2), p. 302-305.
- Manaviat, M. R., M. Rashidi, M. Afkhami-Ardekani, and M. R. Shoja, 2008, Prevalence of dry eye syndrome and diabetic retinopathy in type 2 diabetic patients:

  BMC.Ophthalmol., v. 8, p. 10.
- Mathers, W. D., 2000, Why the eye becomes dry: a cornea and lacrimal gland feedback model: CLAO J., v. 26, no. 3, p. 159-165.
- McCarty, C. A., A. K. Bansal, P. M. Livingston, Y. L. Stanislavsky, and H. R. Taylor, 1998, The epidemiology of dry eye in Melbourne, Australia: Ophthalmology, v. 105, no. 6, p. 1114-1119.
- McDonnell, P. J., M. Taban, M. Sarayba, B. Rao, J. Zhang, R. Schiffman, and Z. Chen, 2003, Dynamic morphology of clear corneal cataract incisions: Ophthalmology, v. 110, no. 12, p. 2342-2348.
- Mehra, K. S., and M. S. Elaraoud, 1992, Total central keratolysis: Ann.Ophthalmol., v. 24, no. 2, p. 54-55.
- Mencucci, R., S. Ambrosini, C. Ponchietti, M. Marini, G. B. Vannelli, and U. Menchini, 2005, Ultrasound thermal damage to rabbit corneas after simulated phacoemulsification: J Cataract Refract.Surg, v. 31, no. 11, p. 2180-2186.
- Moss, S. E., R. Klein, and B. E. Klein, 2000, Prevalence of and risk factors for dry eye syndrome: Arch.Ophthalmol., v. 118, no. 9, p. 1264-1268.

- Muller, L. J., C. F. Marfurt, F. Kruse, and T. M. Tervo, 2003, Corneal nerves: structure, contents and function: Exp.Eye Res., v. 76, no. 5, p. 521-542. Erratum in: Exp Eye Res. 2003 Aug; 77(2):253
- Muller, L. J., L. Pels, and G. F. Vrensen, 1996, Ultrastructural organization of human corneal nerves: Invest Ophthalmol.Vis.Sci., v. 37, no. 4, p. 476-488.
- Muller, L. J., G. F. Vrensen, L. Pels, B. N. Cardozo, and B. Willekens, 1997, Architecture of human corneal nerves: Invest Ophthalmol.Vis.Sci., v. 38, no. 5, p. 985-994.
- Nakamori, K., M. Odawara, T. Nakajima, T. Mizutani, and K. Tsubota, 1997, Blinking is controlled primarily by ocular surface conditions: Am.J.Ophthalmol., v. 124, no. 1, p. 24-30.
- Nichols, K. K., J. J. Nichols, and K. Zadnik, 2000, Frequency of dry eye diagnostic test procedures used in various modes of ophthalmic practice: Cornea, v. 19, no. 4, p. 477-482.
- Ormerod, L. D., L. P. Fong, and C. S. Foster, 1988, Corneal infection in mucosal scarring disorders and Sjogren's syndrome: Am.J Ophthalmol., v. 105, no. 5, p. 512-518.
- Ousler, G. W., P. J. Gomes, D. Welch, and M. B. Abelson, 2005, Methodologies for the study of ocular surface disease: Ocul.Surf., v. 3, no. 3, p. 143-154.
- Ousler, G. W., III, K. W. Hagberg, M. Schindelar, D. Welch, and M. B. Abelson, 2008, The Ocular Protection Index: Cornea, v. 27, no. 5, p. 509-513.
- Pfister, R. R., and G. E. Murphy, 1980, Corneal ulceration and perforation associated with Sjogren's syndrome: Arch.Ophthalmol., v. 98, no. 1, p. 89-94.
- Prause, J. U., and M. Norn, 1987, Relation between blink frequency and break-up time?: Acta Ophthalmol.(Copenh), v. 65, no. 1, p. 19-22.
- Radtke, N., S. Meyers, and H. E. Kaufman, 1978, Sterile corneal ulcers after cataract surgery in keratoconjunctivitis sicca: Arch.Ophthalmol., v. 96, no. 1, p. 51-52.
- Ram, J., A. Gupta, G. Brar, S. Kaushik, and A. Gupta, 2002, Outcomes of phacoemulsification in patients with dry eye: J.Cataract Refract.Surg., v. 28, no. 8, p. 1386-1389.
- Ram, J., A. Sharma, S. S. Pandav, A. Gupta, and P. Bambery, 1998, Cataract surgery in patients with dry eyes: J.Cataract Refract.Surg., v. 24, no. 8, p. 1119-1124.
- Resnikoff, S., D. Pascolini, D. Etya'ale, I. Kocur, R. Pararajasegaram, G. P. Pokharel, and S. P. Mariotti, 2004, Global data on visual impairment in the year 2002: Bull.World Health Organ, v. 82, no. 11, p. 844-851.
- Roberts, C. W., and E. R. Elie, 2007, Dry eye symptoms following cataract surgery: Insight., v. 32, no. 1, p. 14-21.
- Roszkowska, A. M., P. Colosi, F. M. Ferreri, and S. Galasso, 2004, Age-related modifications of corneal sensitivity: Ophthalmologica, v. 218, no. 5, p. 350-355.
- Schein, O. D., B. Munoz, J. M. Tielsch, K. Bandeen-Roche, and S. West, 1997a, Prevalence of dry eye among the elderly: Am.J Ophthalmol., v. 124, no. 6, p. 723-728.
- Schein, O. D., J. M. Tielsch, B. Munoz, K. Bandeen-Roche, and S. West, 1997b, Relation between signs and symptoms of dry eye in the elderly. A population-based perspective: Ophthalmology, v. 104, no. 9, p. 1395-1401.
- Scott, I. U., H. W. Flynn, Jr., W. Feuer, S. C. Pflugfelder, E. C. Alfonso, R. K. Forster, and D. Miller, 1996, Endophthalmitis associated with microbial keratitis: Ophthalmology, v. 103, no. 11, p. 1864-1870.
- Seal, D. V., J. I. McGill, I. A. Mackie, G. M. Liakos, P. Jacobs, and N. J. Goulding, 1986, Bacteriology and tear protein profiles of the dry eye: Br.J Ophthalmol., v. 70, no. 2, p. 122-125.
- Shimmura, S., J. Shimazaki, and K. Tsubota, 1999, Results of a population-based questionnaire on the symptoms and lifestyles associated with dry eye: Cornea, v. 18, no. 4, p. 408-411.

