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Confocal Microscopy in the Study of Corneal Nerve Alterations Post-Refractive Surgery: A Review of Recent Advancements

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Abstract

As more and more people choose to get rid of the bondage of glasses through refractive surgery, there is a corresponding increase in concern about the potential impact of the surgery on corneal nerves. Refractive surgery can cause damage to corneal nerves, leading to abnormal corneal sensitivity, dry eyes, and other adverse reactions. Additionally, different methods of corneal refractive surgery may have varying degrees of impact on corneal nerve changes. Confocal microscopy has high resolution and three-dimensional imaging capabilities, allowing for direct observation of changes in corneal nerve fiber structure. This is of great significance for deeply exploring the mechanisms of corneal nerve changes after refractive surgery. Therefore, this review looks back at existing research with the aim of discussing the impact of refractive surgery on the morphology of corneal nerves.

Keywords: Corneal Nerves; Confocal Microscopy; Corneal Refractive Surgery

Abbrevations: SBNP: Sub-Basal Nerve Plexus; IVCM: In Vivo Confocal Microscopy; CNFD: Corneal Nerve Fiber Density; CNFL: Corneal Nerve Fiber Length; CNBD: Main Nerve Branch Density; CTBD: Total Nerve Branch Density; CNFW: Nerve Fiber Width; SMILE: Small Incision Lenticule Extraction.

Introduction

The human cornea is one of the most densely innervated and highly sensitive tissues in the body, containing an abundance of sensory nerves that can perceive a wide range of stimuli, including changes in temperature, pain, discomfort, and mechanical and chemical irritants. Additionally, corneal nerves play a crucial role in maintaining the normal function of the ocular surface by releasing trophic factors and activating specific brainstem circuits [1]. However, damage to the corneal nerves during refractive surgery can compromise the integrity of ocular surface function and corneal sensitivity, potentially leading to adverse effects on postoperative visual quality and best-corrected visual acuity, and ultimately resulting in decreased patient satisfaction with the surgical outcome [2]. These effects may be either temporary or permanent, necessitating further comprehensive research to fully elucidate the specific impacts of refractive surgery on corneal nerves. The purpose of this review is to collate and summarize the observed changes in corneal nerves using confocal microscopy following refractive surgery and to investigate the effects of refractive surgery on the morphology of corneal nerves.

Overview of Corneal Nerve Fibers

In recent times, there has been a significant amount of detailed and thorough research carried out on the anatomical structure of human corneal nerves. This research has utilized a variety of methods, including immunohistochemistry, optical microscopy, electron microscopy, and confocal microscopy.

The human cornea has an average thickness of 500-550mm and contains approximately 7000 free epithelial nerve endings per square millimeter, which makes it the most densely innervated tissue in the human body. These corneal sensory nerves are derived from the ophthalmic branch of the trigeminal nerve [3], and, together with the ciliary nerves, they reach the limbus of the cornea and sclera, where they form a nerve plexus. From this plexus, 60-80 fiber endings lose their myelin sheath and enter the cornea from its periphery, extending parallel to the surface of the cornea until they reach the space between the basal epithelial layer and the anterior elastic layer, thereby forming the Sub-Basal Nerve Plexus (SBNP). Research has indicated that the SBNP consists of a spiral arrangement of sub-basal nerve fibers, with these fibers converging at a center or vortex. This vortex is situated beneath the apex of the cornea and spirals towards the nasal inferior midline region, moving centripetally towards the center of the cornea in a clockwise direction [2,4]. The SBNP is a crucial component of the corneal nerves and plays a vital role in maintaining the cornea's normal function and aiding the repair of its damaged structure and morphology.

The nerve endings on the corneal nerves can transmit temperature, mechanical, and chemical stimuli as sensations of pain; the corneal nerves can also protect the ocular surface through the blinking reflex mechanism and release various trophic factors to regulate epithelial integrity, proliferation, and promote wound healing. They also strictly control tear gland secretion to maintain the stability of the tear film, which contains water, electrolytes, and numerous proteins, thereby maintaining the total volume and composition of tears [5,6]. Therefore, the corneal nerves play an indispensable role in corneal tissues.

