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# A current review on keratoconus

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## ABSTRACT

Keratoconus is a bilateral, non-inflammatory, usually asymmetric, and relatively less common corneal disorder where there is progressive thinning of central or paracentral cornea and irregular astigmatism owing to steepening of cornea leading to decreased visual acuity. Typically, it starts to manifest in the second and third decades of life and advances until 40 years of age. This condition is typically thought to have an unknown etiology, low prevalence, and affects all racial groups and both genders. An updated assessment of keratoconus description, epidemiology, pathophysiology, clinical manifestation, diagnosis, classification, and management approaches are included in this article.

**Keywords:** Keratoconus, Update, Review

## INTRODUCTION

The present article provides a current review on the topic keratoconus and elaborates recently acquired knowledge about the "definition," "epidemiology," "histopathology," "pathogenesis," "clinical features," "diagnosis," "classification," and "management." Various articles were reviewed and the data were retrieved from search databases such as PubMed, PubMed Central, EMBASE, and Google Scholar till February 2023. In the year 2010, "A comprehensive review of keratoconus" was published in Contact Lens and Anterior Eye, which is so far one of the most cited articles.[1] Here, we intend to provide a comprehensive review of the several advances made in this field in the recent years.

## DEFINITION

The term keratoconus is derived from the Greek words "kéras" and "cōnus," which together mean cone-shaped cornea. In 1854, John Nottingham provided a comprehensive understanding of the condition. In the early 18th and 19th centuries, the presentation, clinical manifestation, and refractive outcomes of keratoconus were precisely defined by a few European oculists.[2]

At present, keratoconus is regarded as a bilateral, asymmetric ocular disease that leads to gradual thinning and steepening of the cornea, commonly involving the central and paracentral cornea, causing irregular astigmatism resulting in impaired visual acuity.[3,4] It affects all ethnicities and gender and can also coexist with other ocular and systemic conditions.[5] Recent investigations have also observed noticeable associations with changes in inflammatory mediators.[6,7]

## EPIDEMIOLOGY

The prevalence of keratoconus varies globally due to ethnic and environmental factors.[8] Incidence rates range from 0.2 to 4 (790/100,000 people), whereas prevalence rates range from 1.5 to 25/100,000 people/year. The second and third decades have the highest prevalence and incidence rates, respectively.[9-11] In Central India, the prevalence is approximately 2300/100,000.[12] Another study suggests that advanced keratoconus is more common in males.[13]

## PATHOGENESIS

Conventionally, keratoconus is not considered to be an inflammatory condition as it shows various pathological findings such as Descemet's membrane folds, Bowman's layer fragmentation, thinning of stroma, and varying degrees of corneal scarring.[14] Corneal epithelial breaks lead to downgrowth of basal cells with buildup of ferritin particles.[15] At times, the subbasal corneal nerve plexus has more visibility due to corneal thinning.[16] On slit-lamp biomicroscopic examination, collagen lamellae under stress appear as alternating dark and light bands which correspond to the appearance of Vogt's striae.[17]

Recent research indicates that free radicals, cytokines, and proteolytic enzymes have a substantial role in keratoconus.[18] Complex imbalance between pro- and anti-inflammatory molecules disturbs the homeostasis within the cornea. Furthermore, due to its correlation with other genetic abnormalities including Down's syndrome,[19] Leber's congenital amaurosis,[20] Ehlers–Danlos syndrome,[21] and Noonan syndrome,[22] keratoconus is also thought to have some amount of genetic component. Another research team observed the proteomics of tear film and found that tears in patients with keratoconus included less lactoferrin, total protein, and secretory IgA than control tears did.[23]

Below are some environmental and inheritable factors linked to keratoconus [Table 1]:[24,25]

## CLINICAL PRESENTATION

A keratoconus patient often presents in their second or third decade of life, but it may progress on to the fourth decade, till it stabilizes.[26] However, cases with early presentation have also been reported.[26] The presenting symptom usually includes progressive changes (blurring or distortion) in vision not easily corrected with eyeglasses or frequent change of glasses.[27]

**Table 1:** Environmental and inheritable factors linked to keratoconus.[24,25]

| Factor | Relative Risk |
|---|---|
| Allergy | 1.4 |
| Asthma | 1.9 |
| Eczema | 3.0 |
| Eye rubbing | 3.1 |
| Family history | 6.4 |

Subclinical keratoconus is a term used to describe an eye having topographic signs of keratoconus with normal corneal slit-lamp findings, whereas forme fruste keratoconus is used to describe an eye with normal topography as well as slit-lamp findings but keratoconus in the fellow eye.[28]

