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# Treatment & Management of Keratoconus: New Clinical Pathways

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## Abstract

Keratoconus is a progressive, non-inflammatory and uncommon corneal disorder characterized by central & para-central corneal thinning, conical protrusion, and central scarring causing high irregular astigmatism. It has been described as bilateral disease with different disease severities. The symptoms of keratoconus include blurring vision, high astigmatism, double vision, habits of eye rubbing and gradual decline in visual acuity & quality of life. This review discusses the history of developments, advances in treatment modalities, and management of keratoconus maps since it was first recognized in 1854. John Nottingham, a British physician is credited with providing the first comprehensive understanding of this condition as keratoconus in 1854. His insights and features allowed the condition to be distinguished from other corneal ectasias are still understood as true today. Before this, there was little mention of the condition. The early history of keratoconus still remains as complex and confusing with several nomenclature including hyperkeratosis, ochlodes, conical formed cornea, sugar loaf cornea and staphyloma diaphanum. The counter and management of keratoconus were major assessed, when the first corneal lenses were developed in 1949. These lenses were much smaller than the original scleral lens. Today, a wide array of these lens options is used to achieve these goals including corneal rigid lens, semi-scleral & scleral contact lens. The collected information from various article are précises the advancement of novel diagnostic, available treatment modalities and management options for keratoconus to provide practical and useful information. This review describes the evolutionary development of the diagnosis and treatment of keratoconus from the earliest written description to present day.

## Keywords:

Keratoconus (KC); Scleral Lens (ScCL); Corneal Collagen Cross-linking (CXL); Penetrating Keratoplasty (PK); Epikeratoplasty (EK); Excimer Laser Phototherapeutic Keratectomy (PTK); Intrastromal Corneal Ring Segment (ICRS); Phakic Intraocular Lens (pIOL); Implantable Collamer Lens (ICL); AvaGen, Genomics & Tear Proteomics.

## Introduction:

Keratoconus is a degenerative non-inflammatory disease of cornea causing corneal thinning and remodeling into a more conical shape. The symptoms of KC include blurring vision, high astigmatism, double vision, habits of eye rubbing, gradual decline in visual acuity and quality of life. KC is usually bilateral, but it can affect each eye with different corneal severities[1]. The description of a keratoconus has existed in the literature in mainly three centuries. This review highlights precisely traced observations of various authors through the 19th, 20th and 21st centuries including the earliest description of keratoconus. The treatment of keratoconus consists of spectacles correction and then rigid contact lenses once spectacle corrected visual acuity become inadequate. The surgical treatment is indicated, when intolerance occurs with contact lenses.

## Methods:

The literature search was performed in conjuction with meaningful headings & sub-headings such as keratoconus, corneal contact lens, scleral lens, conical cornea, cross linking, intrastromal corneal ring segment, keratoplasty, irregular astigmatism and

gene therapy. This review paper tend to include 120-publications from Pubmed, Google Scholar, Research Gate, Embase, Scopus, WorldCat & CORE search engines and text book sources have been reviewed.

## 1. History of Keratoconus: In the Second Half of the 19th Century:

- **In 1854:** John Nottingham, a British physician, described the condition in greater detail and distinguished it from other forms of corneal ectasia [2, 3].
- **In 1859:** Willium Bowman, a British Surgeon was one of the first ophthalmologists to use an ophthalmoscope to examine the cornea and diagnose keratoconus [4].
- **In 1869:** Johann Horner, a Swiss ophthalmologist, conducted a thesis entitled on the treatment of keratoconus. Horner's aim was to attempt to change the physical shape of the cornea and make it a more normal corneal curve. It was not until 1869, that the disorder acquired its name "keratoconus," meaning "horn-shaped" cornea**5**.
- **In 1887:** Friedrich A. Müller & Albert C. Mullerwere created the first clinical application of contact lenses and this new invention transformed the management of keratoconus [6-8].
- **In 1888:** Adolf Eugen Fick, German ophthalmologist invented the first successful contact lens, made from heavy blown glass. His idea was to neutralize the optical effects of the irregular corneal astigmatism and distortion by using a bifocal scleral glass shells [3, 9].
- **In 1889:** Eugene Kalt, a French ophthalmologist, investigated contact lenses as orthopedic appliances in the treatment of keratoconus. He noticed that the contact lens changed the shape of the cornea and thus he laid some of the groundwork that led to orthokeratology [10].

## 2. History of Keratoconus: In the 20th Century:

- **In 1912:** Heinrich Erggelet (Freiburg, Germany), commissioned Zeiss to make made ground glass experimental contact lenses to induce artificial ametropia to test the optical quality of the corrected curve glasses. Obrig, T.E & Salvatori, Zeiss produced their first contact lens trial set for use by ophthalmologists [8, 11].
- **In 1916:** Rugg Gunn (1931), Zeiss produced the first trial set especially for keratoconus [**12]**.
- **In 1918:** Leonhard Koeppe (Halle, Germany), was an ophthalmologist who described a contact lens for specialist observation of internal features of the eye using a slit lamp biomicroscope. This type of short-use lens was termed a gonioscope [13].
- **In 1920:** Stock. W, first pre-formed ground glass fitting sets of pre-scleral lens came into use. Polymethyl-methacrylate (PMMA) was developed at the same time. Zeiss manufactured a four-lens preformed fitting set primarily for keratoconus. It was introduced and developed by Professor W. Stock from Jena University, who was a sufferer of the condition [14].
- **In 1927:** Adolf Wilhelm Müller-Welt (Stuttgart, Germany), an artificial-eye maker, applied for a patent for the first fluidless blown glass lens. Those lenses were made from glass, blown over a series of preformed toric castings, which formed the scleral portion of the lens [15, 16].
- **In 1930s**: Josef Dallos (Budapest, Hungary), an increased potential & thermoplastic property of PMMA material to allow more versatility for fitting from impressions and more precise manufacturing process of rigid lenses [17-20].
- **In 1936:** Willium Feinbloom, American optometrist, was the first to introduce plastic, rigid, lighter and more convenient contact lens than the glass blown contact lenses thus improving the compliance and the management outcome of keratoconus [3, 21].
- **In 1940:** The corneal scleral impression techniques were introduced and enhanced the ability of early scleral contact lens fitters to perform custom fittings. PMMA become the material of choice over glass for scleral lenses [17, 21].
- **In 1946:** The traditional Amsler-Krumeich (AK) keratoconus classification system was established based on a combination of pachymetry, slit lamp findings, central keratometry and refraction [22].
- **In 1946:** Heinrich Wöhlk (Kiel, Germany), an engineer, became interested in contact lenses after his 8D of hypermetropia was corrected by Professor Leopold Heine with Zeiss scleral lenses. Wöhlk's first PMMA lens, the 'Parabolar', was similar in size to modern corneal lenses [23]. Wöhlk also developed a method of making PMMA lenses from raw material polymerised between quartz moulds [8].
- **In 1950:** George Butterfield (Oregon, USA), an optometrist, produced a better-fitting corneal lens than Tuohy's) with progressively flatter peripheral curves, 9.50 mm diameter and 0.2 mm thick, to aid tear exchange.
- **In 1950:** Kyoichi Tanaka (Nagoya, Japan). Glass corneal lenses tended to be heavy and ride very low, whereas PMMA lenses, being much lighter, were raised by the upper lid after each blink, giving better performance. Kelvin Tuohy lens was a mono-curve fitted flatter than flattest K (www.nova.edu), 11 mm in diameter and 0.4 mm thick [8, 23]. The advent of corneal lenses later known as rigid corneal lenses to differentiate them from their larger scleral cousins. Scleral lenses largely fell into disuse but always retained a role in specialized contact lens practice. Frederick Williamson Noble produced several scleral lenses with a small reading zone in the centre of the optic zone [8].
- **In 1952:** Frank Dickinson (St. Annes, England), Wilhelm Sohnges (Munich) and John C. Neil (Philadelphia, USA) cooperated with modifications to the corneal lens and its introduction into all three countries. It was lathe cut in the UK and either lathe cut or moulded in Germany. The mono-curve lenses were fitted approximately 0.65 mm flatter than flattest K with a diameter of 9.5 mm correcting up to 4D of corneal toricity [24].
- **In 1955:** John de Carle, an optometrist in London, developed a bifocal corneal lens of concentric design with a centre portion focused for distance correction, surrounded by the reading portion. This was based on an idea of ophthalmologist Frederick Williamson-Noble, who had observed unlikely distance and reading vision by a patient with central cataracts.
- **In 1960-1970:** corneal lenses continued to develop. Narrower intermediate and peripheral zones in multi-curve lenses led to numerous variations of back surface designs: aspheric corneal lenses with tangential conic peripheries [25, 26],

