Keratoconus – Part 1

In the first of a three-part series on keratoconus, **David O'Brart** and **Robert Petrarca** explain the epidemiology, genetics, pathogenesis, histology, clinical features and prognosis of this condition. (C5066, two contact lens CET points)

KERATOCONUS, (derived from the Greek terms *kerato*, meaning horn, cornea, and *konos* meaning cone) is a degenerative, non-inflammatory disorder of the cornea. It is characterised by central and para-central corneal stromal thinning and subsequent conical ectasia. This conical distortion of the cornea results in irregular astigmatism with associated reduction in visual performance. It typically presents in adolescence and progresses in a variable manner.

It was first described by British physician John Nottingham in his text *Practical observations on conical cornea: and on the short sight, and other defects of vision connected with it* in 1854.[1] In 1859, British surgeon William Bowman described both the ophthalmoscopic features of keratoconus and its diagnosis and the first surgical attempts to restore vision by stretching the pupil into a stenopeic-like slit.[2] In 1869, Swiss ophthalmologist Johan Horner used the term 'keratoconus' in his thesis on the treatment of the condition,[3] which included attempts to reshape the cornea by chemical cauterisation. In 1888, in the first practical application of contact lens technology, French physician Eugène Kalt manufactured a glass scleral shell to improve vision in keratoconic eyes.[4]

EPIDEMIOLOGY

Keratoconus is the most common of all corneal dystrophies, affecting approximately one person in 2,000.[5,6] One long-term study reported a mean incidence of two new cases per 100,000 per year.[7]

Worldwide, it occurs in all ethnic groups, with males and females affected equally. Keratoconus is typically bilateral, but asymmetric with the worse eye continuing to have a poorer prognosis as the condition progresses.[8] Unilateral cases are very rare,[9] and it is not uncommon for keratoconus to be diagnosed first in one eye and then later in the other.

The occurrence of keratoconus is usually an isolated condition, but it has been reported to occur with increased frequency in a number of ocular and systemic disorders. Ocular associations include vernal disease, retinitis pigmentosa, blue sclera, aniridia, ectopia lentis and Leber's congenital amaurosis. Systemic associations include atopy, magnesium deficiency, Down's syndrome, Turner syndrome, connective tissue disorders (such as Marfan's, Ehlers-Danlos, osteogenesis imperfecta and pseudoxanthoma elasticum), mitral valve prolapse, Laurence-Moon-Biedl syndrome, Rieger's syndrome and neurofibromatosis. It has been particularly linked to various forms of ocular trauma such as hard contact lens wear, allergic eye disease and especially eye rubbing.[8,10] An inverse relationship between severity of the condition and diabetes has been reported.[11]

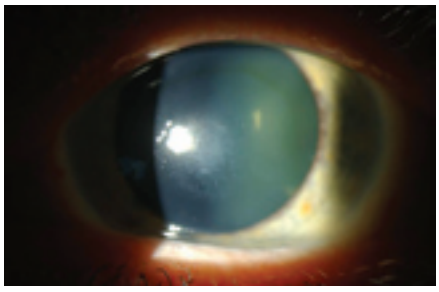

FIGURE 1. Advanced keratoconus with central apical corneal scarring and Fleischer iron ring. Courtesy of Dr Albert Jun MD and Dr Richard Green MD of the Wilmer Eye Institute

GENETICS

A genetic predisposition to keratoconus has been observed,[12,13] with the disease reported with increased incidence in some family groups[14] and reports of concordance in identical twins. The frequency of occurrence in first and second degree family members of affected individuals is variable, although it is known to be considerably higher than that in the general population. Studies have estimated between 6 per cent and 19 per cent of close family members may be affected.[12-14] Genetic linkage studies have demonstrated multiple loci on different chromosomes, suggesting a number of genes may contribute to keratoconus susceptibility[15-16] and while most genetic studies agree on a dominant autosomal model of inheritance, other models of inheritance have been suggested and variable penetrance is well documented.