### Early signs of keratoconus

- Asymmetric refractive error
- High or progressive astigmatism
- Keratometry (K): Significant astigmatism
- Retinoscopy: Scissoring of red reflex
- Computerized corneal topography: Increased keratometry values
- Decreased corneal thickness, particularly in the inferior cornea
- Rizzuti's sign
- Fleischer's ring
- Vogt's striae.[1,5]

### Late signs include

- Breaks in the Bowman's membrane
- Munson's sign
- Acute hydrops
- Stromal scarring.[1,5]

The signs and symptoms of the disease according to the different stages have been mentioned below:[1,5]

- In the subclinical stage, patients are typically asymptomatic or may experience slight blurring of vision. Their best-corrected visual acuity (BCVA) remains normal at 6/6, and slit-lamp examination does not show any abnormalities, but corneal topography findings may suggest the presence of corneal ectasia, prompting further evaluation.
- In the early stage, patients develop blurring of vision and distortion of images. Their BCVA decreases, localized corneal steepening becomes evident, differences in keratometric values can be observed, and the presence of scissoring reflex and Charlouex's oil droplet reflex may be detected as additional signs.
- In the moderate stage, there is a notable increase in the severity of signs and symptoms. Vogt's striae, the presence of Fleischer's ring, and the visibility of corneal nerves become visible, indicating further advancement of the disease.
- In the severe stage, patients may exhibit monocular polyopia, characterized by the perception of multiple "ghost" images. Additional signs include Rizzuti's sign,

Munson's sign, corneal hydrops, corneal scarring, and corneal opacities.

## DIAGNOSIS

The detection of the earliest signs of keratoconus still remains to be a great challenge, as a patient can be asymptomatic or symptoms may resemble that of simple refractive error. Diagnosis, in such cases, is highly unlikely unless a patient is subjected to corneal imaging. Even then, an attempt should be made at diagnosing the condition at the earliest based on clinical history, particularly that of frequent change of glasses, poor best spectacle-corrected vision, and examination findings such as scissoring reflex on retinoscopy, characteristic slit-lamp findings, abnormal keratometry, and corneal topography values which would in turn help in better management as well as long-term prognosis of the patient.

The routine investigations for evaluation of keratoconus include:[1,5]

- Slit-lamp examination: To look for Fleischer's rings and Vogt's striae, which are indicators of advanced keratoconus.
- Retinoscopy: For evaluation of the scissor reflex
- Calculation of K values
- Computerized corneal topography and ultrasound pachymetry are two important studies for establishing the diagnosis
- A trial of hard or gas-permeable contact lenses is recommended since they improve eyesight and eliminate other causes of poor vision, such as amblyopia.

The newer emerging methods of diagnostic procedures for keratoconus detection over the past years have been discussed below:

### Anterior segment-optical coherence tomography (AS-OCT)

The advent of high-resolution AS-OCT helps in investigating all the layers of cornea and their thickness profile.[29,30] Apical thinning with annulus of epithelial thickening may be noted. Furthermore, reduced density of epithelial basal cell and anterior limiting lamina fragmentation are indicative of early keratoconus,[31] thereby being suitable for detecting subclinical keratoconus.

### Evaluation of posterior corneal surface

It is the earliest sign of keratoconus which can be detected clinically. The various options used to measure the posterior corneal metrics are slit scanning tomography, Scheimpflug imaging, or optical coherence tomography. These devices enable us to study the posterior corneal elevation (deviation of posterior cornea with respect to a reference body like sphere or ellipse). It has been reported that to label a case as subclinical keratoconus, abnormalities of posterior corneal elevations must be present.[32-35]

### Measurement of corneal surface area

It is used to assess the ratio of anterior to posterior corneal surface areas, which is significantly decreased in keratoconus. It is a valuable tool to differentiate forme fruste keratoconus from patients not having keratoconus.[36,37]

### Light intensity distribution in the cornea

This has 76–96% sensitivity and 76–88% specificity in differentiating keratoconic from non-keratoconic corneas. Scheimpflug imaging is utilized to study the light intensity distribution.[38,39]

### Artificial intelligence

Methods utilizing artificial intelligence have been now applied to automate the diagnosis and classification of keratoconus depending on various corneal characteristics. These methods encompass machine and deep learning algorithms with over 95% specificity and sensitivity. These algorithms are designed specifically to distinguish between keratoconic and non-keratoconic eyes by utilizing corneal topography, tomography, or OCT data and are considered highly reliable in their performance.[40-42]

