CHAPTER 13

KERATOCONUS

Keratoconus, which was first described in detail in 1854 derives from the Greek words Kerato (cornea) and Konos (cone). Keratoconus is the most common primary ectasia. It is a bilateral and asymmetric corneal degeneration characterised by localised corneal thinning which leads to protrusion of the thinned cornea [120] [163–165]. Corneal thinning normally occurs in the inferior temporal, as well as the central cornea, although superior localisations have also been described. 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, although the disease has also been found to develop earlier and later in life and it typically progresses until the fourth decade of life, where it usually stabilises [163–165]. According to the CLEK study, the average age at diagnosis was 27 years [166]. A recent study has determined that 50% of non-affected eyes of subjects with unilateral keratoconus will develop the disease in 16 years [167]. Prior to advent of corneal topography, it was thought that 85.6% of keratoconus was bilateral. After the advent of topography, it was found that 96% of keratoconus was bilateral [168]. Twenty percent (20%) of individuals with keratoconus progress to such an extent that penetrating keratoplasty becomes necessary [169].

DEFINITION

Keratoconus is a clinical term used to describe a progressive, non-inflammatory, bilateral, predominantly degenerative disease with mechanically induced trauma accelerating its course, causing focal thinning and steepening of the cornea, changes in refractive error with impaired visual acuity eventually leading to an abnormal conical corneal shape [163, 164, 170–172].

WHAT IS THE ROLE OF INFLAMMATION IN THE PATHOGENESIS OF KERATOCONUS?

Traditionally, keratoconus has been classified as a non-inflammatory disease principally due to the lack of the classical signs of inflammation which include heat, redness, swelling and pain. However, loss of function, another cardinal sign attributed to Virchow is present [173]. Histologically, the corneal tissue of keratoconic patients lack the marked cellular infiltration and neovascularisation seen in chronic inflammation [174]. However, inflammation can be seen as a process characterised by the release and activation of toxic cellular mediators that promote tissue injury and result in some, but not all of the clinical signs of inflammation. Given the wide range of inflammatory mediators or cytokines associated with keratoconus, it may be more appropriate to at least classify keratoconus as a quasi-inflammatory or inflammatory-related disease [173]. It is difficult to distinguish primary disease mechanisms from secondary inflammatory or degenerative effects. It might also be possible that the clinical appearance of keratoconus is related to a number of unrelated environmental or genetic effects [173]. For example; eye rubbing related to keratoconus could increase the corneal temperature, over express the levels of pro-inflammatory cytokines and proteinases in the tear film. This can cause epithelial thinning as well as changes in every layer of the cornea [171].

It is evident from the literature, that instead of a simple increase in pro-inflammatory cytokines in the tears and tissues of keratoconus patients, there may be a complex imbalance between pro-inflammatory and anti-inflammatory cytokines and their regulatory functions which can lead to an alteration in epithelial and stromal functions of the cornea. However, it is not clear to what extent the increase in cytokines is related to keratoconus and which is secondary to the disease process as part of the wound healing response caused by rubbing, contact lens wear, and or tear film disturbance [173]. At the time of writing, the pathophysiology of keratoconus can probably be best classified as alterations in the stromal composition, imbalance of pro-inflammatory and anti-inflammatory molecules, imbalance of the enzymes that causes extracellular matrix degeneration and their inhibitors, oxidative stress and cellular hypersensitivity. These events can occur simultaneously and may present a positive feedback between one another [174].

Finally, several discrepancies impede our understanding of the inflammatory model of keratoconus. Despite the evidence collected form several studies, keratoconic corneas strikingly lack the histological and clinical features of inflammation. Furthermore, coexisting diseases or mechanical trauma; such as allergies, MGD, dry eye, rubbing and contact lens wear potentially mask the true underlying inflammation in keratoconus. Ongoing research, may provide tools for further investigation of keratoconus related inflammation elucidating the aetiopathological mysteries of this common corneal malady and more importantly, raise the possibility of beneficial anti-inflammatory interventions.

