Keratoconus: A review

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Abstract

Keratoconus is the most common primary ectasia. It usually occurs in the second decade of life and affects both genders and all ethnicities. The estimated prevalence in the general population is 54 per 100,000. Ocular signs and symptoms vary depending on disease severity. Early forms normally go unnoticed unless corneal topography is performed. Disease progression is manifested with a loss of visual acuity which cannot be compensated for with spectacles. Corneal thinning frequently precedes ectasia. In moderate and advance cases, a hemosiderin arc or circle line, known as Fleischer’s ring, is frequently seen around the cone base. Vogt’s striaes, which are fine vertical lines produced by Descemet’s membrane compression, is another characteristic sign. Most patients eventually develop corneal scarring. Munson’s sign, a V-shape deformation of the lower eyelid in downward position; Rizzuti’s sign, a bright reflection from the nasal area of the limbus when light is directed to the limbus temporal area; and breakages in Descemet’s membrane causing acute stromal oedema, known as hydrops, are observed in advanced stages.

Classifications based on morphology, disease evolution, ocular signs and index-based systems of keratoconus have been proposed. Theories into the genetic, biomechanical and biochemical causes of keratoconus have been suggested. Management varies depending on disease severity. Incipient cases are managed with spectacles, mild to moderate cases with contact lenses and severe cases can be treated with keratoplasty. This article provides a review on the definition, epidemiology, clinical features, classification, histopathology, aetiology and pathogenesis, and management and treatment strategies for keratoconus.

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1. Definition

Keratoconus, which was first described in detail in 1854 [1], derives from the Greek words Kerato (cornea) and Konos (cone). Keratoconus is the most common primary ectasia. It is a bilateral [2,3] and asymmetric [4,5] corneal degeneration characterized by localized corneal thinning which leads to protrusion of the thinned cornea. Corneal thinning normally occurs in the inferior-temporal as well as the central cornea [6], although superior localizations have also been described [7,8]. Corneal protrusion causes high myopia and irregular astigmatism, affecting visual quality. It usually becomes apparent during the second decade of the life, normally during puberty [3,9], although the disease has also been found to develop earlier [10] and latter in life [9], and it typically progresses until the fourth decade of life, when it usually stabilizes [9]. A recent study has determined that 50% of non-affected eyes of subjects with unilateral keratoconus will develop the disease in 16 years [11].

2. Epidemiology

The incidence and prevalence in the general population has been estimated to be between 5 and 23, and 5.4 per 10,000, respectively [3,9,12]. Differences on the rates reported are attributed to different definitions and diagnostic criteria employed between studies. However, it would not be surprising to expect an increase in the incidence and prevalence rates of this disease over the next few years with the current widespread use of corneal topography leading to improved diagnosis.

Keratoconus affects both genders, although it is unclear whether significant differences between males and females exist. Some studies have not found differences in the prevalence between genders [3,13]; others have found a greater prevalence in females [12,14]; while other investigators have found a greater prevalence in males [15–18]. Keratoconus is also known to affect all ethnicities [9,18–20]. In a study conducted in the Midlands area of the United King-
dom, a prevalence of 4:1, and an incidence of 4.4:1 was found in Asians compared to Caucasians [17]. In other study undertaken in Yorkshire, also in the United Kingdom, the incidence found was 7.5 times higher in Asians compared to Caucasians. The latter was hypothesized to be attributed to consanguineous relations, especially first-cousin marriages, which commonly take place in the Asian population of the area assessed [21].

3. Clinical features

The ocular symptoms and signs of keratoconus vary depending on disease severity. At incipient stages, also referred to as subclinical or frustre forms, keratoconus does not normally produce any symptoms and thus can go unnoticed by the patient and practitioner unless specific tests (i.e., corneal topography) are undertaken for diagnosis [22]. Disease progression is manifested by a significant loss of visual acuity which cannot be compensated for with spectacles. Therefore, eye care practitioners should be suspicious about the presence of keratoconus when a visual acuity of 6/6 or better is difficult to achieve with increasing against-the-rule astigmatism [9]. Near visual acuity is generally found to be better than expected from the refraction, distance visual acuity and age of the patient. The appearance of “scissor” shadows while performing retinoscopy suggests the development of irregular astigmatism. Through retinoscopy it is possible to estimate the location of the cone’s apex and its diameter, and the adjustable spectacle corrected visual acuity achievable. The Charleux oil drop that is observed by backlighting the mydriatic pupil also poses a warning sign [9]. Keratometry readings are commonly within the normal range, but may appear irregular. Corneal thinning, where the thinnest part of the cornea is normally located outside the visual axis, is also a common sign preceding ectasia.