continuous offset bi-curve lenses [27, 28], lathe-cut continuous aspheric lenses [29] and the Kelvin continuous curve lens designed by Raymond Kelvin Watson. With increased interest in contact lenses, more comfortable, developments of better-quality designs and materials of contact lenses further enhanced and improved the management option of keratoconus.

- **In 1980:** Re-established scleral lenses (ScCLs) and allowing the manufacture of non-fenestrated scleral contact lens that bring into existence them as a viable clinical option. The development of rigid gas permeable plastics greatly reduced the hypoxic complications associated with daily wear of corneal lenses and added a new dimension to the potential of scleral lenses for the visual rehabilitation of patients with markedly irregular corneas and treatment of ocular surface disorders [30].
- **In 1983:** Ezekiel described the use of preformed, fenestrated, silicone acrylate gas permeable scleral contact lenses in fitting patients with keratoconus, severe myopia, aphakia, and corneal scarring. Since then, new techniques in the manufacture of rigid gas-permeable scleral lenses have been developed [31].
- **In 1983:** Don Ezekiel (Perth, Australia) reported, at the BCLA conference, making scleral lenses using two different rigid gas permeable (RGP) materials. It was later called the Gelflex Scleral and gained Food and Drug Administration (FDA) approval for use in the USA.
- **In 1990:** Several milestones were reached in the developement of scleral lenses. The development of materials with high gas permeability, together with various technological innovations in the design and manufacturing of scleral lenses has opened new perspectives for their use in different ocular surface disease [32].
- **In 1992:** Ken Pullum (Hertford, England) founded innovative sclerals to supply and fit RGP scleral lenses. An impression taken of the eye was then scanned, and the back surface of the lens was lathe cut using CAD CAM technology. The front surface was finished by hand to minimize the thickness; the company was bought by Bausch & Lomb in 2015.
- **In 1998:** Eaglet eye surface profiler was invented by Dr. Frans Jongsma to measure the curvature of 20 mm in diameter of the front surface of the eye. It would take another 15 years to bring it to market.
- **In 2007:** William Masler, Acculens president and Fellow of the Contact Lens Society of America, designed the Maxim scleral lens, later licenced to Bausch & Lomb.
- **In 2008:** Dr. Robert Breece designed the Jupiter lens. Later made by Visionary Optics in the USA and licenced to Essilor. The Jupiter was available in 15 mm and 18 mm diameters and usually had five curves organized into three zones, and it was available in three configurations.
- **In 2009:** Scleral Lens Education Society was founded by Greg DeNaeyer, Christine Sindt and Rob Breece (www.sclerallens.org). With the renewed interest in scleral lenses the Scleral Lens Education Society designed a classification system.

## 3. Classification of Keratoconus:

The earliest symptom is a slight blurring of vision, difficulty seeing at night, glares and halos around lights that are not easily corrected. The greater variability among patients with keratoconus, it is very important to grade this disease in order to provide some general guidance for the clinician regarding the level of progression and the treatment options that can be offered. There are various keratoconus classifications depending on which principal factors are considered. The oldest & most widely used classification is the (Amsler-Krumeich-1946) scale (Table 1) [22]. This scale is based primarily on keratometric criteria but also includes other factors, such as refraction and pachymetry[22]. The grades are:

**Table 1: The Amsler-Krumeich (AK) classification for Keratoconus:**

| Grades | Mean K-reading | Myopia and/ or Induced Astigmatism | Scarring/ or Striae | Corneal Thickness *(At Point of most Thinning)* |
|---|---|---|---|---|
| **Grade-1** | < 48.00D (***Eccentric Steepening***) | < 5.00D | Absence | - |
| **Grade-2** | 48.00D - 53.00D | Between 5.00D & 8.00D | Absence | > 400µm |
| **Grade-3** | 53.00D - 55.00D | Between 8.00D & 10.00D | Absence | Between 300µm & 400µm |
| **Grade-4** | > 55.00D | Refraction not Measurable | Present | Between 200µm & 300µm |

***D: Diopter, **K: Keratometry**

The advances in topographic methods, capable of providing corneal aberrometric data, the (Alió-Shabayek-2006) scale were developed. This scale is better suited to current diagnostic methods. In addition to the factors mentioned previously, it includes aberrometry of the anterior surface of the cornea, with special emphasis on comatic aberrations [33]. These parameters are used because both coma-like aberration values and higher-order aberrations tend to increase with increasing protrusion of the cone; and later with disease progression (Table 2) [33]. This classification establishes the following grades:

**Table 2: The Alió-Shabayek (AS) classification for Keratoconus:**

| Grades | Mean Central K-reading | RMS of Coma-like Aberration (µm) | Spherical Equivalent (D) | Corneal Central Scarring | Corneal Thickness (µm) |
|---|---|---|---|---|---|
| **Grade-1** | ≤ 48.00D | Between 1.50 to 2.50µm | < -5.00D | Absent | > 500µm |
| **Grade-2** | Between 48.00D & 53.00D | Between 2.50 & 3.50µm | -5.00D to -8.00D | Absent | 400 -500µm |
| **Grade-3** | Between 53.00D & 55.00D | Between 3.50 & 4.50µm | > -8.00D | Absent | 300 - 400µm |
| **Grade-4** | > 55.00D | > 4.50µm | Not Measurable | Present | < 200µm |

***RMS: Root Mean Square.** It refers to the quadratic mean of the Zernike coefficients corresponding to a particular aberration.

## 4. Monitoring the Progression of Keratoconus:

The initial identification of keratoconus at an early stage is challenging and clinical findings may not be seen or present until the condition is in advanced stages. Further, some patients with keratoconus that is easily identified on topography can still have good vision. While early diagnosis of the disease is essential and monitoring the disease over time is just as important. It is crucial to define the stage and rate of progression of this disease when making any decision regarding treatment [34]. The modern corneal tomography, including both anterior & posterior elevation, pachymetric data and aberrometry maps are very useful to screen for progression of keratoconus. It is a non-invasive diagnostic test that allows knowing the surface of the cornea. Corneal topography is established that this is the best method of diagnosis in early keratoconus. The integrated software programs such as the Enhanced Reference Surface (ERS) and the Belin-Ambrosio Enhanced Ectasia Display (BAD) display can be employed to diagnose and monitor progression of keratoconus.