EPIDEMIOLOGY

The incidence and prevalence in the general population has been estimated to be between 5–23 and 5.4 per 10,000 respectively or 50–230 per 100 000 and 1 in 2000 [163–165, 169, 175]. Differences on the rates reported are attributed to different definitions and diagnostic criteria employed between studies [169]. With the increase in the use of corneal analysis systems (corneal topography and Scheimpflug tomography) it would not be surprising to expect an increase in the incidence and prevalence rates of this keratoconus in the future [163]. 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 and other have, with male to female ratio: 1.58:1 or 60% more males affected [164–166, 175, 176, 177]. Naderan et al., 2015 found that female patients with keratoconus were significantly younger and had significantly higher keratometry values and lower anterior chamber depths than those of men [180]. Keratoconus is also known to affect all ethnicities with no racial predilection [165]. However, this is questionable with some studies finding a prevalence of 4:1 and an incidence of 4.4:1 in Asians compared to Caucasians [178]. In another study the incidence found was 7.5 times higher in Asians compared to Caucasians [179]. The higher incidence was thought to be due to same bloodline family relationships (first-cousin marriages) and endogamy, which commonly occur in the Asian population [169, 179]. Anecdotal evidence suggests that the incidence of keratoconus is higher in the Indian and mixed race, rather than the African or Caucasian population groups in South Africa. In the Afrikaans population group, the disease is also more common in certain families (sharing the same surname) than others (authors observation).

Table 32: Demographics and diagnostic findings modified from Naderan, et al., 2015

	Keratoconus group	Control group	*P* value
Age	24.5 ± 6,67	24.85 ± 6.08	0.190
Gender ♦ **Male** ♦ **Female**	61.2% 38.8%	61.2% 38.8%	1
Mean age at presentation	21.03 ± 6.17		

	Keratoconus group	Control group	*P* value
Body mass index (BMI) kg/m²	24.73 ± 4.5	25.11 ± 4.19	0.179
Flat K- reading (D)	47.4 ± 4.5	42.6 ± 1.5	<0.001
Steep K-reading (D)	51.7 ± 5.4	42.4.2 ± 1.3	<0.001
Mean K- reading (D)	49.4 ± 4.8	43.2 ± 1.3	<0.001
Central corneal thickness (CCT) µm	455.8 ± 45.4	561.5 ± 25.2	<0.001

This prospective case-control study was completed in Iran and consisted of 992 patients [180]

AETIOLOGY

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.

Heredity

Studies show that the percentage of keratoconus patients having a blood relative with the disease varied from 2.6% – 8.2%, indicating a familial association [169]. Rabinowitz used corneal topography when examining families to aid diagnosis and concluded that keratoconus was consistent with autosomal dominant transmission. He further suggested that blood relatives had less than 1 in 10 chance to get keratoconus [165]. Another study estimated, that relatives of keratoconics have a risk 15–67x higher of developing keratoconus than those who do not have relatives with keratoconus [181]. Genetic corneal dystrophies are universally bilateral. Corneal topography shows only 0.5% to 4.0% of keratoconics have unilateral disease and as previously stated 50% of clinically normal fellow eyes will progress to keratoconus within 16 years, most within the first 6 years after diagnosis [167]. Although an autosomal dominant mode of inheritance has been suggested, keratoconus is possibly caused by multiple genes and different families may have different defects, which cannot be clinically differentiated [165, 169, 180]. Furthermore keratoconus have variable penetrance, expression and complex interactions between genes and the environment may contribute to the development of the disease [164]. Finally, in the words of Rabinowitz; "The greatest challenge to understanding the genetics of keratoconus is the great variability in the phenotypic expression of the disease and the timing of its onset" [165].

