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# Keratoconus: The Conical Corneal Conundrum and its Evolving Treatments

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**Abstract**

*Keratoconus is an eye disease that transforms the shape of the cornea from its normal oval shape to a conical shape. This can lead to a decrease in vision and, if not treated, can lead to a loss of vision. Depending on the severity and progression of each case, many treatment options are now available, ranging from cross linking procedures and special contact lenses to corneal transplants.*

## Introduction

The cornea is the transparent, avascular, dome-shaped structure located at the front of the eye. It is primarily responsible for refracting light onto the lens and focusing it onto the retina. The cornea plays a critical role in maintaining clear vision and protecting the eye. Having a basic understanding of the anatomy and function of the cornea is essential for diagnosing and managing various ocular conditions. (Meek, 2001)

The cornea consists of five distinct layers: epithelium, Bowman's layer, stroma, Descemet's membrane, and endothelium. The epithelium is the outermost layer. This layer acts as a protective barrier against foreign particles and contributes to the smooth appearance of the cornea. Under the epithelium is the Bowman's layer. This layer is a dense layer of collagen that provides support for the structure of the cornea. The stroma is the thickest layer of the cornea. This layer makes up around 90% of the cornea's thickness and consists of highly organized collagen fibers, which are responsible for its transparency. Descemet's membrane is a thin, acellular layer that separates the stroma from the endothelium, and is able to self repair easily after an injury. This is important in the protection of the eyes internal structures. The innermost layer, the endothelium, is a thin single cell layer in a honeycomb shape. It acts as a pump to maintain corneal clarity by regulating fluid balance. (Rehman, 2023)

The cornea's composition is predominantly collagen and proteoglycans, which are responsible for its tensile strength and transparency. Additionally, the cornea contains various other proteins, such as keratins, enzymes, and growth factors that contribute to its structure and function. The cornea has a high water content, which is important for maintaining its transparency. (Meek, 2015)

There are several physiological functions of the cornea:

- Refraction- The cornea, along with the lens, plays a key role in refracting light onto the retina. Its convex shape and the transition of light from the air to the cornea provide approximately two-thirds of the eye's refractive power.
- Barrier Function- The epithelium acts as a barrier against foreign substances, microorganisms entering the eye as well as preventing injury.
- Protection- The cornea, with its tough outer layer and absence of blood vessels, protects the internal structures of the eye from external trauma.
- Transparency- The highly organized collagen fibers in the stroma, combined with the absence of blood vessels and pigmentation, contribute to the cornea's transparency, allowing light to pass through.
- Wound Healing- The cornea has a remarkable capacity for self-repair through various cellular mechanisms, such as cell migration, proliferation, and extracellular matrix remodeling.

There are many diseases that can affect the cornea specifically. Corneal dystrophies are a type of genetic disorder characterized by irregular deposits of substances within different layers of the cornea. There are different types of corneal dystrophies and they can affect specific layers of the cornea. One example is Epithelial basement membrane dystrophy (EBMD), also known as map-dot-fingerprint dystrophy. This affects the corneal epithelium and basement membrane. Patients with EBMD may experience recurrent corneal erosions, leading to pain, foreign body sensation, and fluctuating vision. Treatment options include lubricating eye drops, ointments, and occasionally, the removal of abnormal epithelial cells.

Stromal corneal dystrophies, such as lattice dystrophy and macular dystrophy, primarily affect the middle layer of the cornea, known as the stroma. These dystrophies are described by the deposit of abnormal proteins within the stromal layer. Depending on the type and severity, treatment options range from ointments to remove the protein, to corneal transplantation. (Alkatan et al., 2019)

Fuchs' endothelial dystrophy (FED) is a progressive disorder affecting the corneal endothelium, leading to corneal edema and reduced vision. This disease is seen mostly in older individuals and often presents in both eyes. FED is characterized by a gradual loss of endothelial cells and the development of guttae, which are small, irregular growths on the inner surface of the cornea. As the disease progresses, patients experience worsening visual acuity, glare sensitivity, and pain. The exact cause of FED is not clear, although it is thought to have a genetic component. It is more prevalent in women and tends to run in families. Currently, there is no cure for FED. Treatment initially focuses on managing symptoms through the use of hypertonic saline drops and ointments to reduce corneal edema. In advanced cases, corneal transplantation may be necessary to restore vision. (Soh, 2020)

Herpes simplex keratitis (HSK) is a viral infection caused by the herpes simplex virus (HSV) type 1 or type

2. It is typically seen as a corneal infection that persists and can result in severe vision loss if left untreated. HSK symptoms include eye pain, redness, photophobia, and blurred vision. The way to diagnose HSK is through clinical examination as well as viral cultures or polymerase chain reaction (PCR) testing. HSK is managed using antiviral medications, and can be taken orally or used topically depending on how severe the infection is. In order to manage the disease and prevent recurrences, usual treatment is prophylactic antiviral treatment, especially in individuals with a history of frequent episodes. (Liesegang, 2001).