In moderate and advance cases of keratoconus, a hemosiderin arc or circle line, commonly known as Fleischer’s ring, is frequently seen around the cone base [23]. This line has been suggested to be an accumulation of iron deposits from the tear film onto the cornea as a result of severe corneal curvature changes induced by the disease and/or due to modification of the normal epithelial slide process [24]. Another characteristic sign is the presence of Vogt’s striae (Fig. 1), which are fine vertical lines produced by compression of Descemet’s membrane, which tend to disappear when physical pressure is exerted on the cornea digitally [13] or by gas permeable contact lens wear [25]. The increased visibility of corneal nerves (Fig. 2) and observation of superficial and deep corneal opacities (Fig. 3) are also common signs, which can be present at different severity stages of the disease [13]. The majority of contact lens patients eventually develop corneal scarring. Munson’s sign, a V-shape deformation of the lower eyelid when the eye is in downward position, and Rizzuti’s sign, a bright reflection of the nasal area of the limbus when light is directed to the temporal limbal area, are signs frequently observed in advanced stages [13]. Breaks in Descemet’s membrane have been described in severe keratoconus, causing acute stromal oedema, known as Hydrops, sudden vision loss and significant pain [26].

4. Classification

Several classifications of keratoconus based on morphology, disease evolution, ocular signs and index-based systems have been proposed in the literature:

4.1. Morphology

Classically, keratoconus has been classified into [9,27–29]:

Nipple—The cone has a diameter ≤ 5 mm, round morphology and is located in the central or paracentral cornea, more commonly in the infero-nasal corneal quadrant. Correction with contact lenses is normally relatively easy.
Table 1
Keratoconus classification based on disease evolution. VA, visual acuity; D, dioptres.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Frustre or subclinical form; diagnosed by corneal topography; ~6/6 VA achievable with spectacle correction.</td>
</tr>
<tr>
<td>2</td>
<td>Early form; mild corneal thinning; corneal scarring absent.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate form; corneal scarring and opacities absent; Vogt’s striae; Fleischer’s ring; ~6/6 VA with spectacle correction, but ~6/6 VA with contact lens correction; irregular astigmatism between 2.00–8.00 D; significant corneal thinning.</td>
</tr>
<tr>
<td>4</td>
<td>Severe form; corneal steepening &gt;55.00 D; corneal scarring, &lt;6/7.5 VA with contact lens correction; severe corneal thinning and Munson’s sign.</td>
</tr>
</tbody>
</table>

Oval—The cone has a diameter > 5 mm and a paracentral to peripheral location, more commonly in the infero-temporal corneal quadrant. Contact lens correction is more difficult.

Keratoglobus—The cone is located throughout 75% of the cornea. Contact lens correction is a difficult challenge, except in very limited cases.

The wide spread use of corneal topography has allowed the detection of new keratoconus patterns affecting the superior, nasal and central cornea [30]. More recently, a new D-shape keratoconus pattern, which affects subjects who have undergone Lasik refractive surgery procedures, has been described in the literature [31].

4.2. Disease evolution

The first keratoconus classification based on disease evolution was proposed by Amsler [32,33], who classified the disease in four different severity stages, similar to that reported by Hom and Bruce [28] (Table 1).

4.3. Index-based systems

Disease detection, even at early stages, has become increasingly important particularly in an attempt to prevent iatrogenic ectasia formation – the lost of corneal shape – which has been widely documented in patients with subclinical forms of keratoconus who have undergone refractive surgery procedures [34–36]. For this reason, several index-based classification methods build on corneal topography systems for grading the severity of keratoconus have been developed [26,37–43] (Table 2). Furthermore, optical coherence tomography and corneal aberrometer instruments have demonstrated their utility in keratoconus detection based on the assessment of corneal thickness [44] and the difference in corneal aberrations from normal subjects [45], respectively.

Recently, two relatively new optical instruments for assessing different characteristics of the anterior eye have included built-in software for the detection and monitoring of keratoconus disease: the Pentacam (Oculus, Wetzlar, Germany) [46] and the Ocular Response Analyzer (Reichert Inc., Depew, NY, USA) [47].

The Pentacam instrument, which is based on the Scheimplug working principle, takes 12–50 images of the cornea at different angles using a rotating camera (Fig. 4). This method evaluates disease severity and progression based on changes in corneal volume and anterior chamber angle, depth and volume. The Pentacam has been found useful in discriminating keratoconic from normal corneas, although a relatively low sensitivity in detecting subclinical forms of keratoconus has been reported. The images provided by the instrument should be interpreted with caution because they do not provide enough data on changes in the posterior corneal surface to make a clinical diagnosis of abnormality. Additionally, interpretation of the posterior corneal surface’s aberrations should also be carried out with caution as reported outcomes show the posterior corneal surface to be more aberrated than the anterior surface in keratoconic eyes, which is in contradiction with the theoretical optical properties of the corneal surface [48]. As a result, placido disc–based topographers might be better suited to detecting incipient cases of keratoconus [49].

The Ocular Response Analyzer allows keratoconus diagnosis and classification by assessing corneal hysteresis and resistance. A previous study has found the latter two values to be significantly lower in keratoconus compared to normal and post-lasik subjects [47].

