# Evaluation of corneal sensation after LASIK correction for myopic patients

## Thesis

Submitted for Partial Fulfillment of MD Degree in Ophthalmology by

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# *Corneal Innervation*

The cornea is the most richly innervated surface tissue in the human body[1]. Corneal sensation is essential to maintain the integrity of the ocular surface. [2] The importance of corneal nerves can be attributed to their important role in protecting the cornea from irritants as well as their trophic properties.[3]Interest in the sensitivity of the human cornea dates back to the 19th century.[4] The German physiologist Von Frey in 1894, concluded that pain was the only sensation perceived by the cornea.[5] but we found that human cornea is densely supplied by sensory and autonomic nerve fibers. [6]

***Figure 1 : Side View of the human cornea.*** [7]

The sensory nerves, which form the majority of corneal nerves, are mainly derived from the ophthalmic division of the trigeminal nerve ***8*** **.** These nerve fibers are myelinated till they penetrate the limbus.[9] They have a variety of sensory and efferent functions. Mechanical, thermal and chemical stimulation of the corneal nerves produce predominantly a sensation of pain in humans. The autonomic nerve fibers consist of sympathetic fibers that are derived from the superior cervical ganglion and parasympathetic fibers that originate from the ciliary ganglion. [10]

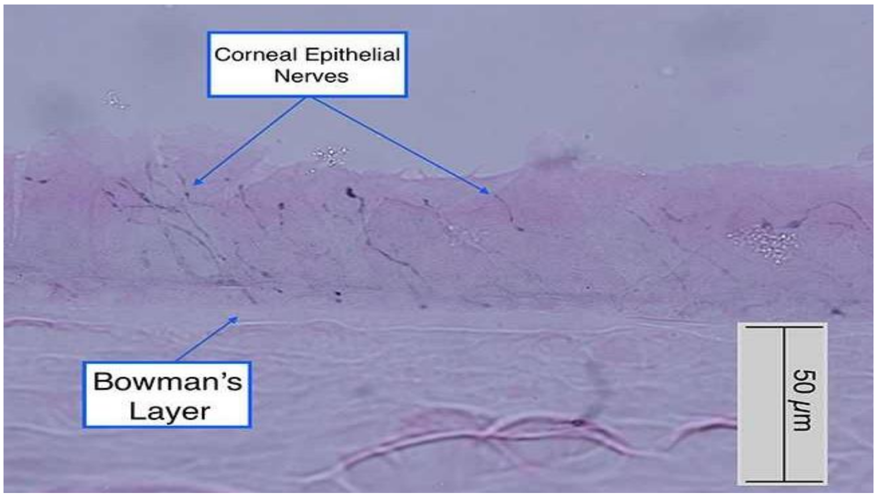


***Figure 2: Histologic section of the corneal epithelial layer which showing unmyelinated nerve fibers extending from the Bowman layer to the top of the epithelial cell layer. Axonal bulbs are occasionally observed and are normal sign of degenerative changes that occur during corneal epithelial cell turnover.*** [7]

Corneal sensitivity varies with eccentricity; cornea is most sensitive at its center and sensitivity gradually decreases towards the periphery. This shows a good correlation with the distribution of the sensory nerve terminals. A diurnal variation in the corneal sensitivity has been noted; the sensitivity is lowest in the morning and highest in the evening , a trend that seems to be related to hypoxia of the cornea during sleep. Diurnal variation is an important consideration in longitudinal studies in which repeated measurements are taken over time. Corneal sensitivity appears to vary little over the first four decades of life but later it shows a gradual decline. Sex differences also require consideration as the hormonal changes which occur during the menstrual cycle and pregnancy may be associated with changes in corneal sensitivity.[11,12,13]

Different techniques have been used to demonstrate corneal nerve patterns in different mammalian corneas. [9]Our recent understanding of corneal nerve morphology derives principally from ex-vivo investigations which use acetylcholinesterase staining[15], immune-histochemical staining and electron microscopy.[16]

In 1951, Zander and Weddell published the earliest detailed observations on the innervation of the mammalian cornea. But, it provided relatively limited knowledge on human corneal nerves and its distribution. [17]

Muller *et al* reported that nerve fiber bundles in the sub-basal plexus across the central and mid-peripheral cornea run first in the 3–9 o'clock hours direction, then after bifurcation, travel in the 6–12 o'clock hours direction and after a second bifurcation again in the 3–9 o'clock hours direction. [14]