Confocal Microscopy Observation of Corneal Nerve Fibers

For the study of corneal nerves, it is also very important to use methods that can better observe, analyze, and understand the morphological and functional changes of corneal nerves.

Compared with observing corneal nerves using immunohistochemical staining technology, immunohistochemical studies of corneal nerves are conducted on corneal tissues of cadavers or enucleated eyeballs. Therefore, the results may be affected by artifacts caused by tissue processing and postmortem or ex vivo nerve degeneration. However, in vivo confocal microscopy (IVCM) can eliminate these influences. It can not only continuously, dynamically, and repeatedly observe living corneal nerve fibers [7], but also is easy to operate and low in cost. Since the direction of the SBNP is parallel to the corneal surface, it is easier to image, and it has obvious morphological attributes, such as the length of the nerve bundle, which is easy to quantify. Therefore, the main object of corneal nerve observation by IVCM is usually the SBNP, and IVCM is the only method that can observe the SBNP in vivo and non-invasively [8]. Many studies have used IVCM to assess the condition of the sub-basal nerve plexus of the cornea to explore the effects of certain ocular and systemic diseases as well as eye surgeries on corneal nerves, such as dry eye [9-11], diabetic neuropathy [12-14], keratoconus [15-17], and post-cataract surgery [18], etc.

Using related software, such as the fully automatic software "ACCMetrics," various aspects of corneal nerve morphology can be quantified, such as corneal nerve fiber density (CNFD), corneal nerve fiber length (CNFL), main nerve branch density (CNBD), total nerve branch density (CTBD), nerve fiber width (CNFW), curvature, beading, branching, reflectivity, and overall direction, migration trend, etc [7]. These software tools can make the research more vivid and specific.

Classification of Corneal Refractive Surgery

According to existing literature studies, the proportion of myopia patients worldwide in 2020 accounted for 33% of the global population, and it is predicted that this proportion will increase to 50% by 2050. This trend suggests that nearly 6 billion people may be affected by myopia [19]. As an important treatment method to improve vision and get rid of the dependence on glasses, corneal refractive surgery has become one of the widely adopted ophthalmic treatments worldwide [20]. For a long time, corneal refractive surgery has won the favor of more and more patients with its efficient, safe, and stable treatment effects. Especially with the widespread application of laser technology in the field of ophthalmology, the number of refractive surgeries is showing a rapid growth trend. Millions of refractive surgeries have been successfully performed worldwide, effectively treating vision problems such as myopia, hyperopia, and astigmatism [21].

Refractive surgery corrects refractive errors by changing the shape of the cornea, reducing or increasing its refractive power. Since the corneal stromal nerves are mainly concentrated in the anterior 1/3 of the corneal stroma, the density and number of branches of the corneal nerves gradually decrease from the epithelial basal cell layer to the middle stromal layer [2]. Regardless of the type of refractive surgery, using lasers to ablate the corneal stroma will affect the densest SBNP, thereby reducing corneal sensitivity.

According to the different surgical methods and equipment, corneal refractive surgery is divided into two major categories: lamellar corneal refractive surgery and surface corneal refractive surgery. Surface corneal refractive surgery involves removing the corneal epithelium using mechanical, chemical, or laser means, or mechanically creating a corneal flap, and performing laser ablation on the surface of the anterior elastic layer and the corneal stroma below. This category includes: photorefractive keratectomy (PRK), laser subepithelial keratomileusis (LASEK), epipolis-laser in situ keratomileusis (Epi-LASIK), and trans-epithelial photorefractive keratectomy (TPRK). Lamellar corneal refractive surgery usually refers to laser in situ keratomileusis (LASIK) and femtosecond LASIK (FS-LASIK), where a corneal flap is created with a mechanical knife or femtosecond laser assistance. It also includes a procedure where only a femtosecond laser is used to complete the corneal stromal lenticule and remove it: small incision lenticule extraction (SMILE) [22].