5. Histopathology

Histopathologically, there are three signs which typically characterize keratoconus: (1) stromal corneal thinning; (2) Bowman’s layer breakage; and (3) iron deposits within the corneal epithelium’s basal layer [9,12].

In keratoconus disease, the corneal epithelium’s basal cells degenerate and grow towards Bowman’s layer and this can be noted by observing accumulation of ferritin particles into and between epithelial cells [50]. Basal cell density is also decreased in comparison to normal corneas [51]. Bowman’s layer often shows

Table 2
Index-based systems for keratoconus detection. A higher value than the point of cut value suggests the presence of keratoconus.

<table>
<thead>
<tr>
<th>Author</th>
<th>Index</th>
<th>Point of cut</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabinowitz/McDonnel [37]</td>
<td>K’ Value</td>
<td>47.2</td>
<td>Diagnosis is performed based on the central keratometry and the inferior–superior asymmetry in keratometric power</td>
</tr>
<tr>
<td></td>
<td>I-S Value</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Maeda/Klyce [38]</td>
<td>KPI</td>
<td>0.23</td>
<td>KPI is derived from eight quantitative videokeratography indexes. KCI% is derived from KPI and other four indexes.</td>
</tr>
<tr>
<td></td>
<td>KCI%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Smolek/Klyce [39,40]</td>
<td>KSI</td>
<td>0.25</td>
<td>Keratoconus detection and the level of severity is assessed using an artificial intelligent system.</td>
</tr>
<tr>
<td>Schwiegerling/Greivenkamp [41]</td>
<td>Z3</td>
<td>0.00233</td>
<td>Diagnosis is performed based in videokeratoscopic height data decomposed into orthogonal Zernike polynomials.</td>
</tr>
<tr>
<td>Rabinowitz/Rasheed [42]</td>
<td>KISA%</td>
<td>100%</td>
<td>Diagnosis is derived from K value, I-S value, AST and SRAX.</td>
</tr>
<tr>
<td>Mc Mahon et al. [43]</td>
<td>KSS</td>
<td>0.5</td>
<td>Diagnosis is performed based on slit-lamp findings, corneal topography, corneal power and higher order first corneal surface wavefront root mean square error.</td>
</tr>
<tr>
<td>Mahmoud et al. [44]</td>
<td>CLMI</td>
<td>&gt;0.45</td>
<td>Diagnosis based in detecting the presence or absence of keratoconic patterns and determining the location and magnitude of the curvature of the cone.</td>
</tr>
</tbody>
</table>
breakages, which are filled with collagen from the stroma and positive nodules of Schiff’s periodic acid. They form Z-shaped interruptions due to collagen bundles separation [52]. In the stroma, a decrease in the number of lamellae and keratocytes, degradation of fibroblasts [52], changes in the gross organization of the lamellae, and uneven distribution of collagen fibrillar mass and inter- and intra-lamellae, particularly around the apex of the cone have been observed [53]. Studies carried out using confocal microscopy have demonstrated a reduction in the number of keratocytes in keratoconus compared to normal subjects; the reduction being greater the more advanced the disease [54]. Descemet’s membrane is usually unaffected, except in cases of breakages of this tissue, and the endothelium is also generally unaffected by the disease [51], although pleomorphism and elongation of endothelial cells pointing towards the cone have been reported [52]. It has also been demonstrated that corneal nerves in keratoconics have thicker fibre bundles, reduced density, and subepithelial plexus compared to normal subjects [55].

6. Aetiology and pathogenesis

Despite the intensive research activity over the last few decades into the aetiology and pathogenesis of keratoconus, the cause(s) and possible mechanisms for its development remain poorly understood. Albeit, there have been several hypotheses proposed into the genetic and biochemical mechanisms. Furthermore, the association of other diseases to keratoconus has also been investigated.

6.1. Genetics

Family, twins and genetic studies have been conducted in an attempt to further understand the genetic nature of keratoconus:

I. Family studies:

Studies carried out before corneal topography techniques became commercially available reported that 6–8% of subjects with keratoconus had close relatives affected by the disease [56]. However, studies assisted by corneal topography have shown that up to 50% of subjects with keratoconus have at least one close relative affected by the disease [57]. A recent study estimated that relatives of keratoconics have a risk 15–67 times higher of developing keratoconus than those who do not have relatives with keratoconus [58]. An autosomal dominant mode of inheritance with variable expression has been suggested [57,59].

II. Twin studies:

To date, 19 pairs of monozygotic twins affected with keratoconus have been described in the literature. In most cases, both twins were affected, although with different [59,60] or similar levels of severity [61], which suggests a strong genetic component of disease development, perhaps also combined with environmental factors. However, another study on two pairs of twins failed to detect keratoconus in both twins [62].

