Introduction

Laser-assisted in situ keratomileusis (LASIK) surgery is an effective and safe procedure for correcting myopia, hypermetropia and astigmatism as long as inclusion and exclusion criteria are strictly respected ***(Kato et al., 2008)***.

Dry eye is one of the most common complications of LASIK surgery. LASIK has a neurotrophic effect on the cornea, along with other changes in corneal shape that affect tear dynamics causing ocular surface desiccation ***(Toda, 2007)***.

Symptoms of dryness may occur in more than 50% of patients, with other complications such as fluctuating vision, decreased best spectacle-corrected visual acuity, and severe discomfort occurring in approximately 10% of patients ***(Konomi et al., 2008)***.

Preoperative dry eye condition is a major risk factor for more severe dry eye after surgery and should be identified prior to surgery. Optimization with artificial tears, nutrition supplementation, punctal occlusion, and topical cyclosporine A in patients with

symptoms or signs of dry eye prior to LASIK decreases the incidence of more bothersome symptoms following surgery. Patients with LASIK-induced neurotrophic epitheliopathy often respond to topical cyclosporine A treatment, which treats the underlying inflammation and may benefit nerve regeneration ***(Ambrósio et al., 2008)***.

As LASIK enhancement by flap-lifting induces less dry eye symptoms and signs. It is suggested that other factors rather than loss of neurotrophic effect may be involved in the mechanisms of post-LASIK dry eye ***(Toda, 2007)***.

Future studies should seek to determine whether additional changes in technology, patient selection criteria, or postoperative treatment could reduce or eliminate these symptoms ***(Bailey and Zadnik, 2007)***.

Aim of the Work

This essay aims to discuss different etiologies of dry eye after LAISK, its predisposing factors, risk factors and possible ways of management.

Anatomy of the Cornea

I. Normal anatomy and physiology:

The lacrimal functional unit (LFU) includes the lacrimal glands, ocular surface (cornea and conjunctiva), eyelids, meibomian glands, and associated sensory and motor nerves **(fig. 1)** ***(International Dry Eye Workshop, 2007a)***.

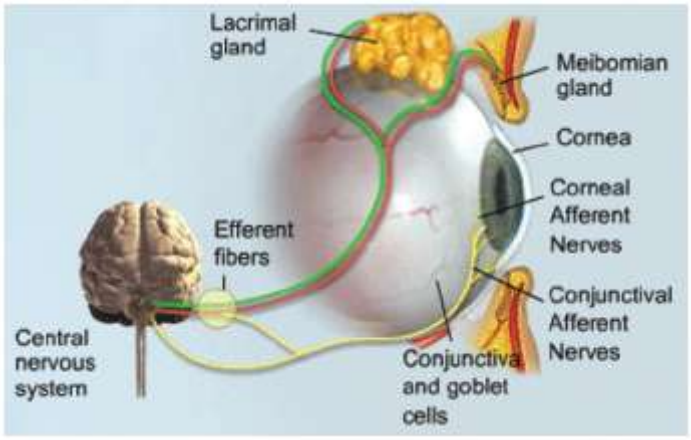

Figure 1: Lacrimal functional unit ***(International Dry Eye Workshop, 2007a)***.

While the most-refractive element is essential in the function of vision, the cornea's role in the realistic appearance of a prosthesis is sometimes overlooked. While several formulae have been offered for drawing the cornea, there is very little reference material for ocularists ***(Warren, 1988)***. Ocularists will recognize that the cornea's shape is the most important element in the reflection of light, and thus to its contribution to a

natural appearance in photographs. This aspect of the cornea becomes particularly noticeable in sectional illustrations **(fig 2)**.