PATHOPHYSIOLOGY

Despite extensive laboratory and clinical research, the aetiology of keratoconus is poorly understood. It is thought to include biochemical, physical and genetic factors, however no single proposed theory explains the various clinical features. It is, therefore, likely that the development of keratoconus is the final common pathway for several different disorders.

Laboratory studies have indicated that keratoconic corneas show signs of increased activity of proteinase enzymes and a reduced activity in the proteinase inhibitors found within the cornea. This imbalance between corneal metalloproteinases (MMP) and its inhibitors (tissue inhibitors of metalloproteinases or TIMPS) can reduce the various extracellular matrices and proteins within the cornea, resulting in stromal thinning and breaks in Bowman's layer/epithelial basement membrane.

Enzyme proteinase inhibitors found to be reduced in keratoconic corneas include α1-proteinase inhibitor, α2-macroglobulin and TIMP-1.[17-19] These deficits may lead to an increase in the degradative enzymes present, including cathepsins, trypsins, and MMPs, including MMP-1, MMP-2 and MMP-13.[20-23] Levels of TIMP-1 are also reduced by the presence of peroxynitrate, a cytotoxic by-product from the nitric oxide pathway.[24]

As yet, the cause for this increased proteinase activity in keratoconic corneas is not known. It may be related to a state of increased oxidative stress found within the keratoconic cornea.[25] It is known that as the cornea is responsible for absorbing most of the UVB light that enters the eye, it has to process the oxygen-free radicals produced. Oxygen-free radicals or reactive oxygen species (ROS) are high energy molecules that can build up and cause oxidative damage to cells by reacting with proteins, DNA and membrane phospholipids.[26] In addition, ROS produce aldehydes via ROS-mediated lipid peroxidation. These aldehydes can be destructive to cells by interfering with proteins and DNA, altering signal transduction and gene expression. Normally the cornea eliminates ROS by various antioxidant enzymes, including superoxide dismutase

(SOD), catalase, glutathione reductase and glutathione peroxidise[27] and protects itself from lipid peroxidation damage by glutathione S-transferase and aldehyde dehydrogenase enzymes (ALDH3). It has been shown that keratoconic corneas are deficient in SOD, catalase and ALDH3. These deficits may cause a significant build up in malondialdehyde (MDA) a cytotoxic aldehyde from both the lipid peroxidation and nitric oxide pathways. MDA results in altered protein functions and the release of lysosomal protoeolytic enzymes.

Another observation has been the evidence of increased apoptosis in keratoconic corneas. Apoptosis is the process of programmed cell death that occurs in tissue development, disease and wound healing. It has been proposed that mechanical trauma to the epithelium from RGP lenses, vigorous eye rubbing and severe atopy could cause apoptosis to occur in the underlying stroma.[28,29] Within the keratoconic cornea there is evidence of an abnormality in the regulation and signalling pathways of cells. There are higher levels of leukocyte common antigen-related protein (LAR) than in normal corneas. The LAR protein has the ability to interfere with the intracellular communication, cellular interaction and induce apoptosis.[30,31]

A possible explanation for how all these observations are connected has not yet been proven. However, keratoconic corneas appear to have underlying defects in their ability to process ROS. Allowing these high energy molecules to build up in the cornea results in a greater level of oxidative damage to the cells and causes cytotoxic by-products such as MDA. These changes may subsequently lead to a cascade of further events including an imbalance in the MMP/TIMP systems, resulting in degradation of the corneal stroma and subsequent thinning and ectasia.[26,31]

HISTOPATHOLOGY

Anomalies of every layer of the cornea can occur in keratoconus and depend and vary with the severity of the disease.[32-33]