Other studies have assessed the mode of transmission in keratoconus disease. A study in an 18-year-old monozygotic keratoconus twin, their 8-year-old sister and parents, who have not been diagnosed with keratoconus [63], suggests the possibility of a recessive mode of inheritance, although it is possible the sister could develop the disease over time. The first case of twins with keratoconus in opposite eyes but with a similar level of severity and clinical features has been recently reported [64]. This may have resulted as a consequence of the rise in genetic and/or environmental factors during the acquisition of the zygote symmetry, before it divides into two monozygotic embryos.

III. Genetic analyses:

Linkage studies carried out in families affected with keratoconus to identify the genetic regions (Loci) have reported genetic susceptibility to the disease [65–72]. Several loci, have been associated to keratoconus disease in different studies (Table 3).

Héon et al. identified four mutations of the VSX1 gene (i.e., R166W, L159M, D144E and H244R) in different keratoconic

<table>
<thead>
<tr>
<th>Author</th>
<th>Locus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fullerton J et al. [66]</td>
<td>20q-12</td>
</tr>
<tr>
<td>Tyynismaa H et al. [67]</td>
<td>16q22.3-q23.1</td>
</tr>
<tr>
<td>Hughes et al. [68]</td>
<td>15q22.3-24.2</td>
</tr>
<tr>
<td>Brancati F et al. [69]</td>
<td>3p14-q13</td>
</tr>
<tr>
<td>Hutchings H et al. [70]</td>
<td>2p24</td>
</tr>
<tr>
<td>Tang YG et al. [71]</td>
<td>5q14.3-q21.1</td>
</tr>
<tr>
<td>Li X et al. [72]</td>
<td>9q</td>
</tr>
<tr>
<td>Bisceglia L et al. [73]</td>
<td>5q21.2</td>
</tr>
</tbody>
</table>
patients [73]. Bisceglia et al. also found four mutations of the VSX1 gene (i.e., D144R, G160D, P247R and L17P) in 7 out of 80 keratoconus subjects assessed [74]. Recently, Eran et al. identified the D144E mutation linkage in a Jewish family affected by keratoconus [75]. In contrast, Aldave et al. reported that just 2 out of 100 keratoconus subjects showed any gene mutation [76]. More recently, Liskova et al. have shown that mutation of D144E is not the direct cause of keratoconus development [77] and Tang et al. have identified that mutations L159M, R166W and H244R are not related to keratoconus [78].

6.2. Biochemical factors

Several biochemical theories for keratoconus development have been proposed to support the hypothesis that corneal thinning occurs as a result of the loss of corneal structural components. Määttä et al. found differences in collagen types XIII [79], XV and XVIII [80] between normal and keratocoric corneas, leading to the suggestion that these differences might play an active role in the wound healing process observed between normal and keratocoric corneas.

The excessive degradation of the corneal stroma commonly observed in keratoconus might be the result of proteolitic enzyme activity that can be initiated by an increased level of proteases and other catabolic enzymes [81], or decreased levels of proteinase inhibitors [82] such as α2-macroglobulin and α1-antiprotease [83]. It has also been found that keratocytes in keratoconus have four times greater numbers of Interleukin-1 receptors compared to normal subjects [84]. As Interleukin-1 has been postulated to be a modulator of keratocytes proliferation, differentiation and death, it has been suggested that the loss of anterior stromal keratocytes might occur due to an excess of apoptotic cell death and stromal mass loss [85]. Furthermore, if epithelial microtrauma leads to an increased release of Interleukin-1, the latter provides support towards the association of keratoconus with eye rubbing, contact lens wear and atopy [86]. Proinflammatory markers Interleukin-6, ICAM-1 and VCAM-1 are over expressed by 2–40 times, whereas anti-inflammatory marker Interleukin-10 is under expressed by 8 times in keratocoric patients who wear contact lenses compared to normal myopic subjects [87]. This suggests that contact lens wear might be a precursor for ectasia development. Interleukin-6 cytokine is over expressed in early forms of keratoconus, which supports the development of chronic inflammatory events in the pathogenesis cascade of the disease [88].

6.3. Biomechanical factors

The different distribution and lower number of stromal lamellae in keratoconic compared with normal corneas [52,53] has been proposed as a precursor for corneal rigidity reduction and thinning, ultimately leading to keratoconus development [89]. Furthermore, oxidative damage has been described as a co-factor in keratoconus progression. Keratoconic corneas have decreased levels of aldehyde dehydrogenase Class 3 [90] and superoxide dismutase enzymes [91]. Both of these enzymes play important roles in the reactive oxygen processes of different species. The reactive oxygen accumulation causes cytotoxic deposition of malondialdehyde and peroxynitrites, which could potentially damage corneal tissues [92]. The main factors related to increased oxidative damage are ultraviolet radiation, atopy and mechanical trauma; the latter could occur as a result of chronic eye rubbing and contact lens wear [92]. Conflicting results have been reported in the literature with regards to whether [93,94] or not [95] atopy is associated with keratoconus development, as keratoconus subjects appear to rub their eyes much more frequently than normal subjects [96–98]. One study found topographic differences [99], whereas another study reported differences in progression between keratoconus patients with and without atopy [100]. Interestingly, the latter study found that keratoconus patients with atopy tend to have faster keratoconus progression and more frequent refractive and immunologic complications leading to the earlier need of keratoplasty [100]. Contact lens wear has also been associated to keratoconus progression [101]; however, whether contact lens wear could trigger keratoconus development remains unclear [9].