However, more recent studies with in-vivo confocal microscopy (IVCM) suggest an alternative model of central subbasal corneal innervation, where leashes of nerve fibers extend across the corneal apex preferentially in the 6–12 o'clock direction and other leashes approach the apex in the 5–11, 3–9, 1–7, 2–8 and 4–10 o'clock directions. [18]

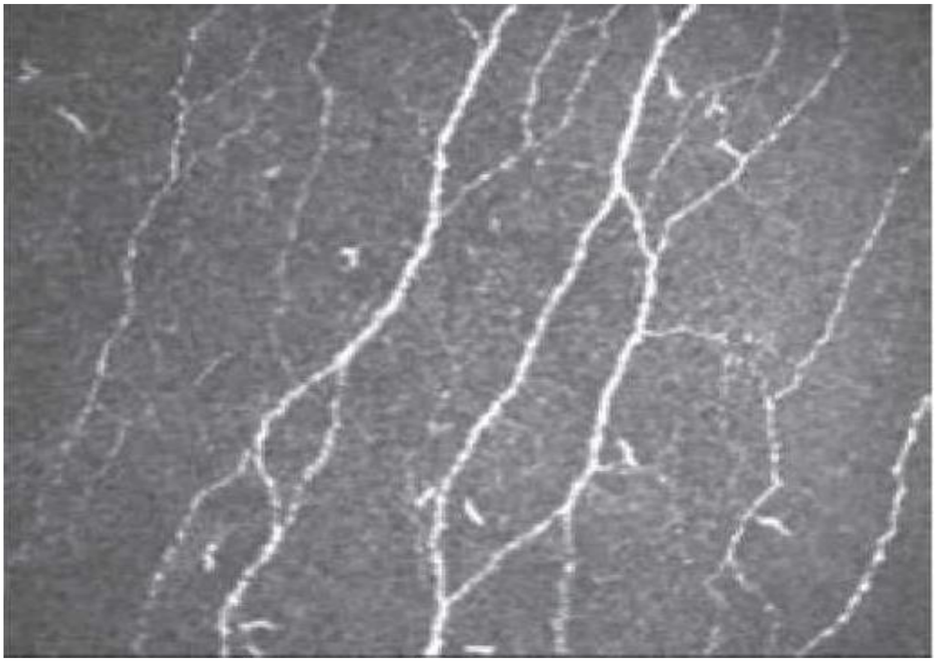

***Figure 3: Normal sub-basal nerve plexus by Laser scanning confocal microscopy (LSCM)*** [11]

Due to technical reasons, in-vivo confocal microscopy (IVCM) images are mostly limited to the corneal apex and cover a small area of the center of the cornea. So, the orientation of sub-basal nerves in peripheral regions of the human cornea remains incompletely understood. In addition, there are few data on the topographical distribution of stromal innervation in human cornea. [20]

Therefore the normal anatomy of the peripheral and central human corneal nerves is verified comprehensively using a whole mount cholinesterase method, that has been proven to be excellent for qualitative and quantitative analysis of corneal nerves in different species, for example rabbits, rats and dogs. [21]

AchE-positive sub-basal nerves were only demonstrated in corneas harvested within the first two post mortem days and in post-surgical specimens. They appear as linear structures running in the superficial layer of the cornea with frequent Y shaped bifurcations and re-unions or unions with other branches and contained densely stained fine granular structures (figure 4A). These nerves originated from the sub-Bowman's nerves that were located in the most anterior part of the corneal stroma. Theses nerves appeared to penetrate the Bowman's layer perpendicularly giving rise to multiple sub-basal nerves (figures 4B and 4C). Interestingly, some of the thicker sub-Bowman's nerves divided into two (figure 4D) or more branches just before perforating Bowman's layer giving a characteristic 'budding and branching pattern' (figures 4E). This branching pattern was more evident in the mid-peripheral cornea. A novel finding was that the perforation sites were mainly located in the mid-peripheral cornea and characterized by densely stained disc or bulb-like thickenings from which the sub-basal nerves arose (figure4 F).[20]