### Corneal biomechanics

Literature have revealed that higher order aberrations of the eye can aid to distinguish between normal eyes and subclinical keratoconus.[43,44] The availability of tools such as the Ocular Response Analyzer and CorVis Scheimpflug technology, which has the capability to quantify viscoelastic properties of cornea *in vivo*, on the basis of deformation response, has renewed the interest in corneal biomechanics.[45,46] New methods such as optical coherence elastography and OCT speckle also aid in early keratoconus diagnosis.[47,48]

Thus, corneal topography analysis systems play a valuable role in identifying the early stages of keratoconus, taking into account the following criteria:[33,49]

1. Corneal steepening
2. Asymmetric astigmatism
3. Corneal thinning using thickness maps
4. Irregular corneal surface
5. Vogt's striae or Fleischer's ring.

Although various diagnostic modalities have been introduced, comprehensive keratoconus diagnosis combines patient history, clinical examination, and additional tests for accuracy and promptness.

## CLASSIFICATION

It is difficult to categorize the severity of keratoconus because the course of disease from onset of the signs and symptoms to their severity varies widely. Despite the fact that a number of approaches for classification have been devised, they mostly depend on changes in corneal morphology.

The classification systems that are frequently employed include:

### Keratometric classification

Based on the value of power of central cornea, keratoconus is divided into:[50]

- Mild (45 D)
- Moderate (between 46 D and 52 D)
- Advanced (between 53 D and 59 D)
- Severe (>59 D).

### Morphological (Buxton) classification

Keratoconus is divided into:[51]

- Globe: Significant portion of the anterior cornea involved (>75%)
- Oval keratoconus: Affects only one or two corneal quadrants
- Nipple: Cone diameter is 5 mm and located in the central or paracentral cornea.

### Hom's classification

This method divides keratoconus into:[5]

- Pre-clinical keratoconus: Asymptomatic
- Mild keratoconus: Mild corneal thinning and scissor reflex
- Moderate keratoconus: Poor visual acuity, thinning of cornea but no scarring
- Severe keratoconus: Corneal scarring and thinning.

### Amsler–Krumeich classification

Commonly used classification system in clinical practice, though outdated, relied on morphological and clinical features.[52]

### Alio–Shabayek classification

This approach considers corneal scarring and anterior corneal aberrations, in addition to keratometric readings and corneal thinning.[53]

### RETICS classification

It takes into account corneal biomechanical measures, such as hysteresis and resistance factor, in addition to clinical features.[54]

### Keratoconus severity score

This system uses topographical pattern of keratoconus and slit-lamp clinical signs to grade the severity of keratoconus from 0 (suspicious) to 5 (severe).[55]

### Belin ABCD grading system

Here, four factors are used to measure the severity of keratoconus:[56]

- Best-corrected visual acuity
- Thinnest pachymetry value
- Corneal curvature of central 3 mm
- Anterior and posterior corneal radius.

## POST-CORNEAL REFRACTIVE SURGERY KERATOCONUS

Post-corneal refractive surgery keratoconus refers to the development or progression of keratoconus after undergoing corneal refractive surgery procedures such as laser-assisted *in situ* keratomileusis or photorefractive keratectomy.[57,58]

The risk assessment for post-corneal refractive surgery keratoconus involves various factors and evaluation methods. Here are some key considerations:[59]

- Pre-operative screening
- Corneal topography
- Pachymetry
- Family history and personal risk factors
- Long-term post-operative monitoring.

It is important to note that the overall risk of developing keratoconus after corneal refractive surgery is relatively low. However, the specific risk assessment and management protocols may vary.

## MANAGEMENT

While maintaining the time-tested principles of contact lens fitting and penetrating keratoplasty (PK), corneal surgeons have accepted new procedures and techniques for the efficient management of keratoconus over the past few decades. The management of keratoconus is a multifaceted approach, which includes lifestyle modifications and management of associated factors as follows:

### Avoid eye rubbing

Mechanical stress on the weakened cornea can worsen the progression.[60]

### Allergy control

Allergic conditions can exacerbate the symptoms and progression of keratoconus. Aggressive control of allergies is advisable.[60,61]

### Regular eye examinations

It plays a crucial role in monitoring the progression of keratoconus and detection of any changes.[62]

### Corrective lenses

Regular follow-up visits are important to ensure the proper fit and function of these lenses.[62]

For mild keratoconus, the primary aim of treatment is visual restoration, for which spectacles can be used. Even though irregular astigmatism cannot be corrected by spectacles, a novel design that takes into account the probable non-orthogonal positions of the optical power meridians of the eye has been tried and it has demonstrated improved BCVA by 1–4 lines in two patients with mild keratoconus (with astigmatism <2.50 D).[63]