Protective steps to reduce oxidative damage and potentially prevent keratoconus development include: (1) the use of ultraviolet filters; (2) improvement of ocular comfort with the use of non-steroidal anti-inflammatory medications; (3) the use of preservative-free artificial tears and allergy medications and; (4) improved contact lens fit to minimize corneal microtrauma [93].

6.4. Related diseases

Keratoconus commonly develops as an isolated condition, although it has also been described in association with many syndromes and diseases [9,13]. Studies have reported that 0.5–15% of subjects with Down’s syndrome suffer from keratoconus, leading to an association 10–300 times higher than that of the normal population [12,102,103]. This association has been suggested to occur as a result of eye rubbing owing to the increased rate of blepharitis seen in approximately 46% of Down’s syndrome individuals [103]. It has also been found that 30–41% of subjects with Leber’s congenital amaurosis, a rare genetic disorder, also suffer from keratoconus [104,105]. Although keratoconus in Leber’s congenital amaurosis has been documented as an oculo-digital sign (i.e., patients rub their eyes with the fingers in a strongly and compulsively manner), genetic rather than eye rubbing mechanisms for keratoconus have also been identified [104]. Other associations between keratoconus and connective tissue disorders, such as Ehlers-Danlos syndrome subtype VI [106,107], Osteogenesis Imperfecta [108] and joint hypermobility [109] have previously been reported. Additionally, some studies have found an association between advanced keratoconus and mitral valve prolapse [109,110]. However, another study reported a lack of association between keratoconus, mitral valve prolapse and joint hypermobility [111].

7. Management and treatment

Keratoconus management varies depending on the disease severity. Traditionally, incipient cases are managed with spectacles, mild to moderate cases with contact lenses, and severe cases can be treated with keratoplasty. Other surgical treatment options include intra-corneal rings segments, corneal cross-linking, laser procedures (i.e., photorefractive keratectomy, phototherapeutic keratotomy, lasik in situ keratomileusis) intra-ocular lens implants or a combination of these.

7.1. Spectacles

Spectacles are normally used in early cases of keratoconus only. As the disease progresses, irregular astigmatism develops and adequate visual acuity cannot be achieved with this type of visual correction [9].

7.2. Contact lenses

The first to describe the use of contact lenses to manage keratoconus was Adolf Fick in 1888 [112]. Since then, contact lens wear has represented the most common and successful treatment option for early to moderate cases of keratoconus. A study which evaluated contact lens prescribing trends in 518 keratoconus patients (1004 eyes) over a 30-year period showed that contact lens wear
Table 4
Contact lens types for keratoconus. Bc, Base curve; Dia, diameter. Power expressed in diopters. *Synergeyes Clear Kone provides vault in microns instead of back surface curve in millimetres.

<table>
<thead>
<tr>
<th>Lens type</th>
<th>Proprietary name</th>
<th>Manufacturer</th>
<th>Bc (mm)</th>
<th>Dia (mm)</th>
<th>Power (D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soft</td>
<td>Kerasoft Ultravision</td>
<td>Softvision</td>
<td>8.00–9.00</td>
<td>14.00–15.00</td>
<td>±30.00</td>
</tr>
<tr>
<td></td>
<td>Soft K</td>
<td>Soflex</td>
<td>7.00–8.20</td>
<td>14.20</td>
<td>+10.00 to −20.00</td>
</tr>
<tr>
<td>Gas permeable</td>
<td>Rose K2</td>
<td>Menicon Co., Ltd.</td>
<td>4.30–8.60</td>
<td>7.90–10.40</td>
<td>±30.00</td>
</tr>
<tr>
<td></td>
<td>IkOne</td>
<td>Valley Contax</td>
<td>4.80–7.70</td>
<td>8.80–10.40</td>
<td>±30.00</td>
</tr>
<tr>
<td></td>
<td>Soper</td>
<td>David Thomas</td>
<td>5.20–7.50</td>
<td>7.50–9.50</td>
<td>±30.00</td>
</tr>
<tr>
<td></td>
<td>McGuire</td>
<td>David Thomas</td>
<td>5.60–7.35</td>
<td>8.60–9.60</td>
<td>±30.00</td>
</tr>
<tr>
<td></td>
<td>Dyna Intralimbal</td>
<td>Lens Dynamics</td>
<td>5.92–9.28</td>
<td>10.4–12.00</td>
<td>±25.00</td>
</tr>
<tr>
<td>Mini-scleral</td>
<td>SoClear</td>
<td>Dakota Science</td>
<td>5.82–7.82</td>
<td>13.30–15.50</td>
<td>+20.00 to −15.00</td>
</tr>
<tr>
<td></td>
<td>Digi Form</td>
<td>Truform</td>
<td>Any</td>
<td>13.50–16.00</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>Maxim</td>
<td>Aculens</td>
<td>Any</td>
<td>15.40–16.40</td>
<td>Any</td>
</tr>
<tr>
<td>Scleral</td>
<td>Innovative</td>
<td>Innovative Sclerals</td>
<td>Any</td>
<td>18.00–24.00</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>GelFlex</td>
<td>Ezekiel Optom.</td>
<td>Any</td>
<td>18.00–24.00</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>Tru-Scleral</td>
<td>Truform</td>
<td>7.25–9.00</td>
<td>16.00–20.00</td>
<td>Any</td>
</tr>
<tr>
<td>Hybrid</td>
<td>Clear-Cone</td>
<td>Synergeyes</td>
<td>100–600‘</td>
<td>14.50</td>
<td>+5.00 to −15.00</td>
</tr>
<tr>
<td></td>
<td>SoftPerm</td>
<td>CibaVision</td>
<td>6.50–8.10</td>
<td>14.30</td>
<td>+6.00 to −16.00</td>
</tr>
</tbody>
</table>