**The following have been identified as factors affecting the progression of keratoconus [35, 36]:**

a) **Age:** At which the disease is detected. So far, the earlier the disease is manifest, the more rapid the progression.
b) **Race:** Also affects progression (Caucasians have the lowest rate of progression once the disease is detected).
c) Several associations have been identified such as Down's syndrome, eye rubbing, diplopia, chronic inflammation of the ocular surface (severe allergic conjunctivitis) have also identified as clearly predisposing progression of keratoconus.
d) **Corneal Curvature:** The higher the corneal curvature, the greater the speed of progression.
e) **High Corneal Cylinders:** Corneal cylinder over 1.9 D represents a poor prognosis in terms of disease progression.
f) **Genetic Factors:** Although family history may be influential in terms of incidence, it is interesting to note that there is no evidence that this affects how quickly the disease evolves.

## 5. Pearls for Treatment & Management of Keratoconus:

In the past several decades, outcome data have accumulated for newer interventions in keratoconus which promise to reduce corneal transplantation. These interventions include Corneal lenses, Scleral Contact Lens (ScCL), Excimer laser phototherapeutic keratectomy (PTK), Corneal Collagen Cross-linking (CXL), Intracorneal Ring Segment (ICRS), Phakic Intraocular Lens (pIOL), Implantable Collamer Lens (ICL), AvaGen Genetic Testing, Genomics and Tear Proteomics in keratoconus. These wide varieties of interventions and strategies continue outlines of new pathways for keratoconus management addressing corneal shape stabilization and restoring good visual rehabilitation.

### 5.1. Conventional Management:

The conventional management of keratoconus disease progression is generally managed with spectacles, rigid contact lens and then corneal transplantation where contact lenses failed. There were not any treatments or interventions available to slow down or arrest the disease progression.

#### 5.1.1. Optical Management:

In the early keratoconus, the patient's refractive error can often be successfully managed with spectacle lenses. Mild to moderate keratoconus can be treated with eyeglasses or contact lenses. When spectacles fail to adequately correct visual acuity, the contact lenses are the next option. Contact lenses often provide better vision than spectacle by neutralizing irregular astigmatism with toric & uncommon refractive errors. This will likely be a long-term correction, especially as the cornea becomes stable with time i.e. no disease progression or any change in corneal power.

#### 5.1.2. Scleral Contact Lens:

Management of patients with keratoconus consists primarily of providing optical correction to maximize visual function. In very mild or early disease, spectacle correction or standard hydrogel or silicone hydrogel lenses may provide adequate vision. However, disease progression results in increasing ectasia, which gives rise to complex optical aberrations. Rigid gas-permeable contact lenses mask these aberrations by allowing a tear lens to form between the contact lens and the irregular corneal surface. Scleral contact lenses have always been considered suitable for the correction of irregular astigmatism in keratoconus. It's able to neutralize irregularities with the tear film meniscus that form with the cornea, while maintaining high levels of comfort. Most of clinical studies on scleral contact lenses in keratoconus have been reported a significant improvement of visual acuity and are a useful tool in the management of keratoconus and corneal transplant patients[37, 38].

### 5.1.3. Piggyback Contact Lens:

Piggyback lens was started date back to the early 1970s. The first Piggyback lens system was introduced in 1970 as a solution for keratoconic patients who were unable to use rigid lenses but had limited success due to the low oxygen permeability of the lens materials used [39-42]. The term piggyback was initially used to describe a rigid contact lens fit on top of another soft contact lens. It is a combination of a rigid gas permeable contact lens, which provides good optical correction especially for irregular astigmatism and a soft contact lens a carrier lens that acts as a bandage lens promoting comfort & enhancement of the corneal irregularities [43]. Today, Piggyback contact lens (PBCL) systems made with a combination of high-Dk silicone hydrogel and gas-permeable rigid materials have been shown to allow adequate oxygen to reach the cornea due to the high oxygen-permeability of both lenses. PBCL system is used for patients with keratoconus who could not tolerate their conventional rigid corneal lenses. Early Piggyback systems consisted of thick, low Dk, soft lenses in combination with low Dk silicone acrylate rigid lenses. However, with the recent introduction of high Dk silicone hydrogel lenses and stable high Dk GP materials, the dual lens system particularly for keratoconus patients experiencing comfort or lens centration [44-46]. In addition, as the movement of both lenses promotes circulation of the tear layer between the lenses in this system, it is possible to benefit from the oxygen dissolved in the tears [43].

Several authors have described in his studies that the PBCL system is a safe and effective method to provide centering and corneal protection against mechanical trauma by the rigid lenses for keratoconus patients and may increase contact lens tolerance. Tomris Sengor et. al. [47], Weissman BA et. al. [48] & Florkey LN et. al.[49] were used the first-generation silicone lotrafilcon A hydrogel lens with Dk/t (oxygen transmissibility) = 150 units (Focus Night and DayR; CIBA Vision, Atlanta, FL) with a steep base curve (8.40 mm) to enable a more stable keratoconic topography; A fluorosilicone methacrylate RGP copolymer with Dk/t = 100 units (Conflex keratoconus 100 UVR, Germany) was their RGP lens of choice. The PBCL system may be preferable for keratoconic patients who experience discomfort, intolerance and inadequate lens stabilization or apical epithelial erosion with rigid gas permeable contact lenses [47, 50].

### 5.1.4. Hybrid Contact Lens:

The first truly hybrid technology, patented by two scientists (Charles A. Erikson and Amar N. Neogi), was acquired by Precision Cosmet Co., Inc. in 1977. Named the Saturn II lens, it gained U.S. Food and Drug Administration (FDA) approval in 1984. Sola Barnes Hind purchased Precision Cosmet in 1986 and released the next generation hybrid, the SoftPerm (Sola/Barnes-Hind Incorporated), in 1989. Subsequently, Ciba Vision, following its acquisition of Pilkington Barnes-Hind, marketed these lenses. A combination of poor durability, reproducibility and fitting challenges, including lens adherence, meant these lenses never became mainstream and were largely used to troubleshoot keratoconic patients with a history of intolerance with RGP contact lenses [51, 52, 8]. Today, these problems have largely been overcome by using materials with high oxygen permeability. Of these, SynergEyes KC (SynergEyes Inc., Carlsbad, CA) HCLs were produced considering the KC using a rigid, high-Dk material at the center, hydrogel material for the periphery and a reinforced fusion zone. They were immediately followed by the introduction of another HCL, ClearKone lenses. The rigid part of ClearKone lenses is made of Paragon HDS 100 (Paragon Vision Sciences, Mesa, AZ) gas-permeable rigid material, with a dome (vault) diameter of 7.4 mm and oxygen permeability of 100x10-11 (cm2/s) x (mLO2/[mL x mmHg]). The rigid center part has a spherical optical zone and a reverse-geometry curve. The soft skirt section is made of nonionic hydrogel material with 27% water content and an oxygen permeability of 9.3x10-11 (cm2/second) x (mLO2/[mL x mmHg]) and can be up to 14.5mm in diameter.