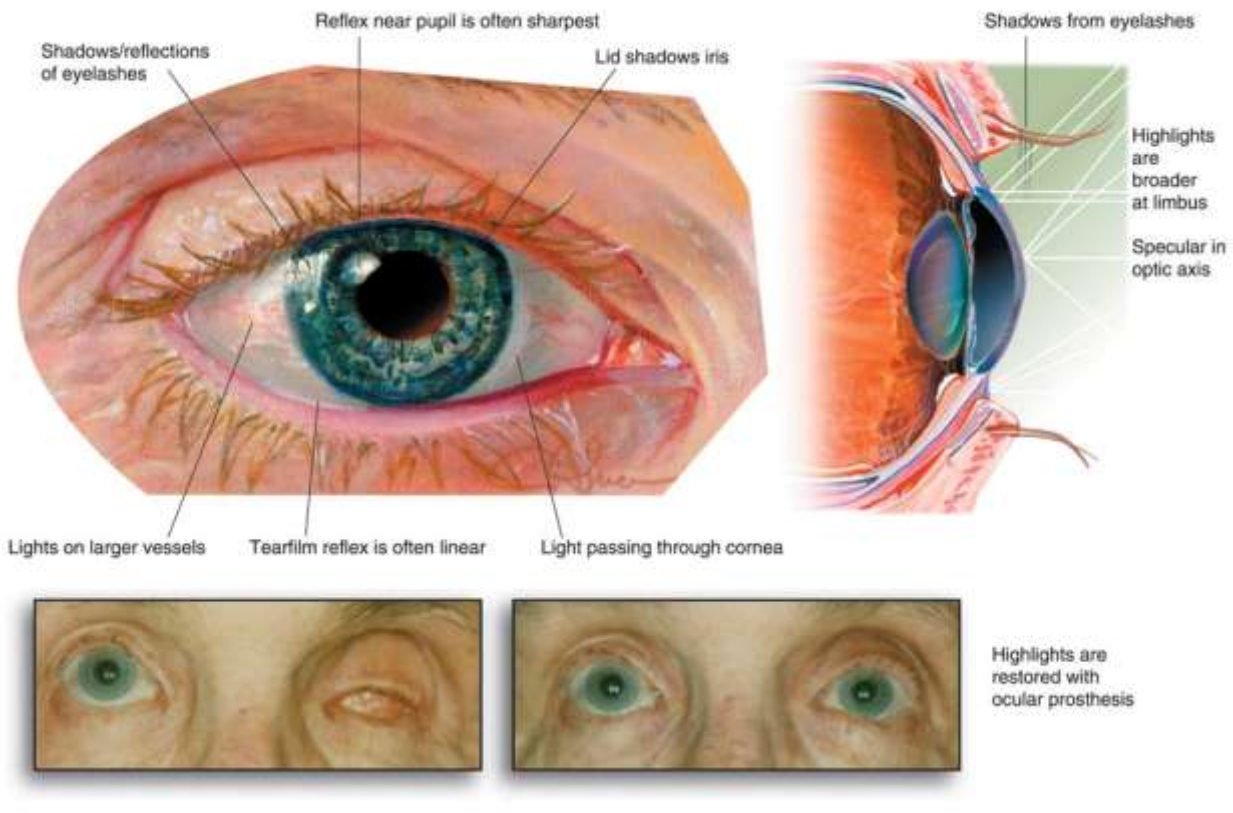

Figure 2: Highlights of cornea. ***(Hughes, 2008)***.

In ocularistry, the cornea is usually made a perfect partial-sphere primarily because of production limitations and convenience. This is perfectly acceptable. In actuality, the cornea is spherical only in its central optical axis portion. Outside the central 3 mm to 6 mm diameter (0.3 mm to 0.5 mm thickness) to the periphery, its curvature is somewhat flatter, and the

curvature at the limbus reverses this. In other words, toward the limbus (0.8 mm to 1.0 mm thickness), the curvature of the cornea is flattened. This flattened curvature is the reason reflections here widen out and become irregular. Thus, anatomical descriptions of the cornea as having a single radius are simplistic. To a general medical audience, this may have little meaning, but to an ocularist or illustrator, it can make the difference between believability and error ***(Hughes, 2008)***.