represented a satisfactory treatment method and delayed the need for surgery in approximately 99% of all fittings [113]. Although contact lenses for keratoconus are manufactured with hydrogel, silicone hydrogel, gas permeable and hybrid (i.e., rigid centre and soft skirt) materials, gas permeable contact lenses remain the most commonly used contact lens type [114,115], as high levels of irregular astigmatism cannot normally be corrected with other contact lens types (Table 4).

Frustré and early forms of keratoconus can be, in some cases, successfully corrected with hydrogel contact lenses. Several soft contact lens designs for keratoconus are currently available (Table 4) [116]. Features such as the higher oxygen permeability and modulus of rigidity of silicone hydrogels makes them better suited for keratoconus correction than conventional hydrogel contact lenses. Recently, several new custom-made aberration-control soft contact lenses have been developed to improve visual performance of mild to moderate keratoconus [117,118].

Three fitting strategies of gas permeable contact lenses, including apical clearance, apical touch and three-point touch, have been traditionally used for keratoconus fitting. Apical clearance provides lens support and bearing directed off the apex and onto the para-central cornea, with clearance (vaulting) of the apex of the cornea; however, this strategy is no longer in current use as it has been associated with poor visual acuity and cone progression control [119]. The apical touch fitting technique is characterized by providing primary lens support on the apex of the cornea, in which the central optic zone of the lens actually touches or “bears on” the central cornea (Fig. 5). This technique provides good visual acuity and keratoconus progression control; however, an increase in corneal scarring has also been documented [119]. The three-point touch fitting technique, perhaps the most popular, allows the contact lens to bear at several points on the cornea, including a light touch on the apex and a heavier touch on the paracentral cornea (Fig. 5). This technique has also been associated with good visual acuity and keratoconus progression control. Previous studies have not found differences in contact lens wearing comfort between apical touch and apical clearance fittings techniques [120]. Furthermore, although corneal scarring might occur with apical touch compared to three-point touch fittings [121], no randomized clinical trial has been carried out to assess which of these two fitting philosophies perform best.

Despite the different keratoconus gas permeable contact lens designs commercially available, including multicurve and aspheric designs with unique or variable asphericity, the most popular and successful design currently available is probably the Rose K lens (Menicon Co., Ltd., Nagoya, Japan) [122]; however, other lens designs have also been reported to be successful in treating keratoconus [123]. More recently, reverse geometry contact lens designs for keratoconus management have also been used with relative success [124].

Hybrid contact lenses, such as SoftPerm (Ciba Vision, Duluth, Georgia, USA) [125], Solotica (Solotica, Brazil) [126] and more recently, Synergeyes (SynergEyes, Carlsbad, CA, USA) [127] have also been used with relative success in keratoconus management.

Fig. 5. Fluorescein patterns of two different gas permeable contact lens fittings in keratoconus. The figure on the left shows a flat fitting with a significant touch of the lens on the central cornea. The figure on the right shows a three-point-touch fitting with slight central touch and peripheral bearing on the cornea.
of keratoconus subjects who were followed-up for 8 years respectively. A recent study has shown that just 12% managed with contact lenses [9,130], its use is limited to a relatively low number of cases. In advanced cases of keratoconus which cannot be successfully managed with contact lenses to sit, whereas the gas permeable contact lens is primarily used for providing adequate visual acuity [128] (Fig. 6). The use of high oxygen permeability soft (i.e., silicone hydrogel) and gas permeable contact lenses is highly recommended for keratoconus management as these corneas are well known to be compromised [129].