## 5.2. Surgical Modalities for Treatment of Keratoconus:

Eduard Zirm was the first ophthalmologist to conduct a successful human corneal transplant in 1905[53]. However, in 1936, the Spanish American ophthalmologist Ramón Castroviejo Briones was the first to perform a successful corneal transplant in an advanced case of keratoconus achieving significant improvement in visual acuity[53-55].

### 5.2.1. Corneal Transplantation:

The modern corneal graft surgery started in the late 1950s, corneal transplantation for keratoconus almost exclusively consisted of a full thickness transplant known as penetrating keratoplasty (PK). This technique involved the removal of all of the layers of the patient's central cornea and replacement with full thickness graft [56]. Corneal transplants can restore vision, reduce pain, comfort and improve the appearance of a damage or disease cornea. It results in a dramatic improvement in vision for most patients. Keratoconus patients are considered for corneal transplantation when spectacle correction is unsuitable, central corneal scarring, contact lens intolerance occurs and deterioration of best corrected visual acuity [57].

### 5.2.2. Epikeratoplasty:

Epikeratoplasty is a form of lamellar refractive corneal surgery introduced in 1980 [19]. The surgical procedure was first used to correct aphakia [58-60] and was then adapted for the treatment of myopia [61]. Epikeratoplasty for a while gained acceptance as a mode of treatment for patients with keratoconus with a clear visual axis. While good long-term results have been reported [62, 63] the procedure has been abandoned for the most part in favor of penetrating keratoplasty because of the superior quality of vision afforded by the latter procedure.

### 5.2.3. Excimer Laser Phototherapeutic Keratectomy:

Excimer laser phototherapeutic keratectomy (PTK) is an important surgical tool & technique in the management of superficial corneal disorders such as anterior corneal dystrophies, degenerations [64] and the treatment of keratoconus nodules [65]. Excimer laser phototherapeutic keratectomy (PTK) is useful in the management of patients with keratoconus, who have nodular sub-epithelial corneal scars and intolerant to contact lens wear [66]. This technique provides a smooth corneal surface and regains contact lens tolerance to the keratoconus patients. It is an

effective method to manage anterior corneal pathologies and offers advantages including repeatability, faster visual recovery and being minimally invasive. Attention to preoperative evaluation and accurate measurement of depth of lesion, corneal thickness and topography may lead to improved outcomes. Risk of haze, hyperopic shifts and recurrence of disease are the important complications that might need to be addressed in the postoperative period [67]. Ward MA et al.68 concluded that PTK may delay or avoid penetrating keratoplasty in selected patients with keratoconus who are contact lens intolerant due to nodular sub-epithelial scars.

### 5.2.4. Deep Anterior Lamellar Keratoplasty:

Deep anterior lamellar keratoplasty (DALK) has been proposed as an excellent alternative to penetrating keratoplasty for corneal diseases that do not affect the endothelium. DALK preserves native endothelium, reduces host immune system reaction and graft rejection [69]. It involves the replacement of the central anterior cornea, leaving the patient's endothelium intact. The advantages are that the risk of endothelial graft rejection is eliminated and there is less risk of traumatic rupture of the globe in the incision, since the endothelium, descemet's membrane and some stroma are left intact; and faster visual rehabilitation [70].

### 5.2.5. Corneal Collagen Cross-linking:

The corneal collagen cross-linking is a new management option for keratoconus, first developed in Germany in 2000 [71]. It consists of the application of riboflavin solution to the eye, saturating the cornea, which is then activated by the illumination with ultraviolet-A light. This method allows the formation of strong new bonds between the corneal collagen strands, improving the shape and the mechanical strength of the cornea [71-73]. It's minimally invasive and advanced therapy slows down or stops the progression. CXL with riboflavin and ultraviolet-A (UV-A) is a procedure of corneal tissue strengthening by using riboflavin as a photosensitizer and UV-A to increase the formation of intra and interfibrillar covalent bonds by photosensitized oxidation [74]. Cross-linking of collagen refers to the ability of collagen fibrils to form strong chemical bonds with adjacent fibrils. In the cornea, collagen cross-linking occurs naturally with aging due to an oxidative deamination reaction that takes place within the end chains of the collagen [75]. Crosslinking is the creation of bonds that connect one polymer chain to another. The bonds can be covalent or ionic. A polymer is defined as a chain of monomeric material either a synthetic polymer or a biologic molecule such as a protein [76]

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### 5.2.6. Intrastromal Corneal Ring Segment

Originally, Intacs were first approved in 1999 for myopia; however, their application in the management of keratoconus was finally approved in 2004 by the Food and Drug Administration (FDA) in the United States [77-79]. ICRS insertion was originally developed for low myopia correction but has now been approved for reduction of myopia and irregular astigmatism associated with keratoconus. These segments are made of PMMA and are inserted in the corneal stroma in a circular arc. Contact lens intolerant patients with clear central corneas may benefit from ICRS. The principal of this technique is that the ring segments flatten the curvature of the cornea and reshapes it to a more naturally curved cornea [77, 78].

### 5.2.7. Phakic Intraocular Lenses:

Phakic intraocular lens is used to eliminate glasses, these tiny artificial lenses are designed to be inserted in front of natural lens. Phakic IOLs can correct myopia, hypermetropia and astigmatism. It is a surgical technique other than corneal refractive procedures should be considered for the correction of residual refractive error in the Post-INTACS keratoconus patients. The combined implantation of ICRS and phakic IOLs is becoming more common with a variety of lenses and techniques. One alternative is the use of anterior or posterior phakic IOLs, including toric lenses, either alone or after implantation of ICRS [80].

### 5.2.8. Implantable Collamer Lens:

The ICL was first developed in 1992 and reach worldwide use from 2005 onwards after FDA approval. It is an artificial lens that's permanently implanted in the eye. ICLs have been implanted in keratoconus patients in various combinations with CXL, INTACS or Post-keratoplasty to provide optimal visual rehabilitation in such type of patients. Shaheen MS et al. [81] concluded that correction of spherical and cylindrical refractive errors in keratoconic eyes by TICL implantation after cross-linking seems to have significantly good outcomes; particularly in the astigmatic component of refraction. They found a significant visual improvement after this procedure. Keratoconus with high myopic and irregular astigmatism causes a lot of visual morbidity to the patients. Various treatment options have been provided for the visual rehabilitation of keratoconus patients. Implantable contact lenses have emerged as a good treatment option for such patients with high degree of efficacy, safety and predictability [82].

### 5.2.9. Cataract Surgery in Patients with Keratoconus:

Although some authors have indicated that cataract development in patients with keratoconus may occur quicker than in normal patients, there are very few studies in medical literature concerning this practice and the number of cases is very small. A study was recently conducted on this topic within the framework of the RETICS which included the most cases described to date (17-eyes). The visual and refractive results were very encouraging. Safety and efficacy rates obtained were $1.38 \pm 0.58$ and $1.17 \pm 0.66$, respectively. Only one eye lost one line of corrected vision and 60% of eyes achieved uncompensated vision of 20/30 or higher. This surgery should be reserved for patients with stable keratoconus; however, it may even be necessary in progressive patients if the visual impairment caused by the cataract is even more limiting than the corneal ectasia [83].

### 5.2.10. Genomics in Keratoconus:

Keratoconus is the most common ectatic disorder of cornea. The disease progresses in a variable speed with corneal thinning included irregular astigmatism, myopia and corneal protrusion. However, despite the intensive investigations, research and imaging modalities, the exact cause is unknown, and the genetic etiology & gene location of keratoconus still remains unclear.