Effects of Different Refractive Surgeries on Corneal Nerve Fibers

PRK

PRK is a refractive surgery that uses excimer laser for surface ablation. After removing the corneal epithelium mechanically or chemically, the laser is applied to the anterior stromal layer for the surgery.

In the study by Wang, et al. [23], they observed that on the seventh day after PRK, corneal nerve fibers appeared extremely sparse and thin outside the central 5mm diameter circular area of the cornea, and within the 3mm diameter range, the distribution of nerve fibers was even rarer. Three months postoperatively, the central corneal nerve fibers had not yet reached the preoperative level and were still recovering. It was found that budding nerves were visible in the anterior stroma 2 months after PRK, unbranched SBNP were visible after 3 months, and regenerated subbasal nerves began to branch and fully recover 24 months after PRK. However, abnormal subbasal nerves could still be observed 3 years after PRK [24].

Five years after PRK, the quantity and density of SBNP in the central cornea basically recovered to the preoperative level, although the nerve fiber density of some patients was lower than before the surgery. These corneas exhibited an SBNP branching pattern similar to that of healthy controls who did not undergo surgery. The study by Tosi, et al. [25] revealed long-term changes in corneal morphology after PRK, finding that even 15 years after PRK, the density and length of SBNP had not fully recovered. At the end of the 25-year follow-up, the density of SBNP was still slowly recovering. However, the study by Bilgihan, et al. [26] found that the morphology of subbasal nerve fibers 20 years and 10 years after PRK was similar, and the morphological differences between the two were not statistically significant. Additionally, the mean CNFD, CNBD, and CNFL in the PRK group were similar to those in the healthy control group, indicating that there was no change in corneal nerves 10 and 20 years after PRK, showing a stable trend.

Regarding nerve regeneration, the regeneration of ablated SBNP can be directly observed using IVCM within one week after PRK [23]. Two months after PRK, nerve growth can be seen in the anterior corneal stroma, and by the third month, unbranched basal nerves have already appeared. The regeneration of basal nerves begins to branch, and it is estimated that it may take 24 months to fully recover [24]. Moreover, according to a report by Erie, et al. [27], the recovery of central corneal sensitivity began 4-6 weeks after PRK, and nerve density returned to normal levels at 24 and 36 months after PRK.

LASEK

LASEK (Laser-Assisted Sub-Epithelial Keratectomy) is a type of laser vision correction surgery that falls under the category of surface ablation procedures. It is similar to PRK, but before the laser treatment, an alcohol solution is used to separate and preserve the corneal epithelial layer. The laser then reshapes the stromal layer of the cornea, and the epithelium is placed back in its original position.

Darwish, et al. [28] found that after LASEK, the diameter and density of subbasal nerve plexus (SBNP) significantly decreased, and these parameters had not recovered to their preoperative state even 6 months postoperatively. Hou, et al. [29] found that up to 12 months postoperatively, the central corneal nerve density had not yet recovered to preoperative levels. At 6 and 12 months postoperatively, nerve fibers in the central and temporal areas in the LASEK group were wider compared to those in the SMILE and FS-LASIK groups. Li, et al. [30] reported that 12 months after LASEK, central nerve fibers were primarily located in a hazy zone 70-90μm from the anterior epithelial surface.

TransPRK

TransPRK (Transepithelial Photorefractive Keratectomy) is a refractive surgical method using an excimer laser. During TransPRK, the laser passes through the corneal epithelium to directly sculpt the cornea, changing its shape, without the need for manually scraping or flipping the epithelium.