7.3. Surgical procedures

Although penetrating keratoplasty (PKP), in which the entire thickness of the cornea is removed and replaced by transparent corneal tissue, is perhaps the most commonly used surgical option for advanced cases of keratoconus which cannot be successfully managed with contact lenses [9,130], its use is limited to a relatively low number of cases. A recent study has shown that just 12% of 1065 keratoconus subjects who were followed-up for 8 years required PKP [131]. Another study in which keratoconus subjects were followed-up for 48 years reported that less than 20% of them required PKP intervention [3]. In a 7 years follow-up study of 2363 keratoconus subjects, 21.6% required PKP [132]. The risk factors reported to increase the likelihood of keratoconic patients having to undergo PKP are the presence of corneal scarring, visual acuity worse than 6/12 (20/40) with contact lens correction, corneal keratometry steeper than 55 D, corneal astigmatism > 10 D, early age of keratoconus development and poor contact lens tolerance [130,132,133].

Deep Lamellar Keratoplasty (DLK), in which superficial corneal layers are removed (descememt’s layer and endothelium remain intact) and replaced with healthy donor tissue has been employed in keratoconus management in recent years [134–136]. However, eyes undergoing PKP are more likely to achieve 6/6 (20/20) vision than those undergoing DLK [134]. On the other hand, a higher risk of endothelial cells loss and graft rejection has been reported with the use of PKP in comparison with DLK [134,136].

Radial keratotomy, in which longitudinal incisions along the peripheral cornea are performed, has been used for the treatment of keratoconus with very limited success. Thus, the technique is no longer conventionally performed for the treatment of keratoconus [137,138].

Photorefractive keratectomy (PRK), a technique which permanently changes the shape of the anterior central cornea using an excimer laser to ablate (i.e., remove by vaporization) a small amount of tissue from the corneal stroma has been used in the treatment of keratoconus with modest success. Although some studies have reported a significant reduction in cone progression in subjects with early keratoconus [139] as well as an increase in visual acuity and a decrease in high-order aberrations [140,141], the technique has been frequently associated with the development of ectasias post-treatment and thus, this procedure is not longer commonly used. However, it has been reported that some corneas with inferior steepening on corneal topography should not always represent a contraindication for PRK treatment [142].

Other corneal surgical procedures for the treatment of moderate keratoconus include excimer laser-assisted anterior lamellar keratoplasty [143], epikeratoplasty [144] and laser-assisted in situ keratomileusis [144]. Although laser refractive surgery procedures following PKP and DLK have been commonly used to correct high levels of surgery-induced astigmatism [134–136,145–148], a higher risk of ectasia has been reported following the use of these surgical techniques [35,36].

Intra corneal rings segments, a surgical technique originally developed for the treatment of low myopia [149], has been recently adapted for the treatment of keratoconus [150]. The technique consists in the implantation of one or two polymethyl methacrylate segments in the corneal stroma to reshape its abnormal shape in an attempt to improve visual acuity, contact lens tolerance [151] and prevent or, at least, delay the need for corneal graft [152]. It is commonly used to treat mild to moderate cases of keratoconus, as normal corneal transparency and a minimum corneal thickness of 450 μm at the site of the incision are required [153]. This surgical option has been associated with an improvement in uncorrected and best corrected visual acuity [152,153], and a decrease in high-order corneal aberrations, especially coma [154].

Corneal cross-linking is a technique which aims to increase corneal rigidity and biomechanical stability. The procedure involves removing the corneal epithelium in a 6–7 mm diameter central zone followed by riboflavin 0.1% solution application and corneal radiation with ultraviolet-A light at 370 nm. Ultraviolet-A light radiation activates riboflavin generating reactive oxygen species that induce covalent bonds between collagen fibrils in the corneal stroma. The irradiation level at the corneal endothelium, lens and retina is significantly smaller than the damage threshold [155]. It has been recommended not to perform this technique in corneas thinner than 400 μm [155] as toxic reactions could take place in the corneal endothelium. Several long-term studies on subjects who underwent corneal cross-linking have reported an improvement in best corrected visual acuity, a flattening of keratometric readings and a significant reduction in cone progression [156,157]. Also, this technique has been successfully used in combination with other surgery techniques, such as corneal rings segments [158]. The use of corneal cross-linking, however, has been associated with a decrease in the number of keratocytes immediately after treatment, followed by a progressive recovery post-operatively reaching baseline levels six months after treatment, accompanied by an increase in the density of stromal fibres [159].

The implantation of an intraocular lens for the management of keratoconus is normally undertaken in combination with other types of corneal refractive surgery techniques, such as corneal rings or keratoplasty, as intraocular lens implantation does not normally affect corneal shape and cone progression. Furthermore, the combination of these techniques, which allows the correction of high
levels of astigmatism by placing an intraocular lens in the ante-
rior or posterior chamber, has been used with relative success in a
limited number of subjects, normally intolerant contact lens
wearers, who has shown significant improvement in visual acuity
[160–162].