Keratoconus is associated with many ocular disorders included changes at molecular, physiological and genetic conditions. Recent advances in genome sequencing will significantly advance the genetic research of keratoconus. It will improve our understanding of the genes of keratoconus and leading to future development of improved diagnosis, treatment and targeted therapeutic management [84]. Rabinowitz, YS [85] was reported based on twin and cohort studies, keratoconus has a genetic component associated with it, however the effect of these genes on keratoconus disease process could not be identified reliably. It has been shown that 6% to 23% of keratoconus patients do have a family history of the disease [85]. In another study that was headed by Rabinowitz, YS et al. [86], concluded about the database of genes expressed in the human cornea and provides insights into keratoconus. KC6 is a novel gene of unknown function that shows cornea preferred expression, whereas the suppression of transcripts for AQP5 provides the first clear evidence of a molecular defect identified in keratoconus [86]. The KC cornea cDNA library is an excellent source of clones for genes expressed in human cornea and greatly expands the representation of such genes in the databases. However, the analysis to date has already identified approximately 4000 cornea-expressed genes and provides new candidates for genes whose expression may be affected in KC. This analysis increases the database of genes expressed in the human cornea and provides insights into KC.

The expression of KC6 reveals an unexpected new marker for cornea. So far, this mysterious gene seems to have a preference for expression in cornea but is also expressed in embryonic stem cells. The corneal epithelium is known to have populations of stem cells that respond to corneal wounding and to the normal loss of epithelial cells by differentiation and replacement of the lost cells. No molecular markers for these stem cells have yet been identified87. A genetic predisposition to keratoconus is well documented with increased incidence in some familial groups and numerous reports of concordance between monozygotic twins [88-93]. Familial keratoconus cases are common with reports of incomplete penetrance in first- and second-degree family members of affected individuals [88, 94, 95]. Similar to other ocular genetic disorders, studies have indicated that relatives of keratoconus patients have an elevated risk of 15-67 times higher risk of developing keratoconus compared to those with unaffected relatives [95, 96]. In another study in which relatives first-degree and others were evaluated topographically, 14% of family members were found to have KC [88]. The majority of familial keratoconus is inherited through an autosomal dominant pattern [97].

### 6.3. Genetic Test for Keratoconus:

The promising insights and offering great potential hope for the earlier diagnosis of patients with keratoconus is identifying the underlying role of genetics. There is no one single gene responsible for keratoconus. Currently, an AvaGen genetic test to quantify the risk and presence of corneal dystrophies for keratoconus to evaluate the mild, moderate and high-risk genes associated with keratoconus [98]. It helps to determine a patient's risk of keratoconus and the presence of other corneal dystrophies. This test allows for more confident management and treatment for patients with these conditions in order to protect and preserve patient vision [99, 100].

### 6.4. Future Direction in Genetic Studies of Keratoconus:

The recent genome technology development has enabled novel and high throughput genetic approaches to study both Mendelian and complex disorders. Among these approaches, whole exome or genome sequencing will be very powerful to identify the causal mutations in multiplex families with keratoconus [101-103]. The recent studies have indicated that the existing family-based linkage data is tremendously useful in the interpretation of exome sequencing data. A genome-wide association study (GWAS) is an approach used in genetics research to associate specific genetic variations with particular diseases. This method involves scanning the genomes from many different people and looking for genetic markers that can be used to predict the presence of a disease. The available genome-wide genotype data will make it possible to study potential gene-environment interactions. Other approaches to perform genome-wide association studies in a large number of keratoconus cases and controls using high density SNP arrays. This approach has been shown to be very promising in keratoconus [104-107].

### 6.5. Tear Fluid Proteomics in Keratoconus:

Tear fluid is used as a source of biomarkers in ocular & systemic conditions and has been shown to have translational potential. It has been an important source of information in understanding ocular physiology [108]. A large number of proteases and protease inhibitors have been identified in tears [109]. Zhou L et al. [110] have identified over 1500 proteins in the tear fluid; majorly involved in carbohydrate catabolism, proteolysis, protein transport besides immune response and regulation of apoptosis. The disease specific molecular signature from tear fluid analysis can help in understanding the etiology of the disease and to help in prognosis. Moreover, tear fluid can serve as an optimal source of molecular targets for treating ocular diseases [111]. The previous studies performed on tear fluid in patients of keratoconus provided insights into the pathology of the disease and has revealed probable prognostic as well as diagnostic biomarkers for the disease. More importantly, the recent studies and data from tear analysis establish the definitive role of inflammation as a driver of corneal collagen loss and deformity in keratoconus patients [112]. The results of previous studies findings in tear fluid have shown the implication of several biological processes in the KC pathophysiology such as oxidative stress, matrix degradation, cellular death and immune or inflammatory responses, pathways that have also been referred to in the corneal tissues [113-116]. Therefore, tear fluid becomes a good alternative for the study of the KC pathophysiology, being able to reflect the molecular mechanisms that determine the pathologic conditions of the disease.

### 6.6. Environment and Keratoconus:

There are several environmental factors including eye rubbing, atopy, floppy eyelid syndrome, pregnancy, UV exposure and thyroid hormones have been shown to be linked with keratoconus. Eye rubbing shows the strongest association with keratoconus. It can induce ocular surface inflammation, release of stromal matrix degrading enzymes, epithelial thinning and keratocytes death consistent with the etiology of keratoconus. Corneas with

keratoconus have been exposed to a number of factors that can produce reactive oxygen species (i.e. free radicals). The susceptible corneas exhibit an inability to process reactive oxygen species because they lack the necessary protective enzymes (e.g. ALDH3 and Superoxide Dismutase). The reactive oxygen species result in an accumulation of toxic by-products such as MDA and Peroxynitrites that can damage corneal proteins and trigger a cascade of events that disrupt the cornea's cellular structure and function. This can result in corneal thinning, scarring and apoptosis. Atopy is an important cause of eye rubbing and hence by association with keratoconus, although atopy as an independent factor is not established. Floppy eyelid syndrome causes release of matrix-degrading enzymes and dry eye, which can also induce eye rubbing [117-119].

## The Summary:

Keratoconus has been described as a degenerative, ectatic, non-inflammatory corneal disease-causing thinning, protrusion, weakening and remodeling into a more conical shape of the cornea. It causes gradual decrease the visual acuity [1]. It was first described in greater depth and distinguished from other form of corneal ectasia in 185 [42]. During several years of advances, development in diagnosis and research work improved our understanding of the disease and management options since it was first recognized to until now. From beginning to now, the key management of keratoconus is to primarily reshape & remodel the keratoconic cornea into a more normal cornea [3]. The management option of keratoconus was nascent stage in the first half of the 19th century. Further research & development in the 20th and a new decade of the 21st century, radical technologies based surgical interventions, innovative corneal contact lenses, reshaping the cornea, genome sequencing, genetic eye testing and tear proteomics are good methods for management and treatment of keratoconus. Nowadays, Artificial Intelligence (AI), Deep Learning (DL) with a Convolutional Neural Network (CNN) is better understanding of the disease [120]. The recent advances in corneal imaging and novel corneal refractive surgeries have allowed to diagnose much earlier & easier than in past.