The shape of the cornea is revealed by "highlights." These highlights are the brightest reflections we see in another person's eyes, also known as "reflexes," "wet-lights," or "catchlights." This highlight is in the same place on both the corneas, thus telling the viewer that the eyes are looking in the same direction. Otherwise, the eyes appear to diverge or converge, making the sitter look cross-eyed (suboptimal at best). Highlights at the margin of the lid tell us whether the eye is wet or dry **(fig. 2)**.

While a point source of light, such as a camera flash, is seen as a point in the central portion of the cornea, it spreads in the periphery, and makes a sclera-corneal reflection that is usually wider and less uniform because of the changing curvature of the cornea and conjunctiva being flattened at the limbus ***(Ott et al., 2002)***.

A. Corneal structure:

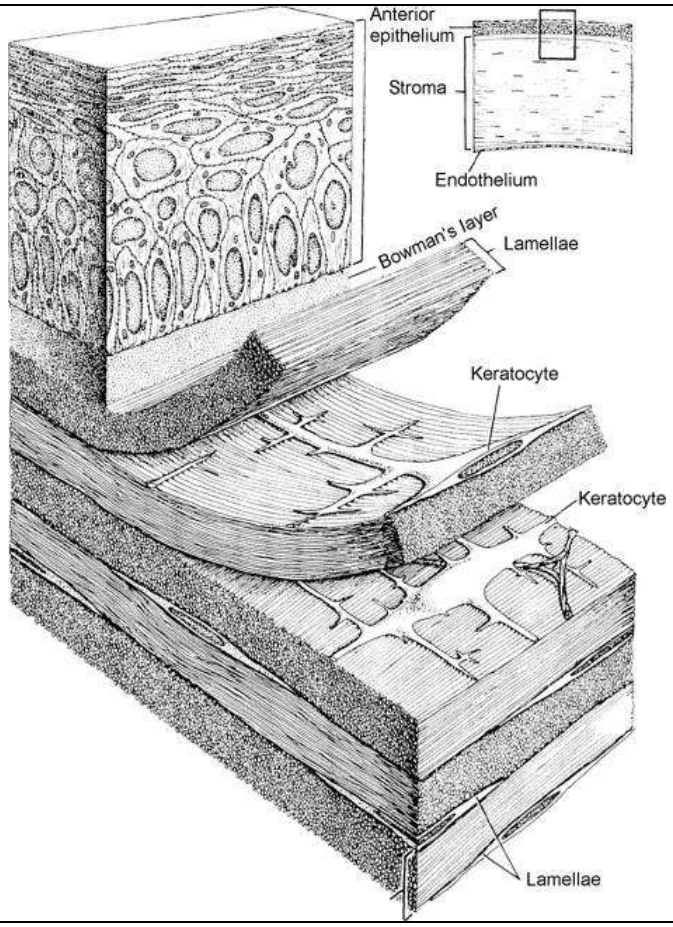

Figure 3: Block diagram of cornea illustrating stromal lamellae and flat keratocytes ***(Ehlers and Hjortdal, 2006)***.

An avascular, perfectly shaped and clear cornea is the most powerful refractive lens of the eye, comprising

in average 45 D of the approx. 60-70 D total refractive power of the eye. The smallest errors in its shape and transparency impair visual performance. Tear fluid changes, tissue remodulation and scar formation in the cornea or other refractive media (lens, vitreous) following e.g. corneal laser surgery, or in dry eye syndromes, keratitis, or hereditary degenerative diseases, can reduce the optical quality of the cornea.

The cornea consists of three distinctive layers **(fig. 3)**: 1) The 50 µm thick epithelium; 2) the 450-500 µm thick stroma; and 3) the endothelium. the epithelium and the stroma are divided by the epithelial basement membrane (BM) and the 8-10 µm thick Bowman's layer posterior to the BM ***(Ehlers and Hjortdal, 2006)***. Furthermore, between the stroma and the endothelium is the Descemet's membrane. On average, the cornea is thinner centrally (500-550 µm) than peripherally (600-700 µm).