**Method:** Data was collected by analyzing several research papers on the National Library of Medicine, the American Journal of Ophthalmology, PubMed, and other online databases with access provided by Touro University.

**Keywords:** keratoconus, cornea, epithelium, Bowman's layer, stroma, Descemet's membrane, endothelium

**Discussion**

Of significant interest is a disorder known as Keratoconus. Keratoconus is a progressive corneal disorder characterized by thinning and bulging of the cornea, resulting in visual impairment. Keratoconus is a non-inflammatory, bilateral corneal ectatic disorder that typically manifests during adolescence or early adulthood (Kennedy et. al., 1986). It is estimated to affect approximately 1 in 2,000 individuals (Rabinowitz, 1998). The hallmark of keratoconus is the progressive thinning and protrusion of the cornea, leading to irregular astigmatism and visual distortion. Early detection and diagnosis are vital to prevent disease progression, preserve visual functionality, and optimize treatment outcomes. (Krachmer, 1984)

There are several signs and symptoms which can help to detect the disease in its early stages. Blurred vision, often accompanied by visual distortion, is one of the primary symptoms experienced by individuals with keratoconus. It is typically more pronounced in one eye initially and may progress to affect both eyes over time (Rabinowitz, 1998). Frequent changes in eyeglass prescription is also a red flag. Keratoconus can cause rapid changes in the shape of the cornea, which is what causes the frequent changes in eyeglass prescription. This frequent need to adjust a prescription result in a patient's repeated dissatisfaction with their glasses, since the glasses no longer provide satisfactory visual correction (Barr, 2006). Many patients with keratoconus report heightened sensitivity to bright light, also known as photophobia. This symptom often accompanies other visual disturbances and can significantly impact daily activities. Nearsightedness, or progressive myopia, is a common finding in individuals with keratoconus. Patients may notice a gradual worsening of their distance vision over time, which is not adequately corrected by glasses or contact lenses (Tuft et. al., 1994). Another symptom often experienced by keratoconus patients is Monocular Diplopia which can be described as Ghosting or Multiple Images. This can be more plainly described as seeing a halo-like shadow around objects or letters. This symptom is more noticeable in low-light conditions or when looking at bright objects (Kymes et. at., 2008).

There are several approaches in diagnosing Keratoconus. Corneal topography, a non-invasive imaging technique, is widely used for the diagnosis and monitoring of keratoconus. It provides detailed information about the corneal curvature, elevation, and shape irregularities, aiding in the detection of early keratoconus and monitoring disease progression (Gomes et. al., 2015). Another tool in detecting keratoconus is by performing a slit-lamp biomicroscopy, which provides direct visualization of the cornea, allowing ophthalmologists to detect characteristic signs of keratoconus, such as corneal thinning, Vogt's striae, and corneal scarring (Krachmer, 1984). Optical Coherence Tomography or (OCT) is a high-resolution imaging technique that provides cross-sectional images of the cornea. It allows for detailed evaluation of corneal thickness, epithelial mapping, and stromal changes associated with keratoconus (Kanellopoulos and Asimellis, 2013). Corneal wavefront analysis measures the aberrations in the cornea, providing important understandings of the irregular astigmatism and higher-order aberrations present in keratoconus. This diagnostic tool aids in the detection and quantification of corneal irregularities (Moscovici et. al., 2021). Early detection of the signs and symptoms of this condition is crucial in diagnosing keratoconus.

There are various diagnostic methods employed in the identification of keratoconus and it is important to ensure differential diagnosis. The primary tool for diagnosis of keratoconus is a clinical examination. A comprehensive evaluation includes a detailed patient history, visual acuity assessment, slit-lamp biomicroscopy, and corneal topography (Rabinowitz, 1998). As previously mentioned, Corneal topography is a non-invasive imaging technique that measures the shape and curvature of the cornea. It helps identify the characteristic findings in keratoconus, such as corneal steepening, irregular astigmatism, and localized thinning (Wang et. al., 2022). Corneal tomography provides detailed three-dimensional images of the cornea, allowing for a comprehensive evaluation of its thickness and shape. This technology aids in detecting subtle changes in corneal structure associated with keratoconus (Belin et. al., 2013). Anterior Segment Optical Coherence Tomography, or AS-OCT, enables high-resolution imaging of the cornea and anterior segment structures. It

provides cross-sectional views of corneal layers and helps in assessing corneal thickness and identifying signs of keratoconus (Brenner et. al., 2012).