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## References:


1. Nordan LT (1997). Keratoconus: Diagnosis and treatment. Int. Ophthalmol. Clin.; 37 (1): 51-63.
2. Nottingham J (1854). Practical observations on conical cornea: And on the short sight and other defects of vision connected with it. London J Churchill; 23-26.
3. Abdelaziz L, Barbara R (2013). History of the development of the treatment of keratoconus. Int. J Kerat Ect Cor Dis.; 2 (1): 31-33.
4. Bowmann W (1859). On conical cornea and its treatment by operation Ophthalmic Hosp Rep and J R Lond Ophthalmic Hosp.; 9: 157.
5. Pearson AR, Soneji B, Sarvanathan N, Sandford-Smith JH (2000). Does ethnic origin influence the incidence or severity of keratoconus? Eye; 14 (4): 625-628.
6. Ţalu S, Ţalu M, Giovanzana S, Shah R (2011). A brief history of contact lenses. HVM Bioflux.; S3 (1): 33-37.
7. Müller, F.A., Müller, A.C. (1910). Das Kunstliche Auge. J.F. Bergmann, Wiesbaden, Germany, pp. 68-75.
8. Bowden, T.J. (2009). Contact Lenses: The Story. Bower House Publications.
9. Fick, A.E. (1888). A contact lens (trans. C. H. May). Arch. Ophthalmol. 19, 215-226.
10. Pearson RM. Kalt (1989). Keratoconus and the contact lens. Optom Vis Sci.; 66 (9): 643-646.
11. Obrig, T.E., Salvatori, P.L. (1957a). Contact Lenses, third ed. Obrig Laboratories, New York, pp. 340-345.
12. Rugg Gunn, A. (1931). Contact glasses. Br. J. Ophthalmol. 5th Oct.
13. Koeppe, L. (1918). Die mikroskopie des lebenden augenhintergrundes mit starken vergrösserungen im fokalen lichte der Gullstrandschen Nernstspaltlampe. Graefes Arch. Ophthalmol.; 95, 282-306.
14. Stock, W. (1920). Über Korrektion des keratokonus durch verbesserte gechliffene kontaktgläser. Brichte der Deutschen Ophthalmologischen Gesellschaft Heidelberg, 352-354.
15. Müller-Welt, A. (1950). The Müller-Welt fluidless contact lens. Optom. Wkly. 41, 831-834.
16. https://books.google.com/books?hl=en&lr=&id=AON8DwAAQBAJ&oi=fnd&pg=PA2&dq=16.%09Schiller,+F.+(1969).+Testimonial+to+Dr+Adolf+Wilhelm+M%C3%BCller-Welt,+D.O.S.+Online.+Available:+www.m%C3%BCller-welt.com.&ots=YbjRT2PmLv&sig=aa20za0wUbRwrjQ5D96rJC0CchA
17. Mandell RB (1988). Contact lens practices (4th ed.) Spingerfield, IL: Charles C Thomas, 43-45.
18. Dickinson, F., Hall, K.G.C. (1946). An Introduction to the Prescribing and Fitting of Contact Lenses. Hammond and Hammond, London.
19. Sabell, A.G. (1980a). An ophthalmic museum. Contact Lens J. 9 (2), 15-19.9 (3), 16-22.
20. Sabell, A.G. (1980c). An ophthalmic museum. Contact Lens J. 9 (4), 10-18.
21. Holmes-Walker, Willium A (2004). Life-enhancing plastics. Imperial College Press:78.
22. Amsler M (1946). Classic keratocene and crude keratocene; Unitary arguments. Ophthalmologica.; 111: 96-101.
23. Bier, N. (1957). Contact Lens Routine and Practice, second ed. Butterworths, London, pp. 141-145.
24. Dickinson, F. (1954). Report on a new corneal lens. Optician 128 (3303), 3-6.
25. Thomas, P. (1968). The prescribing and fitting of conoid contact lenses. Contacto 12 (1), 66-69.
26. Stek, A.W., 1969. The Percon contact lens design and fitting techniques. Contact Lens 2 (2), 12-14.
27. Ruben, M. (1966). The use of conoidal curves in corneal contact lenses. Br. J. Ophthalmol. 50, 642-645.
28. Nissel, G. (1967). Offset corneal contact lenses. Ophthal. Opt. 6, 857-860.
29. Nissel, G. (1968). Aspheric contact lenses. Ophthal. Opt. 7, 1007-1010.
30. Morris, J. (1980). Contact lenses in the eighties. Contact Lens J. 9 (2), 3-5.
31. Ezekiel D (1983). Gas permeable haptic lenses. J Br Contact Lens Assoc.; 6: 158-161.