Smith, J., K. K. Nichols, and E. K. Baldwin, 2008, Current patterns in the use of diagnostic tests in dry eye evaluation: Cornea, v. 27, no. 6, p. 656-662.

- Solomon, A., D. Dursun, Z. Liu, Y. Xie, A. Macri, and S. C. Pflugfelder, 2001, Pro- and antiinflammatory forms of interleukin-1 in the tear fluid and conjunctiva of patients with dry-eye disease: Invest Ophthalmol.Vis.Sci., v. 42, no. 10, p. 2283-2292.
- Stern, M. E., R. W. Beuerman, R. I. Fox, J. Gao, A. K. Mircheff, and S. C. Pflugfelder, 1998, The pathology of dry eye: the interaction between the ocular surface and lacrimal glands: Cornea, v. 17, no. 6, p. 584-589.
- Taylor, H. R., 1980, Studies on the tear film in climatic droplet keratopathy and pterygium: Arch.Ophthalmol., v. 98, no. 1, p. 86-88.
- Tomlinson, A., J. P. Craig, and G. E. Lowther, 1998, The biophysical role in tear regulation: Adv.Exp.Med.Biol., v. 438, p. 371-380.
- Tuominen, I. S., Y. T. Konttinen, M. H. Vesaluoma, J. A. Moilanen, M. Helinto, and T. M. Tervo, 2003, Corneal innervation and morphology in primary Sjogren's syndrome: Invest Ophthalmol.Vis.Sci., v. 44, no. 6, p. 2545-2549.
- Ueda, S., C. M. del, J. A. LoCascio, and J. V. Aquavella, 1989, Peptidergic and catecholaminergic fibers in the human corneal epithelium. An immunohistochemical and electron microscopic study: Acta Ophthalmol.Suppl, v. 192, p. 80-90.
- Villani, E., D. Galimberti, F. Viola, C. Mapelli, and R. Ratiglia, 2007, The cornea in Sjogren's syndrome: an in vivo confocal study: Invest Ophthalmol.Vis.Sci., v. 48, no. 5, p. 2017-2022.
- Vroman, D. T., H. P. Sandoval, L. E. Fernandez de Castro, T. J. Kasper, M. P. Holzer, and K. D. Solomon, 2005, Effect of hinge location on corneal sensation and dry eye after laser in situ keratomileusis for myopia: J.Cataract Refract.Surg., v. 31, no. 10, p. 1881-1887.
- Walker, P. M., K. J. Lane, G. W. Ousler, III, and M. B. Abelson, 2010, Diurnal variation of visual function and the signs and symptoms of dry eye: Cornea, v. 29, no. 6, p. 607-612.
- Walker, T. D., 2004, Benzalkonium toxicity: Clin. Experiment. Ophthalmol., v. 32, no. 6, p. 657.
- Wolfe, F., and K. Michaud, 2008, Prevalence, risk, and risk factors for oral and ocular dryness with particular emphasis on rheumatoid arthritis: J Rheumatol., v. 35, no. 6, p. 1023-1030.
- Wolkoff, P., J. K. Nojgaard, C. Franck, and P. Skov, 2006, The modern office environment desiccates the eyes?: Indoor.Air, v. 16, no. 4, p. 258-265.
- Wolkoff, P., J. K. Nojgaard, P. Troiano, and B. Piccoli, 2005, Eye complaints in the office environment: precorneal tear film integrity influenced by eye blinking efficiency: Occup.Environ.Med., v. 62, no. 1, p. 4-12.
- Xu, K. P., Y. Yagi, and K. Tsubota, 1996, Decrease in corneal sensitivity and change in tear function in dry eye: Cornea, v. 15, no. 3, p. 235-239.
- Yazdani, C., T. McLaughlin, J. E. Smeeding, and J. Walt, 2001, Prevalence of treated dry eye disease in a managed care population: Clin.Ther., v. 23, no. 10, p. 1672-1682.
- Yoon, K. C., I. Y. Jeong, Y. G. Park, and S. Y. Yang, 2007, Interleukin-6 and tumor necrosis factoralpha levels in tears of patients with dry eye syndrome: Cornea, v. 26, no. 4, p. 431-437.
- Zabel, R. W., G. Mintsioulis, I. M. MacDonald, J. Valberg, and S. J. Tuft, 1989, Corneal toxic changes after cataract extraction: Can.J Ophthalmol., v. 24, no. 7, p. 311-316.
- Zhang, M., J. Chen, L. Luo, Q. Xiao, M. Sun, and Z. Liu, 2005, Altered corneal nerves in aqueous tear deficiency viewed by in vivo confocal microscopy: Cornea, v. 24, no. 7, p. 818-824.