Associated Systemic Disorders

Keratoconus commonly develops as an isolated condition, although it has also been described in association with many syndromes and diseases [165]. Individuals with Down syndrome have an incidence from 0.5–15% or 10 to 300x that of the general population. This is possibly due to eye rubbing caused by blepharitis, which is common in these patients, 46% of Downs patients have blepharitis. Thirty to forty one percent of individuals with Leber's congenital amaurosis, older than 15 years have keratoconus. This is possibly due to oculo-digital sign and eye rubbing, which is common in this group of patients. Advanced keratoconus is associated with Mitral valve prolapse (58% compared to 7%). Ehlers-Danlos syndrome and Osteogenesis Imperfecta's association is not clear. Atopic diseases such as hay fever, asthma, eczema and food allergies are common in keratoconus patients with and incidence as high as 35% [165, 176].

Associations With Multi-System Syndromes [165]

- Alagille Syndrome
- Albers-Schonberg Syndrome
- Apert's Syndrome
- Autographism
- Bardet-Biedl Syndrome
- Crouzon's Syndrome
- Ehlers-Danlos Syndrome
- Goltz-Gorlin Syndrome
- Hyperornithemia
- Icthyosis
- Kurz Syndrome
- Laurence-Moon-Beidl Syndrome
- Marfan Syndrome
- Mulvihil-Smith Syndrome
- Nail-patella Syndrome
- Neurocutaneous angiomatosis
- Neurofibromatosis
- Noonan's Syndrome
- Osteogenesis imperfecta
- Oculodentodigital Syndrome
- Pseudoxanthoma elasticum
- Reigers Syndrome
- Rothmund's Syndrome
- Tourette's Syndrome
- Turner's Syndrome
- Xeroderma pigmentosa

Associated Ocular Conditions [165]

- Anetoderma and bilateral subcapsular cataracts
- Microcornea
- Persistent pupillary membrane
- Posterior lenticonus
- Retinitis pigmetosa
- Retinopathy of prematurity
- Retrolental fibroplasia
- Vernal conjunctivitis
- Atopic keratoconjuntivitis
- Axenfeld's anomaly
- Chandler's syndrome
- Corneal amyoidosis
- Deep filiform corneal dystrophy
- Essential iris atrophy
- Fleck corneal dystrophy

- Pellucid marginal degeneration
- Posterior polymorphous dystrophy
- Terrien's marginal degeneration
- Fuch's corneal dystrophy
- Iridocorneal dysgenesis
- Lattice dystrophy

Eye Rubbing

Eye rubbing among keratoconus patients is common with some authors reporting rubbing rates as high as 66% to 80%. McMonnies reported rubbing in keratoconus, was almost double compared to patients without keratoconus [182]. Some researchers believe, that corneas already weakened by inflammation can develop thinning and protrusion due to the mechanical trauma caused by rubbing [165, 169, 177, 180, 182–184]. However, a cause-and-effect relationship has not been established. The biomechanical corneal response to abnormal rubbing includes [182, 183]:

- Very high intraocular pressure (>60 mmHg)
- High hydrostatic tissue pressure affects cell shape and cellular enzyme function
- Viscoelastic or thixotropically increased fluidity of the corneal proteoglycan ground substance

Rubbing "tenderises" the cornea increasing its susceptibility to becoming irregular in shape or develop ectasia.

Why Do People Rub Their Eyes?

Itch or pruritus can be one of the most noxious sensations in the human experience. Ocular itch is particularly frustrating, due to inability to scratch and eliminate the sensation. Rubbing the eye with force, provides a more tolerable "pain" sensation. In addition, rubbing also relieves stress via the oculo-cardiac reflex causing bradycardia [182, 183].

Atopy is a hypersensitivity reaction, which compromises allergy, asthma and eczema. The literature is conflicting on the association between atopy and keratoconus. Some authors report a positive relationship while others did not find a statistically significant association when compared to a control group [165, 169]. Bawazeer et al., 2000 concluded that atopy was not significantly associated with keratoconus, but it was associated with eye rubbing which occur frequently in atopic patients [185].