Thermal therapy, a surgical technique consisting of the appli-
cation of heat at the cone, gained some popularity in the mid-1970s
[163]; however, its wide use was abandoned as a result of its poor
predictability [164] and induced adverse effects such as corneal
scars and opacities [165]. Recently, radiofrequency techniques,
consisting of the application of radiofrequency energy through the
corneal stroma using a probe tip, have been used for keratoconus
treatment [166,167]. The energy heats the collagen fibrils causing
them to shrink. Eight or 16 thermal spots are normally applied
around a 5 mm optical zone, inducing a flattening of the cone and
subsequent improvement in visual acuity [166]. Additionally, the
use of thermal therapy in conjunction with infrared diode lasers
have been shown to reduce irregular astigmatism in keratoconus by
improving corneal shape regularity [168].

8. Conclusion
Keratoconus is the most common corneal ectasia. It usually
appears in the second decade of the life and affects both genders
and all ethnicities. The prevalence in the general population has
been estimated to be approximately 54 per 100,000. The ocular
symptoms and signs of keratoconus vary depending on disease
severity. Despite the intensity of research activity over the last few
decades into its aetiology and pathogenesis, the cause(s) and possi-
ble mechanisms for development remain poorly understood. There
have been, however, several hypotheses proposed into the genetic,
environmental, biomechanical and biochemical causes and mechan-
isms. Keratoconus treatment and management has improved
substantially in recent times. While contact lens wear remains the
most successful option for managing mild to moderate cases of
keratoconus, new surgical options, such as corneal rings and cross-
linking procedures, have been developed to treat moderate
to severe cases. The substantial amount of research currently
being conducted is promising for further understanding this dis-
ease.

Conflict of interest
MR-J and JSW report no conflicts of interest. JS-R is a full-time
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References
[1] Nottingham J. Practical observations on conical cornea. London: Churchill,
[6] Chopra I, Jain AK. Between eye asymmetry in keratoconus in an Indian pop-
[8] Piñeiro D, Alió JL, Alesón A, Escaf M, Miranda M. Pentacam posterior and
[9] Stein HA, Stein RM, Freeman MI. The ophthalmic assistant: a text for allied
[13] Li X, Rabinowitz YS, Rasheed K, Yang H. Longitudinal study of the normal eyes
[14] Stein HA, Stein RM, Freeman MI. The ophthalmic assistant: a text for allied
[16] Weed KH, McGhee CN. Refractive patterns, treatment management and visual
influence the incidence or severity of keratoconus? Eye 2000;14:625–8.
[18] Wagner H, Barr JT, Zadinik K. Collaborative longitudinal evaluation of kerato-
conus (CLEK) study: methods and findings to date. Contact Lens Anterior Eye
2007;30:23–32.
Scottish Keratoconus study: demographics, corneal signs, associated diseases,
indications of emerging keratoconus in teenage New Zealanders. Cornea
on the incidence of keratoconus and associated atopic disease in Asians and
[22] Arzt A, Duran JA, Pujol JA. Subclinical keratoconus diagnosis by elevation
[24] Barcaro-Somers E, Chang CC, Green WR. Corneal epithelial iron deposition.
[25] Davis LJ, Barr JT, Vanotteren D. Transient rigid lens-induced striae in kera-
including confocal and histopathological considerations. Contact Lens Ante-
rior Eye 2006;29:69–73.
[27] Perry HD, Buxton JN, Fine BS. Round and oval cones in Keratoconus. Ophthal-
[28] Hon M, Bruce AS. Manual of contact lens prescribing and fitting. London:
found in keratoconus. CLAO J 1991;17:198–204.
topographic pattern in some keratoconus suspects. Ophthalmology
[31] Amsler M. Keratocone classique et keratocone fruste, arguments unitaires.
[33] Rabinowitz YS, Rasheed K. KISA% index: a quantitative videokeratography
algorithm embodying minimal topographic criteria for diagnosing kerato-
[34] McMahon TT, Szczotka-Flynn L, Barr JT, Anderson RJ, Slaughter ME, Lass JH,
et al. A new method for grading the severity of keratoconus: the keratoconus
[35] Maeda N, Klyce SD, Smolek MK. Neural network classification of
1997;38:1346–53.
classification with corneal topography analysis. Invest Ophthalmol Vis Sci
[37] Mahmoud AM, Roberts CJ, Lembach RG, Twa MD, Herderick EE, McMahon TT.
[38] Maeda N, Klyce SD, Smolek MK. Corneal wavefront aberration measurement to detect
classification and all ethnicities. The prevalence in the general population has
been estimated to be approximately 54 per 100,000. The ocular
symptoms and signs of keratoconus vary depending on disease
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keratoconus, new surgical options, such as corneal rings and cross-
linking procedures, have been developed to treat moderate
to severe cases. The substantial amount of research currently
being conducted is promising for further understanding this dis-
ease.
Kasparova EA. Pathogenetic basis for treatment of primary keratoconus by a
Funnell CL, Ball J, Noble BA. Comparative cohort study of the outcomes of