Research regarding the morphological changes of corneal nerves after TransPRK is somewhat limited. Wang, et al. [23] found that 7 days after TransPRK, the number of corneal nerve fibers reached its lowest point, and even 3 months postoperatively, the central corneal nerve fibers had not yet reached preoperative levels. Liu, et al. [31] studied 51 eyes and found that both the density and length of corneal nerves immediately decreased after TransPRK and had not recovered to preoperative levels even one year after the operation. They also found that sensitivity to mechanical stimuli temporarily decreased postoperatively. Although sensitivity was slightly lower than preoperative levels one week post-surgery, it returned to preoperative levels within a month.

These studies suggest that changes in the structure of corneal nerves do not always proceed in sync with functional changes. The postoperative decrease in nerve density could lead to a temporary reduction in sensitivity to mechanical stimuli. This might affect the patient's blink rate and tear film stability, potentially resulting in postoperative dry eye syndrome. However, the recovery of corneal sensitivity and changes in blink rate are not directly related to the regeneration process of SBNP.

LASIK and FS-LASIK

In LASIK and FS-LASIK, a thin and smooth corneal flap is created in the deeper layers of the cornea using a microkeratome or femtosecond laser. Then, the laser reshapes the cornea, and the corneal flap is repositioned.

According to a study by Chao, et al. [32], there were abnormal regenerative nerve structures after LASIK, with more nerve branches. These new nerve fibers had roughly the same path and direction as before the surgery, but there were increased bifurcations and tortuosity, and the nerve fibers were more randomly arranged. Postoperatively, the most significant changes in nerve direction were in the central and temporal cornea, especially in the central part, which had changes significantly higher than the temporal and upper parts. These changes might be related to the speed of corneal epithelialization exceeding nerve regeneration and the need for new nerves to avoid areas previously without nerve innervation. At 12 months postoperatively, the corneal density in the central 6 mm and 6-12 mm diameter range and the total area was lower in the LASIK group than in the FS-LASIK and LASEK groups.

Zhao, et al. [33] studied the changes in corneal nerves after LASIK in patients with different degrees of myopia and found that patients with high myopia needed a longer time for corneal nerve fiber recovery after surgery.

Liu, et al. [34] studied the long-term effects of LASIK and found that an average of 4.1 years after surgery, the corneal nerve fiber density, the number of nerve branches, and the nerve fiber length all significantly decreased, while new nerves significantly increased, especially in high myopia. Additionally, even 2.7 years postoperatively, nerve regeneration activity could still be observed, and even 5.5 years after the operation, the nerve status had not returned to normal.

Wang, et al. [23] found that 7 days after FS-LASIK, the number of corneal nerve fibers reached its lowest point, and even 3 months postoperatively, the central corneal nerve fibers of patients had not yet recovered to preoperative levels. Recchioni, et al. [35] pointed out that FS-LASIK led to a significant decrease in CNFD, CNBD, and CNFL, and the impact of FS-LASIK was greater than SMILE. On the other hand, Hou, et al. [29] found that 6 to 12 months after FS-LASIK, the nerve fiber width in the upper cornea increased. The study also found that before and after surgery, the temporal corneal nerve fibers were denser than the nasal nerve fibers, especially in the temporal cornea area, where the CNFL in the FS-LASIK group was significantly shorter than in the SMILE group. Six months after FS-LASIK, the nerve distribution in the upper cornea was denser and covered a large number of Langerhans cells. Twelve months after surgery, in patients with well-healed incisions, nerves could be observed growing directly across the incisions, whereas in cases of tortuous incisions or epithelialization, nerves could be observed growing along or beneath the incision.

SMILE

In SMILE (Small Incision Lenticule Extraction) surgery, a small piece of corneal stroma, called a lenticule, is removed through a small incision. The angle of this incision is usually only 30° to 40°, much smaller than the nearly 300° incision in FS-LASIK.