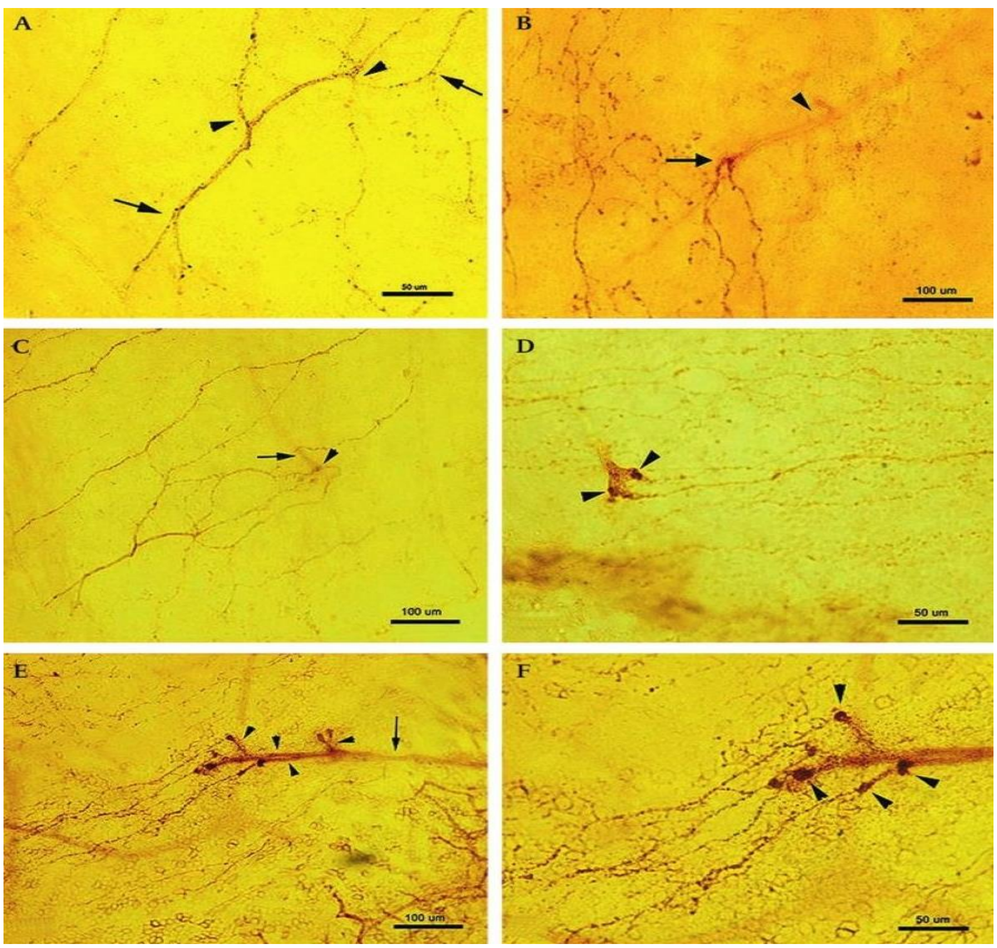


***Figure 4: Photomicrographs of whole human corneal mount stained by acetyl - cholinesterase technique*** [21]

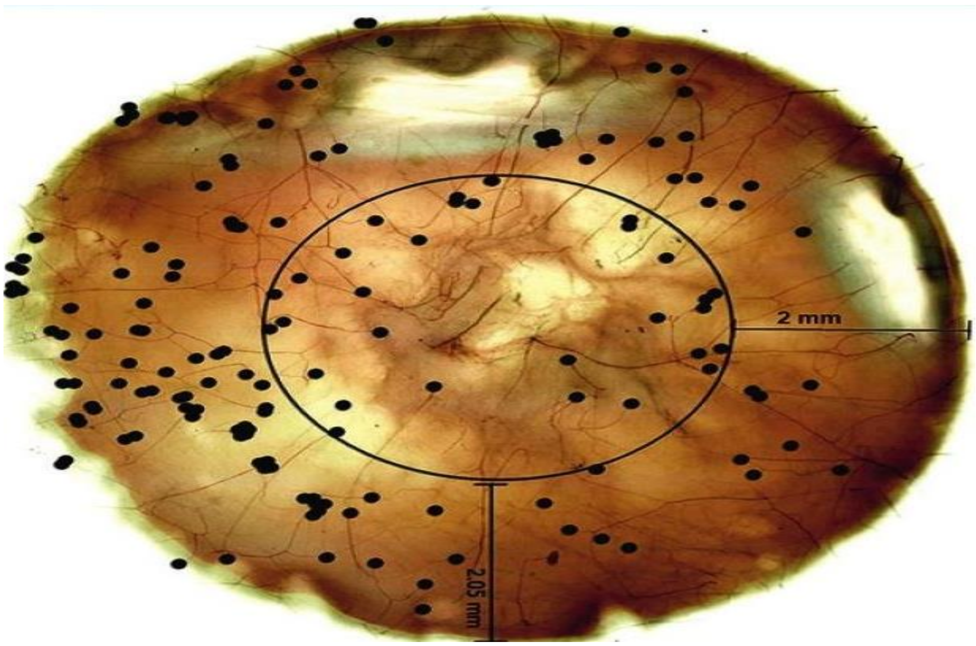


***Figure 5: Photomicrograph of whole human corneal mount stained by the acetylcholinesterase technique showing the perforation sites (marked with black dots), which are distributed in the mid-peripheral cornea. There are about 30 perforation sites in the central cornea (area within the circle) and 125 in the mid-peripheral zone (outside the circle)*** [22]