At the apex of the cone, the epithelium is often thinned (especially with contact lens wear) with irregular, elongated, exfoliating superficial cells, irregular wing cell nuclei and flattened and reduced basal epithelium integrity with apoptotic cells. The epithelial basement membrane is often broken and irregular in appearance. There is reduced corneal nerve density and thickening of nerves, especially in the nerve fibre layers found in close association with deformities in Bowman's layer and keratocytes. Bowman's layer has structural abnormalities and defects with regions where the epithelium and stroma are in direct contact. In the stroma there is thinning due to progressive reduction in the number of collagen lamellae, altered orientation of the fibrils, especially around the apex of the cone and a reduction in the volume of proteoglycans present between the fibrils. There is a loss of keratocytes with irregular arrangement immediately under Bowman's layer and folds in both the anterior and posterior stroma. Descemet's membrane often shows folds and ruptures in acute hydrops. The endothelium is usually normal in appearance, however there maybe intracellular dark structures, pleomorphism, cellular enlargement and guttata.

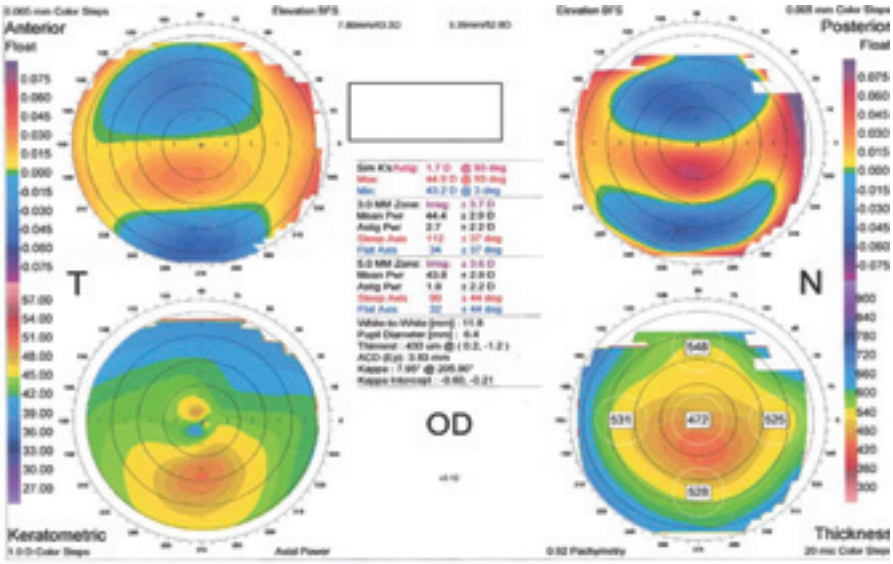

FIGURE 2. Orbscan corneal topography showing early keratoconus with inferior corneal steepening and inferocentral corneal thinning

CLINICAL FEATURES

Symptoms

Individuals with keratoconus typically present for optometric assessment with blurred vision, usually in one eye, which may be of a fairly rapid onset. Photophobia and reports of eye-strain are not uncommon. Symptoms of monocular polyopia with multiple ghost images and flaring around light sources are common. There is often a history of worsening and variable myopia and astigmatism, although the very early stages can be difficult to detect with only one eye being affected initially.[35] More established cases have prescription changes at increasingly frequent intervals. The refractive error is difficult to correct with spectacles or soft contact lenses and there is a need for rigid contact lens correction.

Signs

Identifying patients with moderate or advanced keratoconus is clinically straightforward. However, diagnosing keratoconus in its early stages is often more difficult requiring a thorough history and examination and a careful refractive assessment.

Early signs

- Refraction often reveals irregular oblique astigmatism
- Retinoscopy shows an irregular 'scissor' reflex
- Keratometry shows irregular astigmatism where the principal meridians are no longer 90° apart and the mires cannot be superimposed
- Direct ophthalmoscopy may show an 'oil droplet' reflex when the red reflex is observed[36]
- A light reflex projected from the temporal side will be displaced beyond the nasal limbal sulcus when high astigmatism and steep curvatures are present. (Rizzuti light reflex)[37]
- Slit-lamp biomicroscopy shows very fine, vertical, deep stromal striae (Vogt lines) which disappear with external pressure on the globe through the lid (Figure 1)
- Fleisher's ring is a yellow-brown to olive-green ring of pigment seen at the base of the cone in approximately 50 per cent of patients. It is formed when haemosiderin (iron) pigment is deposited deep in the epithelium anterior to Bowman's layer. It is easier to find using a cobalt blue filter and carefully focusing on the superior half of the cornea (Figure 1)
- The corneal nerves may be more visible
- Corneal topography is the most sensitive method for detecting very early keratoconus by identifying subtle, inferior corneal steepening (Figure 2).[38]