The cornea is one of the most densely innervated organs of the human body ***(Müller et al., 2003)***. Nerve injury delays or even arrests corneal wound healing, which may lead to formation of optical aberrations

related to corneal irregularities, corneal ulcers and even perforations ***(Bonini et al., 2003)***. Diseases and surgical operations can lead to permanent and/or long standing neuronal injuries. The correlation between nerve loss and cellular alterations remains unknown.

1. Epithelium:

The non-keratinized squamous stratified epithelium consists of three morphologically different cell types ***(Beuermann and Pedroza, 1996; Ehlers and Hjortdal, 2006)***: 1) an average of 2-3 layers of flat polygonal surface cells, located most superficially, containing apical microvilli in contact with the tear film. These cells are joined by tight junctions, adherens junctions and desmosomes, restricting the entry of tears into the intercellular spaces and providing mechanical strength between adjacent cells ***(Petroll et al., 1999; Ban et al., 2003)***; 2) 2-3 layers of intermediate wing cells; and 3) a single layer of columnar basal epithelial cells. These basal cells are approx. 20 µm tall and show a limited division capacity ***(Ehlers and Hjortdal, 2006)***. Basal cells serve as the source for differentiation into wing and superficial cells. Hemidesmosomes attach basal

epithelial cells to the underlying BM ***(Gipson et al., 1987)***. The 0.05 µm thick basement membrane is composed mainly of type IV collagens and laminins produced by the basal epithelial cells ***(Tuori et al., 1996)***.

Stem cells are located in Vogt's gridles in the corneal limbal area ***(Tseng 1989; Lavker et al., 2004; Sun and Lavker, 2004)***. These cells are continuously proliferating, providing a resupply for shedding epithelial cells, thus maintaining corneal integrity. A complete turnover of corneal epithelial cells occurs in ca. 7 to 10 days ***(Hanna et al., 1961, Cenedella and Fleschner, 1990; Ehlers and Hjortdal, 2006)***.

2. Bowman's layer:

The uppermost part of the corneal stroma is the Bowman's layer, which is an acellular, unorganized array of fibrils of collagen types I, III, V, and VI, and is ca. 8-12 µm thick ***(Marshall et al., 1993)***. It develops from processes of the superficial mesenchymal cells of the corneal stroma ***(Sevel and Isaacs, 1988)*** and

connects to the adjacent basement membrane through anchoring fibrils and plaques ***(Gipson et al., 1987)***.

3. Stroma:

The corneal stroma makes up ca. 90% of the corneal thickness and is composed of a heterodimeric complex of type I, III, and V collagen bundles arranged parallel to the corneal surface in specific lamellae ***(Ihanamäki et al., 2004)***. Additionally, the corneal stroma contains non-lamellar collagen of types IV, VI, and VII ***(Assil and Quantock, 1993)***. Keratocytes are the major cell population located between the collagen lamellae. Additionally, there are bone-marrow derived dendritic antigen presenting cells (APC), and Langerhans cells ***(Latina et al., 1988, Hamrah et al., 2003)***, in the corneal stroma that are participants in immune and inflammatory responses. Also macrophages have been found at least in mouse corneas and act as potent APC cells as well ***(Hamrah et al., 2003; Yamagami and Amano, 2003)***. The special quality of these cells in the cornea protects against pathogens but also prevents inflammatory and immunological damage to the eye.

Keratocytes are quiescent, mesenchyme-derived fibroblast-like cells of the mature cornea ***(Hay, 1979; Ehlers and Hjortdal, 2006; West-Mays and Dwivedi, 2006)***. However, keratocytes contain many stacks of rough endoplasmic reticulum and large Golgi fields suggesting high activity in protein synthesis and storage ***(Müller et al., 1995)***. Furthermore, keratocytes contain twice as many mitochondria in the anterior stroma as in the mid- or posterior stroma. Keratocyte density is also significantly higher in the anterior stroma [(50,000–60,000 cells/mm^3 ***(Moller-Pedersen et al., 1997; Erie et al., 2006)***, 800 cells/mm^2 ***(Prydal et al., 1998)***] than in the posterior stroma [23,000 cells/mm^3 ***(Erie et al., 2006)***, 65 cells/mm^2 ***(Prydal et al., 1998)***]. Keratocytes are organized in a clockwise, spiral manner so as to be evenly distributed and located in the cornea ***(Muller et al., 1995)***. This specific organization may be beneficial in that light traverses through a similar system in every part of the cornea.