In addition to these diagnostic methods, it is also important to ensure differential diagnosis of Keratoconus. Corneal ectasia refers to the progressive thinning and protrusion of the cornea, similar to keratoconus. Differential diagnosis involves distinguishing between iatrogenic ectasia caused by corneal refractive surgery and primary ectatic disorders like keratoconus (Renato, 2016). Pellucid marginal degeneration (PMD) shares clinical features with keratoconus, such as inferior corneal thinning and steepening. Differentiating between these conditions can be challenging but is important for appropriate management (Krachmer et. al., 1984). Terrien's marginal degeneration generally affects the peripheral cornea and can appear similar to keratoconus. Clinical examination and corneal imaging techniques aid in differentiating between the two conditions (Esporcatte et. al., 2022).

Early and accurate diagnosis of keratoconus is vital for ensuring the right treatment strategies and to ensure that further visual impairment is prevented. These diagnostic tools are essential to help with early and accurate diagnosis of keratoconus and make sure that doctors can distinguish keratoconus from other corneal diseases.

The progression of keratoconus and the increasing impairment that follows can have a significant impact on the individual as well as daily activities and quality of life. Of significance is the visual impairment that accompanies keratoconus. This can come in many forms. Keratoconus causes the cornea to progressively thin and bulge, leading to irregular astigmatism and distorted vision (Rabinowitz, 1998). As the condition progresses, patients may experience reduced visual acuity, increased sensitivity to light (photophobia), glare, and multiple images (polyopia) (Kennedy et. al., 1986). Corrective lenses such as glasses or contact lenses may initially help, but as the corneal irregularities worsen, specialized lenses or surgical intervention may be necessary (Sorkin and Varssano, 2014).

The progressively decreasing visual acuity and contrast sensitivity of keratoconus can also significantly affect one's daily activities such as reading, driving, and recognizing faces (Sedaghat et. al., 2015). Several studies have reported reduced visual acuity and contrast sensitivity in keratoconus patients, even with optimal corrective measures. This visual impairment can negatively impact the overall quality of life of affected individuals (O'Brart, 2014).

The visual impairment associated with keratoconus can limit a person's ability to further their education as well as their career choices. Tasks that require good visual acuity, such as reading small print, working with computer screens, or performing fine manual tasks, may be challenging for individuals with keratoconus (Guggenheim et. al., 2013). This may lead to decreased work productivity, difficulty in pursuing higher education, and potential psychosocial deficiencies. Many aspects of daily living can also be affected. These include a person's personal grooming and ability to participate in sports activities and other leisure activities. Other basic tasks such as applying makeup or shaving may be a problem due to distorted vision, and swimming or sports may have to be restricted due to the risk of corneal damage or lens displacement.

Ongoing treatments and the possible need for special lenses or surgery may also place an additional financial burden on affected patients. These all add to quality-of-life issues that may arise as a result of the diagnosis (O'Brart et. al., 2018).

Several surgical treatment options have been developed to address both the visual and structural abnormalities associated with keratoconus:

**Penetrating Keratoplasty (PKP)** is a surgical procedure that involves the replacement of the entire thickness of the cornea with a donor cornea. This procedure has been the most prevalent treatment for advanced cases of keratoconus for many years. The resulting visual outcomes following this surgery have been good. However, there are some disadvantages including long visual recovery time, high risk of rejection, and the development of an astigmatism in the eye (Williams et. al, 2008).

**Deep Anterior Lamellar Keratoplasty (DALK)** is a procedure that selectively removes the anterior corneal layers while preserving the recipient's endothelium and Descemet's membrane. This method avoids the risk of endothelial rejection associated with PKP and reduces the need for long-term immunosuppression. DALK also shows better graft survival rates, faster recovery compared to PKP and better visual outcomes. One downside to the DALK procedure is that it is technically challenging and may have a higher risk of operative complications (Karimiam and Feizi, 2010).

**Descemet's Stripping Automated Endothelial Keratoplasty (DSAEK).** This procedure involves the replacement of only the endothelium and Descemet's membrane with a donor graft. Some stromal cells are often removed as well. This procedure offers faster visual recovery and reduced astigmatism compared to PKP. Additionally, DSAEK is a shorter surgery and has a reduced risk of complications. Some issues with DSAEK are the potential risk that the graft may dislocate and there may also be a need for postoperative care for an extended period of time (Terry, 2006).