According to a study by Wang, et al. [23], on the 7th day after SMILE surgery, the corneal nerve fibers were at their lowest, but by the 3rd month postoperatively, a large number of nerve fibers had recovered in the central corneal area of most patients, with some even reaching or exceeding preoperative levels. However, these regenerated nerve fibers were relatively thin. At the same time, the central corneal nerve fiber density of patients who underwent FS-LASIK and T-PRK did not recover to preoperative levels. In terms of recovery of CNFD, CNFL, CNBD, and CTBD, SMILE was superior to the other two surgical methods.

Recchioni, et al. [35] found that one month after SMILE surgery, the length, density, and branch number of corneal nerve fibers significantly decreased. Similar results were also validated in a study by Mamirez, et al. [36], where they found that one month after SMILE, the subepithelial nerve plexus disappeared.

Another study by Jiang, et al. [37] compared SMILE and FS-LASIK surgeries. They found that corneal nerve density was significantly lower after SMILE than before, but in the first and third months postoperatively, the corneal nerve density of the SMILE group increased and showed excellent performance in nerve injury repair and reinnervation. However, by the 6th month postoperatively, the difference between the two groups was not significant. At 1, 3, and 6 months postoperatively, the corneal nerve density and main trunk number of both SMILE and FS-LASIK groups significantly decreased. They suggested that due to the smaller incision in SMILE, it might cause less damage to the corneal nerves, so the corneal nerve density after SMILE in the early stages is better than after FS-LASIK. A study by Hou, et al. [29] found that 12 months after SMILE, the nerve distribution and morphology in the SMILE group were similar to preoperative levels.

Li, et al. [38] found that one year postoperatively, the CNFL and CNFD of younger patients recovered to preoperative levels, while those of older patients were still lower than preoperative levels after one year. This indicates that age may affect the recovery of corneal nerves after surgery.

According to a study by Li, et al. [30], one year after performing SMILE on patients with high myopia, although the nerve repair around the upper corneal incision was slightly inferior to FS-LASIK and LASEK, the nerve repair in other areas had certain advantages. Liu et al. [34] focused on the long-term effects of SMILE and found that even 2.7 years postoperatively, nerve regeneration activity could still be observed and even 5.5 years after surgery, the nerve status had not returned to normal.

Conclusion and Prospects

In summary, all types of refractive surgery will cause damage to the corneal nerves to some extent, and the degree of regeneration of the corneal nerves may vary due to individual differences and different surgical methods, and some may recover to the preoperative state. In addition, factors such as the patient's age, postoperative recovery time, surgical incision design, cutting depth and range may all affect the recovery of the corneal nerves. According to comparative studies on the recovery of corneal nerves after various types of refractive surgery, it can be found that the recovery of corneal nerves after SMILE surgery is usually better than other refractive surgeries. This may be related to the characteristics of SMILE surgery: the incision range of SMILE surgery is small, the surgical trauma is less, which may enhance the regeneration of nerves after surgery; the surgery retains the integrity of the corneal epithelium and Bowman's membrane, thus retaining most of the corneal nerves; SMILE has less stimulation to the cornea than other surgeries, reducing postoperative inflammatory reactions, which is conducive to the recovery of corneal nerves after surgery.

A large number of studies have clearly defined the impact of different refractive surgeries on corneal nerves, but in-depth research in this field still needs to be improved. The regeneration mechanism of corneal nerves after injury also needs to be further clarified, such as the molecular and cellular mechanisms of corneal nerve injury and repair. With the development of new technologies and new types of refractive surgery, it is crucial to evaluate the impact of these surgeries on corneal nerves, which requires us to conduct more comprehensive and in-depth research. In addition, the early identification and treatment of postoperative dry eye and other complications are extremely important for improving the quality of life of patients. We need to find better strategies and new treatment methods. And surgeons should consider various factors when choosing refractive surgery, especially when patients may have a reduced sub-basal nerve plexus, such as dry eye disease or contact lens wearers. They are likely to develop severe dry eyes after refractive surgery. Therefore, when choosing and implementing refractive surgery, we need to fully consider its impact on corneal nerves to protect the visual health and quality of life of patients to the greatest extent.

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