The directional orientation of sub-basal nerves at their origin at the perforation sites was mainly vertical, that is running downward (superior to inferior) for nerves arising from perforation sites in the superior and central cornea and upward (inferior to superior) for those arising in the inferior cornea. The nerves also ran parallel to each other. Interestingly, the orientation of the sub-basal nerves arising from nasally and temporally located perforation sites, were

also vertical, running downwards (superior to inferior) and obliquely towards the central cornea. Nerves from all quadrants converged towards the central cornea and formed a whorl pattern inferior to corneal apex.[22]

AchE-positive stromal nerves were demonstrated in all corneal specimens. Nerves were found to enter the corneal limbus at different levels predominantly in the mid and deep stroma. Most of them were noted to be a continuation of the nerves in the suprachoroidal space.[20]

The numbers of limbal nerves entering each quadrant were counted and the average was as follows: superior (11.00), medial (9.43), inferior (11.43) and lateral (11.86) (figure 4). Overall, corneas were found to be innervated by an average of 43.72 AchE-positive thick nerve bundles, which were distributed evenly round the limbus.[19]

Studying corneal nerves entry sites,number of nerves entering each corneal quadrant and intra corneal pathway is essential to evaluate the effect of hinge position in post LASIK corneal healing.

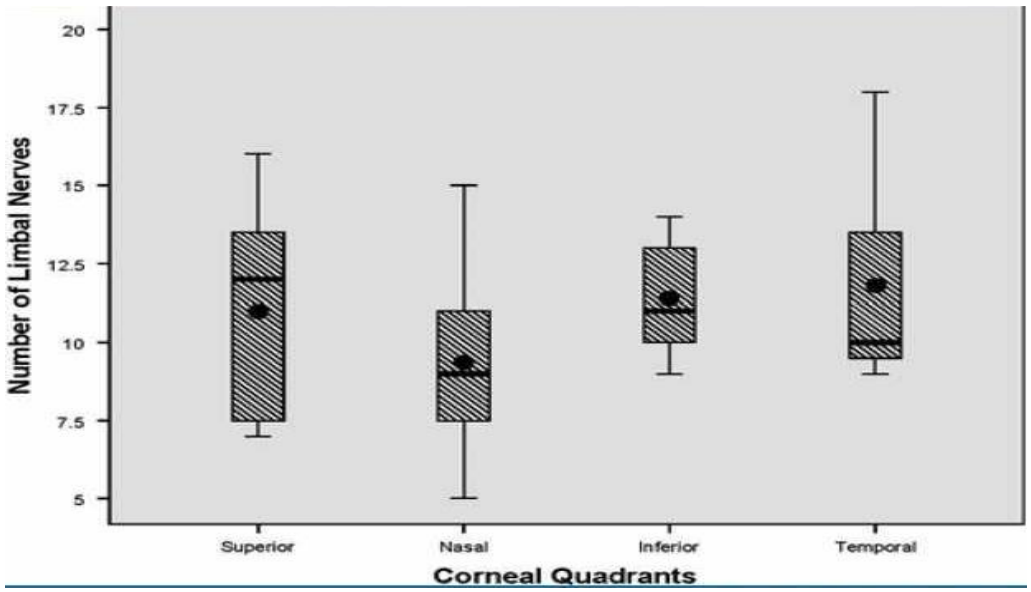


***Figure 6:A box plot showing the distribution of corneal nerves around the human limbus in four corneal regions (superior, medial, inferior and lateral). Means are indicated by solid circles.*[22]**

# Different LASIK Techniques

Corneal surgical procedures may disrupt normal organization of corneal innervation; this includes refractive surgery, which has been shown to cause decreased corneal sensation. [23]

The subject of corneal innervation has gained importance in recent years because of the observation that corneal nerves are routinely injured following modern refractive surgeries. [24]

***Figure 7: Schematic representation of LASIK with formation of a corneal flap followed by ablation of the stroma. The flap is then replaced into its original position.*** [25]