The integrity of the corneal basement membrane is critical in minimizing the fibrotic response of keratocytes and subsequent scarring and loss of corneal

clarity ***(West-Mays and Dwivedi, 2006)***. When injured, keratocytes either undergo rapid apoptosis or transform into repair phenotypes of migrating keratocytes/myofibroblasts ***(Jester et al., 1999; Fini and Stramer, 2005; West-Mays and Dwivedi, 2006)***. These cells eventually form a fibrotic scar. This, together with a decreased expression of crystallins ***(Jester et al., 1999)*** in altered/migratory keratocytes contributes to decreased transparency in wounded, healing corneas. A physiological 0.3 % annual decline of keratocyte density has been observed during aging ***(Moller-Pedersen, 1997)***. There is also evidence that, after LASIK, stromal keratocyte density decreases ***(Vesaluoma et al., 2000; Mohan et al., 2003; Erie et al., 2006)***. This type of keratocyte loss might affect the integrity of the cornea, but the reason for keratocyte loss remains elusive.

4. Descemet's membrane and the endothelium:

The main function of the corneal endothelium is to dehydrate the corneal stroma to maintain its clarity by an active pump mechanism, compensating the leak to the

stroma from the aqueous humor ***(Maurice, 1972; Waring et al., 1982)***. At birth, the endothelium consists of ca. 400,000 hexagonal cells, arranged uniformly in a continuous 5 µm-thick monolayer. The density of the endothelial cells decreases with age but considerable variation occurs: Under age 5, the endothelial cell density is ~3,000 cells/mm^2, by age 50 the range is usually from 1,000 to 3,500 cells/mm^2, and by age 80 the variation can be from 900 to 4,000 cells/mm^2 ***(Hiles et al., 1979; Hoffer and Kraff, 1980; Waring et al., 1980)***.

Interposed to the stroma, endothelial cells produce a basement membrane called the Descemet's membrane. It is composed of regularly arranged, stratified layers of predominantly type IV and VIII collagen, laminins and glycoproteins ***(Marshall et al., 1993; Beuerman and Pedroza, 1996)***. The Descemet's membrane thickens with age, from some 2 µm in childhood to 10 µm in adults ***(Johnson et al., 1982)***.

B. Corneal innervation:

The nerve fibers in the human cornea are mostly sensory by type, but also autonomous nerves exist. The

sensory innervation derives from the ophthalmic and maxillary branch of the trigeminal nerve ***(Müller at al., 2003)***. Anatomically, the corneal sensory nerves can be divided into the stromal, the subbasal and the intraepithelial ***(Müller et al., 2003)***. Functionally, there are three different modalities of sensory nerves: 1) polymodal nociceptors that respond to mechanical energy, heat, and exogenous irritants and endogenous chemical mediators, 2) mechano-nociceptors that react to mechanical forces of a magnitude close to that required to damage corneal epithelial cells, and 3) cold-sensitive receptors that respond to decreases in the normal corneal temperature ***(Belmonte et al., 2004)***.

1. Stromal nerves:

Through animal experiments ***(Morgan et al., 1978; Tervo and Palkama, 1978a and 1978b; Tervo et al., 1979; Marfurt et al., 1989; LaVail et al., 1993)***, it has been estimated that some 200 to 450 nerve bundles from the ophthalmic and maxillary branches of the trigeminal nerve enter the cornea at the corneal periphery. These nerve bundles lose their perineurium and myelin sheaths ca. 1 mm from the limbus, but retain their Schwann cell