Late signs

- Progressive corneal thinning (to one-third of the normal thickness), associated with poor visual acuity from marked irregular, myopic astigmatism and steep keratometry readings. The thinnest part of the cornea being the steepest, with the ▶

apex of the cone usually being displaced inferiorly[38]
◆ Corneal protrusion causing bulging of the lower lid on downgaze (Munson sign) (Figure 3)[39]
◆ Stromal scarring in severe cases occurs as the disorder progresses, with ruptures in Bowman's membrane which then become filled with connective tissue (Figure 1).[40]

Acute hydrops

In advanced cases, spontaneous ruptures of Descemet's membrane can occur, causing a crescent-shaped tear in Descemet's and the endothelium near the apex of the cone. The rupture allows aqueous to pass into the stroma, resulting in significant corneal oedema and opacification (Figure 4).

The patient will report a sudden loss of vision, discomfort and a visible white spot on the cornea. Although the break usually heals within six to 10 weeks and the corneal oedema clears, a variable amount of stromal scarring may develop. Corneas that do not recover transparency may require keratoplasty surgery. Occasionally, hydrops can benefit patients with extremely steep corneas as the scar can flatten the cornea, making it easier to fit with contact lenses. [40,41]

Corneal topography

The advent of computerised videokeratoscopic topographic assessment has vastly improved the early detection, monitoring and management (in terms of contact lens fitting and surgical interventions, such as intacs insertion and post-keratoplasty astigmatism management) of keratoconus.

These systems allow the rapid assessment of thousands of data points from the anterior corneal surface to provide accurate maps of the corneal surface in early and moderate disease. [38] Such maps can give accurate information in terms of height and curvature on the location, morphology and severity of the cone.

In the case of combined scanning slit-lamp and Placido-based systems such as the Orb Scan system (Bausch & Lomb), very valuable pachymetric data and posterior corneal curvature maps can also be obtained. Such systems are vital for the refractive laser surgeon in preventing eyes with early and sub-clinical 'forme fruste' keratoconus from undergoing inadvertent excimer laser ablation with the possibility of exacerbating the ectatic process post-operatively. [42]

In early and moderate cases of keratoconus the videokeratoscopy mires are distorted and typically lie closest together in the inferocentral region at the apex of the cone where the cornea is steepest (Figure 5). Information from these mires can provide:

◆ Height maps which allow the localisation and characterisation of the cone and its apex
◆ Curvature maps which in early cases may only show an asymmetrical bow-tie pattern, but in more advanced eyes show obvious areas of corneal steepening and ectasia (Figure 6)
◆ Corneal higher-order wavefront anomalies, which have recently been shown to be valuable in early detection and grading of the condition[43-44]
◆ Statistical indices, which are useful in detection and monitoring progression.

FIGURE 3. Corneal protrusion causing bulging of the lower lid on downgaze (Munson sign). Courtesy of Dr Albert Jun MD and Dr Richard Green MD of the Wilmer Eye Institute

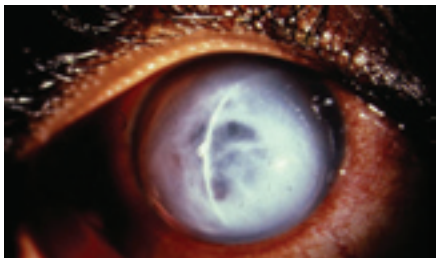

FIGURE 4. Acute hydrops with significant corneal oedema and opacification. Courtesy of Dr Albert Jun MD and Dr Richard Green MD of the Wilmer Eye Institute