For moderate keratoconus, contact lenses are still the mainstay of optical correction. In the recent years, several lenses with special designs have evolved with multiple types of gas-permeable polymers and hydrogels.[64]

### Soft contact lenses

These are provided in treatment of early cases of keratoconus, rigid lens intolerance, decentered cones but usually provide suboptimal visual correction. As such, several modifications have been made in the design and optics which are relatively comfortable and also provide comparable clinical performance. Currently available such soft toric contact lenses include HydroCone®, KeraSoft® IC, and Rose K2 Soft.[65]

### Rigid gas-permeable lenses

These provide an exceptional degree of adaptability for managing keratoconus patients by neutralizing the tear film.[66]

### Hybrid lenses (rigid center and soft peripheral hydrophilic skirt)

Quality of vision with these lenses is comparable to soft lenses, but there are reports of associated discomfort, owing to low oxygen permeability and reduced durability which has led to its lesser popularity.[67]

### Corneoscleral and scleral lenses

Any hard contact lens with shared bearing between the corneal periphery and conjunctiva covering the sclera is referred to as a corneoscleral lens, whereas scleral lenses are defined as any rigid lens that vaults the cornea entirely, including the limbus. They have a higher comfort level because of minimal lens edge–eyelid interaction and upgraded stability.[68]

### Piggyback system (rigid lens on soft lens)

Soft contact lens use improves comfort and a rigid corneal contact over it provides lens centration and stability. However, an increase in corneal scarring has been reported.[69]

For severe keratoconus, contact lens fitting like scleral lenses may be used which when fails may require corneal surgery or multiple refractive surgery for visual rehabilitation. Currently, even in mild-to-moderate keratoconus, newer procedures such as corneal cross-linking are employed, which can halt the disease progression.

## SURGICAL MANAGEMENT

### Corneal cross-linking (CXL)

This method includes removal of the central 6–7 mm of corneal epithelium, followed by the application of a 0.1% riboflavin solution and exposure to ultraviolet-A light at 370 nm, which activates riboflavin and leads to formation of covalent bonds between collagen fibrils and corneal stroma, increasing the corneal biomechanical stability and rigidity in an effort to halt the progression of keratoconus. Various modifications such as epithelium on technique, customized collagen cross linking (C-CXL), use of new molecules, and strategies have been introduced now.[70,71]

### Refractive surgery

The most popular options can be categorized into:

- **Corneal:** It includes intracorneal ring segments (ICRS), excimer laser surgery, radial keratotomy, and thermal therapy. ICRS are small devices implanted within the corneal stroma to induce a change in the refractive power, providing improvement in visual acuity.[72]
- **Intraocular:** Visual rehabilitation in stable and non-progressive keratoconus can be successfully achieved with implantation of toric intraocular lenses.[73]
- **Combinations** of these procedures.

### Keratoplasty

PK and deep anterior lamellar keratoplasty are used for advanced keratoconus, not controlled with contact lenses.[74]

### Transplantation of anterior limiting lamina

Isolated Bowman's layer is transplanted in some cases of keratoconus with extreme corneal thinning.[75]

### Additive keratoplasty

This surgery refers to insertion of a donor corneal lamella with the help of femtosecond laser that increases corneal thickness and provides flattening in the conic area, thereby improving biomechanical stability.[76]

### Cellular therapy (implantation of stem cells)

Pre-clinical studies to regenerate or replace the corneal stroma *in vivo* have been investigated like intrastromal injection of stem cells, with scaffold.[77]

## CONCLUSION

With early diagnosis and prompt intervention, patients with keratoconus may retain adequate visual function throughout their lifetime. While chalking out the management protocol, it is pertinent to define the stage and progression of disease. Newer modalities such as ICRS, in conjunction with contact lens use, can provide long-term success for patients with keratoconus, however, few patients may ultimately require a corneal transplant for visual rehabilitation. Progression of keratoconus, even after corneal surgery, has been reported, hence disease monitoring over time is essential. Comprehensive evaluation is warranted biannually for proper monitoring of the disease. Most commonly, keratoconus progresses for a certain period in life and the course of the disease generally ceases in the third and fourth decades. Several new modalities of treatment have been devised in the past few years and more research is being done to develop better diagnostic and therapeutic options, thus bestowing patients with a higher visual outcome and rehabilitation.

### Ethical approval

Not applicable.

### Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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### Conflicts of interest

There are no conflicts of interest.

### Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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