32. Visser ES, Visser R, Van Lier Henk J.J, Otten HM (2007). Modern scleral lenses part-I: Clinical features. Eye & Contact Lens; 733 (1): 13-20.
33. Alió JL, Shabayek MH (2006). Corneal higher-order aberrations: A method to grade keratoconus. J Refract Surg.; 22 (6): 539-545.
34. Piñero DP, Alió JL, Tomás J, Maldonado MJ, Teus MA, Barraquer RI (2011). Vector analysis of evolutive corneal astigmatic changes in keratoconus. Invest Ophthalmol Vis Sci.; 52 (7): 4054-4062.
35. Tuft SJ, Moodaley LC, Gregory WM, Davison CR, Buckley RJ (1994). Prognostic factors for the progression of keratoconus. Ophthalmol.; 101 (3): 439-447.
36. Wagner H, Barr JT, Zadnik K (2007). Collaborative longitudinal evaluation of keratoconus study: Methods and findings to date. Cont Lens Anterior Eye; 30 (4): 223-232.
37. Farid Afshar, Ken W. Pullum, Linda Ficker (2011). Scleral Contact Lenses in the Management of Keratoconus and Corneal Transplant Patients. Investigative Ophthalmology & Visual Science; Vol.52, 6522.
38. Piñero Llorens D.P. (2019). Management of Keratoconus with Scleral Contact Lenses. In: Barbara A. (eds) Controversies in the Management of Keratoconus pp 327-342. Springer, Cham.
39. Polse KA, Decker MR, Sarver MD (1977). Soft and hard contact lenses worn in combination. Am J Optom Physiol Opt.; 54 (10): 660-5.
40. Little L. (1971). Soft lenses in keratoconus. Optician.; 162: 26.
41. Mavani MR, Mody KK (1976). The concept of the correction of high astigmatism with a combination of hard and soft lenses. Contacto.; 20: 31-33.
42. Westerhout D (1973). The combination lens and therapeutic uses of soft lenses. Contact Lens J; 4: 3-22.
43. López-Alemany A, González-Méijome JM, Almeida JB, et al (2006). Oxygen Transmissibility of Piggyback Systems with Conventional Soft and Silicone Hydrogel Contact Lenses. Cornea; 25 (2): 214-219.
44. Westerhout D (1973). The combination lens and therapeutic uses of soft lenses. Contact Lens; 4: 3-9.
45. Polse KA, Decker MR, Sarver MD. (1977). Soft and hard contact lenses worn in combination. Am J Optom Physiol Opt.; 54 (10): 660-5.
46. Baldone JA (1973). The fitting of hard contact lenses onto soft contact lenses in certain diseased conditions. Contact Lens Med Bull.; 6: 15-7.
47. Tomris Sengor, Sevda Aydin Kurna, Suat Aki,Yelda Özkurt T (2011). High Dk piggyback contact lens system for contact lens-intolerant keratoconus patients. Clinical Ophthalmology, 5: 331-335.
48. Weissman BA, Ye P (2006). Calculated tear oxygen tension under contact lenses offering resistance in series: piggyback and scleral lenses. Contact Lens and Anterior Eye; 29: 231-237.
49. Florkey LN, Fink BA, Mitchell GL, Hill RM (2007). Corneal oxygen uptake associated with piggyback contact lens systems. Cornea; 26: 324-335.
50. O' Donnell C, Maldonado-Codina C. (2004). A hyper-Dk piggyback contact lens system for keratoconus. Eye Contact Lens; 30 (1): 44-8.
51. Nau AC (2008). A comparison of synergeyes versus traditional rigid gas permeable lens designs for patients with irregular corneas. Eye Contact Lens; 34 (4): 198-200.
52. Ozkurt Y, Oral Y, Karaman A, Ozgür O, Doğan OK (2007). A retrospective case series: Use of Soft Perm contact lenses in patients with keratoconus. Eye Contact Lens; 33 (2): 103-5.
53. Zirm EK (1905). Die erste geglückte organ transplantation. Die erste erfolgreiche organ transplantation durchgeführt von.; 12-13.
54. Castroviejo R (1948). Keratoplasty for the treatment of keratoconus. Trans Am Ophthalmol Soc; 46: 127-53.
55. Castroviejo R (1973). Keratoplasty for the Treatment of Keratoconus. International Abstract of Surgery; 65: 5.
56. Dermot Cassidy, Jacqueline Beltz, Vishal Jhaji, Michael S Loughnan (2013). Recent advances in corneal transplantation for keratoconus. Clinical and Experimental Optometry; 96 (2), 165-172.
57. Parker JS, Van Dijk K, Melles GR (2015). Treatment options for advanced keratoconus: A review. Surv Ophthalmol.; 60 (5): 459-480.
58. Kaufman HE (1980). The correction of aphakia. XXXVI Edward Jackson Memorial Lecture. Am J Ophthalmol.; 89: 1-10.
59. Werblin TP, Kaufman HE, Friedlander MH (1981). Epikeratophakia: The surgical correction of aphakia. III. Prelimnary results of a prospective clinical trial. Arch Ophthalmol.; 99: 1957-1960.
60. McDonald MB, Kaufman HE, Aquavella JV (1987). The nationwide study of epikeratophakia for aphakia in adults. Am J Ophthalmol.; 103: 358-365.
61. McDonald MB, Kaufman HE, Aquavella JV (1987). The nationwide study of epikeratophakia for myopia. Am J Ophthalmol.; 103: 375-383.
62. Lass JH, Stocker EG, Fritz ME, Collie DM (1987). Epikeratoplasty. The surgical correction of aphakia, myopia and keratoconus. Ophthalmology; 94: 912-925.
63. Waller SG, Steinert RF, Wagoner MD (1995). Long-term results of epikeratoplasty for keratoconus. Cornea; 14: 84-88.
64. C J Rapuano (2001). Excimer laser phototherapeutic keratectomy, Current Opinion in Ophthalmology; 12 (4): 288-293.
65. A F Elsahn, C J Rapuano, V A Antunes, Y F Abdalla, E J Cohen (2009). Excimer laser phototherapeutic keratectomy for keratoconus nodules. Cornea; 28 (2): 144-147.
66. Ward MA, Artunduaga G, Thompson KP (1995). Phototherapeutic keratectomy for the treatment of nodular sub-epithelial corneal scars in patients with keratoconus who are contact lens intolerant. CLAO J; 21: 130-132.
67. Deshmukh R, Reddy JC, Rapuano CJ, Vaddavalli PK (2020). Phototherapeutic keratectomy: Indications, methods and decision making. Indian J Ophthalmol.; 68 (12): 2856-2866.
68. Ward MA, Artunduaga G, Thompson KP, Wilson LA, Stulting RD (1995). Phototherapeutic keratectomy for the treatment of nodular sub-epithelial corneal scars in patients with keratoconus who are contact lens intolerant. CLAO J; 21 (2): 130-2.
69. Watson SL, Ramsay A, Dart JK, Bunce C, Craig E (2004). Comparison of deep lamellar keratoplasty and penetrating keratoplasty in patients with keratoconus, Ophthalmology; 111: 1676-1682.
70. Bisbe L, Deveney T, Asbell PA (2009). Big Bubble