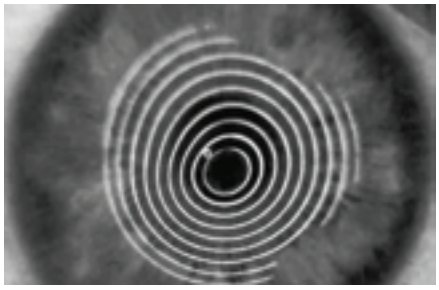

FIGURE 5. Placido disc image from videokeratoscopy, showing distorted mires, lying closest together in the inferocentral region at the apex of the cone where the cornea is steepest in a case of early keratoconus. Courtesy of Dr Albert Jun MD and Dr Richard Green MD of the Wilmer Eye Institute

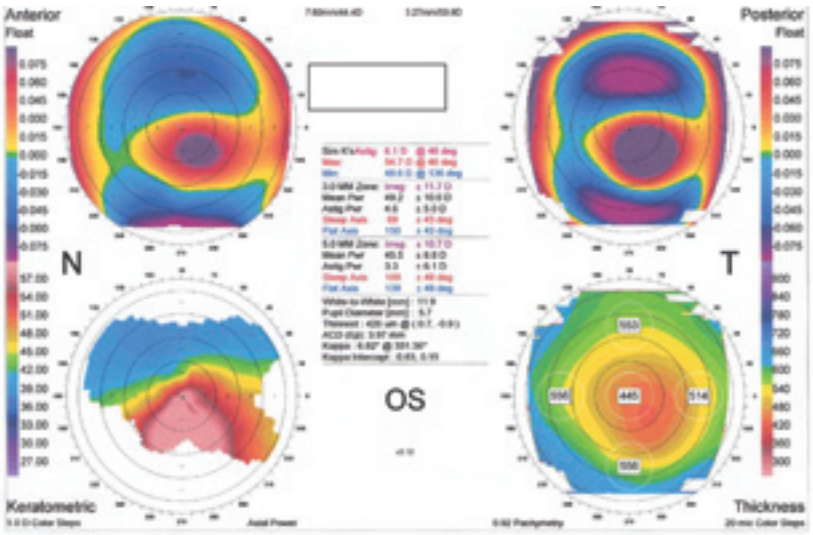

FIGURE 6. Orbscan corneal topography map in advanced keratoconus, showing severe inferior corneal steepening with posterior and anterior ectatic changes on the elevation maps and inferocentral corneal thinning

However, as most commercially available systems rely on the analysis of clear Placido disc and scanning slit-lamp images in advanced disease with corneal scarring and surface irregularities associated with very steep cones, little or no useful data can be obtained.

CLASSIFICATION

A number of classification systems exist based on keratometry, morphological topographical appearances and corneal pachymetric assessment.[41,45,46]

◆ Keratometry: mild (<45D); advanced (up to 52D); or severe (>52D)
◆ Morphology: nipple (small: 5mm and near-central); oval (larger, below-centre and often sagging); globus (more than 75 per cent of cornea affected)
◆ The corneal thickness: mild (>506µm); advanced (<446µm).

The increasing use of corneal topography has led to a decline in the use of these terms by some practitioners. Most recently the use of wavefront analysis and measurement of corneal high-order aberrations ▶

have proven a useful tool both in the early detection of keratoconus and grading of disease severity, particularly in relation to third-order coma aberrations.[43,44]

PROGNOSIS

Individuals with keratoconus typically present with mild astigmatism in adolescence – initially correctable with spectacles and soft contact lenses – and are usually diagnosed a few years after initial presentation, as the best spectacle corrected acuity falls and/or clinical signs progress. In rare cases, keratoconus presents in childhood or later in adulthood. Early age of onset appears to indicate a greater risk of disease severity later in life.[47]

The course of the disorder can be quite variable, with some patients remaining stable for years or indefinitely, while others progress rapidly or experience occasional exacerbations over a long and otherwise steady course. Most commonly, keratoconus progresses for a period of 10 to 20 years[8] before the course of the disease stabilises in middle age.