**Descemet Membrane Endothelial Keratoplasty (DMEK)** is a procedure by which the thin Descemet membrane and endothelium of a donor are transplanted into the affected eye. DMEK has shown very good visual outcomes and faster visual recovery and minimal chance of a resulting astigmatism. Visual quality of DMEK has been found to be better than DSAEK but great surgical expertise is needed in this procedure, since there is a higher risk of graft detachment.

**Femtosecond Laser-Assisted Keratoplasty (FLAK)** combines the use of laser technology with either the PKP or DALK procedures. This provides for a more precise and controlled corneal dissection, which allows for improved visual outcomes and faster healing of the wound. Visual acuity has been shown to be better and graft survival is promising with FLAK. However, the equipment required for this procedure is significantly more expensive and it requires specialized training. (Rodrigues et. al., 2019)

**Intrastromal Corneal Ring Segments (ICRS)** are small devices implanted into the cornea to flatten and reshape its curvature. This reduces the irregular astigmatism and improves vision. The rings help to reinforce the cornea which has become weakened and provides the ability to focus with greater ease. (Zadnik et. al., 2019) Topography-Guided Photorefractive Keratectomy (TG-PRK) uses data from an eye scan combined with an excimer laser ablation, which is used to reshape the cornea and correct irregular astigmatism caused by keratoconus. By smoothing irregularities and optimizing corneal curvature, TG-PRK can improve visual acuity and reduce the need for corrective lenses. However, its effectiveness may vary depending on the severity of the condition.

While surgical interventions such as those described above have been the typical treatment for advanced cases, with early detection there are now non-surgical treatment options that have gained popularity in recent years. These non-surgical options are aimed at correcting refractive errors, improving visual acuity, slowing disease progression and postponing or possibly avoiding the need for surgery at all.

Glasses may provide relief for some initial visual distortion due to mild cases of keratoconus. However, this may not be enough to address advanced stages of keratoconus. There are several types of contact lenses that may help in mild cases as well. Rigid Gas Permeable Contact Lenses help to mask corneal irregularities, which provides better visual correctness compared to glasses. The fact that they are rigid ensures that the optical surface will be smooth, reducing the impact of corneal distortion (Gencaga et. al., 2021). These RGP lenses can also help to stabilize the cornea by redistributing tear film, which has the potential to slow the progression of keratoconus. Another type of contact lens which can help are hybrid lenses which combine the benefits of RGP lenses and soft contact lenses. They have a rigid center and a soft outer layer which may be more comfortable for some patients and are able to mask any irregular astigmatism in addition to providing excellent visual acuity. Hybrid lenses offer improved comfort and stability, while providing excellent visual acuity (Akcay et. al., 2021). These hybrid lenses have been shown to be especially helpful for patients with severe keratoconus or corneal scarring.

Of significance in the non-surgical treatments for keratoconus, has been the development of Corneal cross-linking (CXL). This is a minimally invasive procedure that strengthens the cornea by inducing additional cross-links within the collagen fibers. This procedure stops the progression of keratoconus and stabilizes the cornea.

Cross-linking of collagen involves the collagen fibril's ability to create chemical bonds with adjacent fibrils. Collagen cross-linking occurs naturally in the cornea as one ages due to a reaction that takes place within the end chains of the collagen. Experts believe that this natural cross linking is why keratectasia (corneal ectasia) usually progresses most rapidly in adolescence or early adulthood but tends to stabilize in patients after middle-age. While crosslinking tends to occur naturally over time, there appear to be causes of early crosslinking. For example, in patients with diabetes, there is a reaction that can lead to the formation of additional bonds between collagen called Glycation. (Cingu , et. al., 2015)

Researchers in Europe developed the current corneal collagen cross-linking techniques at the University of Dresden in the late 1990s. The researchers used UV light to induce collagen cross-linking in riboflavin soaked porcine and rabbit corneas via the oxidation pathway. As a result, the corneas appeared stiffer and more resistant to enzymatic digestion. The research also proved that treated corneas contained higher molecular weight polymers of collagen due to fibril crosslinking. Safety studies showed that the endothelium was not damaged by the treatment if proper UV irradiance was maintained and if the corneal thickness was maintained. Human studies of this UV-induced corneal cross-linking began in 2003 in Dresden. The initial study involved sixteen patients who all exhibited fast progressing keratoconus. The results were all positive. The patient's illness stopped progressing after treatment. Furthermore, a significant percentage had additional flattening of their corneal curvatures and had an improvement in visual acuity as well with no reported complications. The treatment became known as the Dresden protocol and was designed by Wollensak, it

is described as the follows:

- Instill topical anesthetic drops in the eye.
- Debride the central 7-9mm of corneal epithelium.
- Instill 0.1% riboflavin 5-phosphate drops and 20% dextran solution every 5 minutes for 30 minutes.
- Exposure to UVA (370nm, 3mw/cm2) for 30 minutes while continuing instilling the above drops every 5 minutes.
- At the end of the procedure, apply topical antibiotics and soft Bandage Contact Lens with good oxygen permeability. (Wollensak et. al., 2003)

Of greatest significance is the fact that corneal cross linking has been shown to significantly reduce the need for more invasive treatments like corneal transplantation (Farjadnia and Naderan, 2015). CXL is typically performed with the application of riboflavin and ultraviolet A (UVA) light. This treatment is followed by a course of antibiotics and autologous serum eye drops (ASEDs), more commonly known as serum tears, which are made from the patient's own blood supply.

There is another form of the cross linking procedure which is called Epithelium On (CXL epi-on). This procedure differs slightly from cross linking Epithelium Off (CXL epi-off) discussed above. The major difference is that the corneal epithelial layer is not removed from the eye before the drops and UVA light are applied. This approach reduces the possibility of post operation corneal infection, subepithelial haze, sterile infiltrates, reactivation of herpetic keratitis, and endothelial damage, which is all a risk of the CXL epi off. This transepithelial method may be safer, but because the corneal epithelium was not removed, its tight junctions makes it more difficult for the riboflavin to diffuse into the stroma. Some methods used to try and increase the diffusion is adding chemical enhancers to change the physicochemical properties of the riboflavin molecule.

Studies were done to see which crosslinking procedure might be the more efficient procedure in increasing patients' vision and stopping the progression of keratoconus. The studies showed that overall, the outcome for vision is about the same. However, since the Epi Off involves removal of the epithelial corneal layer and Epi On does not, one might think the Epi On is the better option because there is less chance of post operation infection. Nevertheless, the epi on, which does not remove the epithelial corneal layer, might not be the better of the two. This is because there is more of a chance of the procedure failing and more treatment needed further on (Cifariello et. al., 2018). One important factor in deciding between the Epi On versus the Epi Off procedure is the fact that the Epi On procedure has not yet been FDA approved. At the writing of this report studies were underway to give FDA approval to the Epi On procedure.

While the traditional treatment options discussed above have been effective to varying degrees, emerging therapies are showing promise in providing more efficient and long-lasting solutions. Artificial corneas, also known as keratoprostheses, have developed as a possible option for patients with keratoconus who are not candidates for corneal transplantation. The development of synthetic materials and advancements in biomaterial sciences have helped in the development of biocompatible and optically transparent artificial corneas (Greiner et. al., 2011). Another treatment that shows potential in the treatment of keratoconus is gene therapy. This deals with the underlying genetic factors involved in the specific genetics of the disease. Recent research has identified specific genetic variants associated with keratoconus and gene therapy attempts to correct these genetic irregularities using viral vectors or gene-editing techniques. There have been studies done in animal models that have advanced the feasibility of gene therapy as an effective approach for stopping the progression of keratoconus (Lin et. al., 2020). However, there still needs to be further research to find better ways to deliver the gene therapy and ensure long term safety in human patients.

**Discussion**

Of the many conditions affecting the cornea, keratoconus has garnered significant attention. Understanding the characteristics of this disease is essential for early detection, appropriate management, and preservation of visual function. The focus on keratoconus has led to the development of many emerging treatments, both surgical and non-surgical. The surgical treatments for keratoconus will depend on the severity of the disease progression, the corneal thickness, and the surgical expertise of the doctor. Non-surgical treatments are beginning to provide viable alternatives to surgery. Significant studies has been conducted related to non-surgical treatment options whose main goal is to postpone or completely avoid the need for surgery. These continued studies and advancements in treatments are significant in the improved outcomes for individuals affected by this condition.

Early diagnosis of keratoconus is essential for successful treated. The best treatment right now seems to be the cross-linking epi off procedure, since there are rarely any post operation complications. Although crosslinking epi on seems promising since it is the least invasive with the quickest recovery, there is still a chance a patient will need more treatment later. Again, this all depends on when the patient is diagnosed. At a certain

point crosslinking surgery may not be enough to help the patient and further procedures might be needed as discussed above.

Keratoconus can be a visually debilitating eye disease if not detected early and treated properly. In the world of medicine today, there are so many possible treatments for a doctor and patient to choose from, that if monitored and treated properly, there is no reason for keratoconic progression to continue. With continued scientific study, visual debilitation due to keratoconus can be a thing of the past.

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