Keratoplasty, Expert Rev Ophthalmol.; 4 (5): 553-561.
71. Spoerl E, Wollensak G, Seiler T (2004). Increased resistance of cross-linked cornea against enzymatic digestion. Curr Eye Res.; 29 (1): 35-40.
72. Spoerl E, Wollensak G, Dittert DD, Seiler T (2004). Thermo-mechanical behavior of collagen cross-linked porcine cornea. Ophthalmologica; 218 (2): 136-140.
73. Kanellopolous A (2009). Comparison of sequential vs. same-day simultaneous collagen cross-linking and topography guided PRK for treatment of keratoconus. J Refract Surg.; 25 (9): S812-S818.
74. Jenkins AD, Kratochvil P, Stepto RFT, Suter UW (1996): Glossary of basic terms in polymer science. Pure Appl Chem.; 68: 2287-2311.
75. Wollensak G, Spörl E, Seiler T (2003): Treatment of keratoconus by collagen cross linking (in German). Ophthalmologe; 100: 44-49.
76. Sung HW, Chang WH, Ma CY, Lee MH (2003): Crosslinking of biological tissues using genipin and/or carbodiimide. J Biomed Mater Res A; 64: 427-438.
77. Miranda D, Sartori M, Francesconi C, Allemann N, Ferrara P, Campos M (2003). Ferrara intrastromal corneal ring segments for severe keratoconus. J Refract Surgery; 19 (6): 645-53.
78. Boxer Wachler BS, Christie JP, Chandra NS, Chou B, Korn T, Nepomuceno R (2003). Intacs for keratoconus. Ophthalmology; 110 (5): 1031-40.
79. Sharma M, Boxer Wachler BS (2006). Comparison of single-segment and double-segment Intacs for keratoconus and post-LASIK ectasia. Am J Ophthalmol.; 141 (5): 891-95.
80. Espandar L, Meyer J (2010). Keratoconus: overview and update on treatment. Middle East Afr J Ophthalmol.; 17 (1): 15-20.
81. Shaheen MS, Zaghloul H (2017). Toric implantable collamer lens for correction of myopia and astigmatism in keratoconus. In book: Keratoconus; pp. 335-348.
82. Gupta S (2016). Implantable Contact Lenses in Keratoconus. Int J Kerat Ect Cor Dis.; 5 (1): 17-20.
83. Alió JL, Peña-García P, Fidan Abdulla GF, Soria FA, Zein G, Abu-Mustafa SK (2014). MICS with toric intraocular lenses in keratoconus: Outcomes and predictability analysis of postoperative refraction. Br J Ophthalmol.; 98 (3): 365-370.
84. Wheeler J, Hauser MA, Afshari NA, Allingham RR, Liu Y (2012). The Genetics of keratoconus: A Review. Reproductive Sys Sexual Disord.; S6: 001.
85. Rabinowitz, YS (2003). The genetics of keratoconus. Ophthalmol Clin North Amer.; 16: 607-620.
86. Rabinowitz, YS, Dong L, Wistow G (2005). Gene expression profile studies of human keratoconus cornea for NEI Bank: A novel cornea-expressed gene and the absence of transcripts for aquaporin 5. Invest Ophthalmol Vis. Sci.; 46: 1239-1246.
87. Boulton M, Albon J (2004). Stem cells in the eye. Int J Biochem Cell Biol.; 36: 643-657.
88. Karimian F, Aramesh S, Rabei HM, Javadi MA, Rafati N (2008). Topographic evaluation of relatives of patients with keratoconus. Cornea; 27: 874-878.
89. Aknin C, Allart JF, Rouland JF (2007). Unilateral keratoconus and mirror image in a pair of monozygotic twins. J Fr Ophtalmol.; 30: 899-902.
90. Weed KH, MacEwen CJ, McGhee CN (2006). The variable expression of keratoconus within monozygotic twins: dundee University Scottish Keratoconus Study (DUSKS). Cont Lens Anterior Eye; 29: 123-126.
91. Owens H, Gamble G (2003). A profile of keratoconus in New Zealand. Cornea; 22: 122-125.
92. Schmitt-Bernard C, Schneider CD, Blanc D, Arnaud B (2000). Keratographic analysis of a family with keratoconus in identical twins. J Cataract Refract Surg.; 26: 1830-1832.
93. Parker J, Ko WW, Pavlopoulos G, Wolfe PJ, Rabinowitz YS, et al. (1996). Videokeratography of keratoconus in monozygotic twins. J Refract Surg.; 12: 180-183.
94. Hughes AE, Dash DP, Jackson AJ, Frazer DG, Silvestri G (2003). Familial keratoconus with cataract: Linkage to the long arm of chromosome 15 and exclusion of candidate genes. Invest Ophthalmol Vis Sci.; 44: 5063-5066.
95. Rabinowitz YS (2003). The genetics of keratoconus. Ophthalmol Clin North Am.; 16: 607-620.
96. Rabinowitz YS (1998). Keratoconus. Surv Ophthalmol 42: 297-319.
97. Romero-Jimenez M, Santodomingo-Rubido J, Wolffsohn JS (2010). Keratoconus: a review. Cont Lens Anterior Eye; 33: 157-166.
98. Hashemi H, Heydarian S, Hooshmand E, Saatchi M, Yekta A, Aghamirsalim M, Valadkhan M, Mortazavi M, Hashemi A, Khabazkhoob M (2020). The Prevalence and Risk Factors for Keratoconus: A Systematic Review and Meta-Analysis. Cornea; 39 (2): 263-270.
99. Godefrooij DA, De Wit GA, Uiterwaal CS, Imhof SM, Wisse RPL (2017). Age-specific incidence and prevalence of keratoconus: A nationwide registration study. American Journal of Ophthalmology; 175: 169-172.
100. Musch DC, Niziol LM, Stein JD, Kamyar RM, Sugar A (2011). Prevalence of corneal dystrophies in the United States: Estimates from claims data. Invest Ophthalmol Vis Sci.; 52 (9): 6959-63.
101. Teer JK, Mullikin JC (2010). Exome sequencing: The sweet spot before whole genomes. Hum Mol Genet.; 19: R145-151.
102. Bick D, Dimmock D (2011). Whole exome and whole genome sequencing. Curr Opin Pediatr.; 23: 594-600.
103. Bamshad MJ, Ng SB, Bigham AW, Tabor HK, Emond MJ, et al. (2011). Exome sequencing as a tool for Mendelian disease gene discovery. Nat Rev Genet.; 12: 745-755.
104. Li X, Bykhovskaya Y, Haritunians T, Siscovick D, Aldave A, et al. (2012). A genome-wide association study identifies a potential novel gene locus for keratoconus, one of the commonest causes for corneal transplantation in developed countries. Hum Mol Genet.; 21: 421-429.
105. Morris-Rosendahl DJ, Segel R, Born AP, Conrad C, Loeys B, et al. (2010). New RAB3GAP1 mutations in patients with Warburg Micro Syndrome from different ethnic backgrounds and a possible founder effect in the Danish. Eur J Hum Genet.; 18:1100-1106.
106. 106.Aligianis IA, Johnson CA, Gissen P, Chen D, Hampshire D, et al. (2005). Mutations of the catalytic subunit of RAB3GAP cause Warburg Micro syndrome. Nat Genet.; 37: 221-223.
107. Burdon KP, Macgregor S, Bykhovskaya Y, Javadiyan S, Li X, et al. (2011). Association of polymorphisms in the hepatocyte growth factor gene promoter with keratoconus. Invest Ophthalmol Vis Sci.; 52: 8514-8519.
108. Pieragostino D, D Alessandro M, di Ioia M, Di Ilio C,

Sacchetta P, Del Boccio P (2015). Unraveling the molecular repertoire of tears as a source of biomarkers: Beyond ocular diseases. Proteomics Clin Appl.; 9 (1-2): 169-186.

109. De Souza GA, Godoy LM, Mann M (2006). Identification of 491-proteins in the tear fluid proteome reveals a large number of proteases and protease inhibitors. Genome Biol.; 7 (8): R72.
110. Zhou L, Zhao SZ, Koh SK, Chen L, Vaz C, Tanavde V (2012). In-depth analysis of the human tear proteome. J Proteomics; 75 (13): 3877-3885.
111. Von Thun Und Hohenstein-Blaul N, Funke S, Grus FH (2013). Tears as a source of biomarkers for ocular and systemic diseases. Exp Eye Res.; 117: 126-137.
112. Nishtala K, Pahuja N, Shetty R, Nuijts RMMA, Ghosh A (2016). Tear biomarkers for keratoconus. Eye and Vision; 3:19.
113. Regueiro U, Pérez-Mato M, Hervella P, Campos F, Sobrino T, Lema I (2020). Toll-like receptors as diagnostic targets in pellucid marginal degeneration. Exp Eye Res.; 200: 108211.
114. Arnal E, Peris-Martínez C, Menezo JL, Johnsen-Soriano S, Romero FJ (2011). Oxidative stress in keratoconus? Invest Opthalmol Vis Sci.; 52 (12): 8592-8597.
115. Pahuja N, Kumar NR, Shroff R, et al. (2016). Differential molecular expression of extracellular matrix and inflammatory genes at the corneal cone apex drives focal weakening in keratoconus. Invest Ophthalmol Vis Sci.; 57 (13): 5372-5382.
116. Collier SA, Madigan MC, Penfold PL (2000). Expression of membrane-type-1 matrix metalloproteinase (MT1-MMP) and MMP-2 in normal and keratoconus corneas. Curr Eye Res.; 21 (2): 662-668.
117. Crawford, Alexandra Z. MBChB, Zhang, Jie, Gokul, Akilesh, McGhee, Charles N.J, Ormonde, Sue E (2020). The Enigma of Environmental Factors in Keratoconus, Asia-Pacific Journal of Ophthalmology; 9 (6): 549-556.
118. Gordon-Shaag A, Millodot M, Shneor E, Liu Y (2015). The genetic and environmental factors for keratoconus. Biomed Res Int.; 2015: 795738.
119. de Azevedo Magalhães O, Gonçalves MC, Gatinel D (2021). The role of environment in the pathogenesis of keratoconus. Curr Opin Ophthalmol.; 32 (4): 379-384.
120. Kuo BI, Chang WY, Liao TS, Liu FY, Liu HY, Chu HS, Chen WL, Hu FR, Yen JY, Wang IJ (2020). Keratoconus Screening Based on Deep Learning Approach of Corneal Topography. Transl Vis Sci Technol.; 9 (2): 53 (1-11).