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MULTIPLE-CHOICE QUESTIONS

1 What is the approximate prevalence of keratoconus?
A 2 in 100,000
B 1 in 2,000
C 2 in 2,000
D 1 in 200,000

2 Which of the following ocular conditions has NOT been linked with a predisposition to keratoconus?
A Retinitis pigmentosa
B Glaucoma
C Aniridia
D Leber's congenital amaurosis

3 Which of the following systemic conditions is not thought to be a predisposing factor for keratoconus?
A Magnesium deficiency
B Osteogenesis imperfecta
C Ankylosing spondylitis
D Pseudoxanthoma elasticum

4 Which of the following statements about the genetic component of keratoconus is NOT true?
A Estimates suggest that between 6 per cent and 19 per cent of close family members may be affected
B Multiple gene loci may be involved in inheritance
C Variable penetrance is well documented
D Inheritance is thought to be via an autosomal recessive pattern

5 Which of the following is found in keratoconic corneas?
A Increased activity of proteinase enzymes
B Increased activity of proteinase inhibitors
C Decreased activity of proteinase enzymes
D No difference in proteinase enzyme activity from normal corneas

6 Which of the following is NOT a proteinase enzyme inhibitor?
A TIMP-1
B Alpha1-proteinase inhibitor
C MMP-2
D Alpha2-macroglobulin

7 Which of the following histological changes is NOT observed in keratoconus?
A Increased corneal nerve density
B Epithelial basement membrane irregularities
C Flattened basal epithelium
D Apical epithelial thinning

8 Which of the following symptoms is NOT associated with keratoconus
A Monocular polyopia
B Binocular instability
C Photophobia
D Asthenopia

9 Which of the following is a late sign of keratoconus?
A Refractive instability
B Rizzuti light reflex
C Fleisher's ring
D Munson sign

10 Which of the following statements about Fleisher's ring is NOT true?
A It is epithelial
B It is iron based
C It occurs in 80 per cent of keratoconics
D It is best viewed using the cobalt blue filter

11 What is 'forme fruste' keratoconus?
A Subclinical early presentation of keratoconus
B End-stage keratoconus
C Loss of corneal transparency subsequent to endothelial rupture
D Post surgical ectasia

12 Which of the following might be described as globus?
A Less than 45 dioptres on keratometry
B Corneal changes near centre (5mm)
C Thinning below 446 microns
D Over 75 per cent corneal involvement

The deadline for response is November 23

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Eternal City revisited

Optician discovers that this year's debut Rome-based CET event was successful enough to merit running again next year

At the start of this year, *Optician* reported on a new CET programme being developed for the late spring to be held in Rome. Based on a similar model to some of the US CET programmes, the idea was to run education and training alongside leisure activities in a holiday location.

Organiser of the event, Alan Currie of Ukita, explains: 'Undertaking CET these days has all the usual options. But the idea of UK practitioners having a weekend away to learn is not so usual, although long haul holidays with the odd lecture is not unknown.

'However, this summer a number of practitioners and lecturers did some CET in Rome. After this very full day of learning which all enjoyed, speakers and delegates were given a tour of Rome and a good Italian meal.

'This idea will be repeated next year in mid May, again in Rome, so anyone wanting a slightly different slant to learning and obtaining CE points should think about signing up.'

Among a list of eminent speakers, including Professor David Thomson, Dr Catherine Chisholm and Deacon Harle, keynote speaker John Phillis will be looking at the thorny subject of information security, how data may be held safely and where the law stands with regard to information theft.

For more information and bookings, call 07738114516, email acurrie@ukitadesign.com or visit the Ukita website, www.ukitadesign.com.