Hormonal Changes

Keratoconus often develops around the time of puberty and during pregnancy. It can also advance severely during pregnancy. Therefore, hormonal changes which occur during these periods, have been thought to contribute to the aetiology. However, no direct evidence of a cause-and-effect relationship has been found [169].

Sun Exposure

The higher prevalence of keratoconus in hot and sunny countries, may indicate that sun exposure accounts for the higher prevalence. UV exposure is a source of reactive oxygen species (ROS) and excessive exposure to sunlight may lead to oxidative damage in keratoconus corneas [169]. This has been shown in animal experiments, in which mice were exposed to high levels of UV light which induced degeneration of the stromal collagen, apoptosis of the keratocytes and stromal thinning [186, 187]. However, the basis of corneal crosslinking relies on UVA radiation of the anterior cornea to mitigate the progression of keratoconus. Therefore, UV in moderate doses may have a beneficial effect in keratoconus [188].

Kenny and Brown, 2003 proposed a "Cascade Hypothesis" stating that keratoconus corneas have abnormal or defective enzymes in the lipid peroxidation and/or nitric oxide pathways leading to oxidative damage. The accumulation of oxidative cytotoxic by products causes an alteration of various corneal proteins, triggering a cascade

of events. Based upon this hypothesis, one can speculate that keratoconus patients should minimise their exposure to oxidative stress. Protective steps should include wearing ultraviolet (UV) protection (in the contact lenses and/or sunglasses), minimising the mechanical trauma (eye rubbing, poorly fit contact lenses) and keeping eyes comfortable with artificial tears, non-steroidal anti-inflammatory drugs and/or allergy medications [189].

Geographic Location

Although keratoconus can be found in all countries [165], the prevalence differs throughout the world. Northern Europe, the USA, Japan, Russia and the Urals have a low prevalence. While the Middle East, China, India and West Indies have a high prevalence [190, 191]. The reason for these differences are not clear, but it could be related to climate - higher prevalence in hot sunny climates, nutrition, socioeconomic status - chronic diseases are more prevalent among poor people, or ethnic differences among the population groups [169]. Environmental, ethnic factors and the cohort of patients selected for such studies may also explain the wide variation in the reported rates [190].

Rigid Contact Lenses

Constant rigid lens movement, mechanical trauma and hypoxia from especially PMMA lens wear may cause corneal tissue changes common to keratoconus. Around 89% of patients, that developed keratoconus after contact lens wear used PMMA lenses for an average of 12.2 years and 15.3 hours wear per day. However, early signs of keratoconus include mild myopic astigmatism with clinically normal-looking corneas, best corrected with RGP lenses. It is difficult to determine what came first, the keratoconus, or the contact lenses. Newer corneal analysis systems improve diagnosis, which will shed more light on the association between lens wear and the development of keratoconus [165].

Aetiology Summary

The most common presentation of keratoconus is as an isolated sporadic disorder with no other associated systemic or ocular disease detectable on clinical evaluation. Rabinowitz analysed a group of 300 consecutive keratoconus patients. He found that 2 or 0.6% had Downs syndrome, 2 or 0.6% had neurofibromatosis and 296 or 99% had isolated keratoconus with no associated genetic or systemic disease [165].

Risk Factors for Keratoconus Development

Family history, eye rubbing, itchy eyes, low educational levels are all independent predictors of keratoconus [163, 165, 166, 169, 184].

Table 33: Risk factors associated with development of keratoconus modified from Naderan, et al., 2015

	Keratoconus group (n = 461)	Control group (n = 461)	Odds Ratio (95% CI)	*P* value
Education				
♦ **Elementary (<6 years)**	23.9%	10.4%	1	<0.001
♦ **Diploma (12 years)**	34.9%	42.3%	2.78(1.86–4.13)	
♦ **Bachelor (>12 years)**	38.8%	41.4%	2.45(1.65–3.63)	
♦ **MsC**	2.2%	5%	5.27(2.33–11.92)	
♦ **PhD**	0.2%	0.9%	9.17(1–84.18)	
Smoking	10.2%	13%	0.76(0.51–1.14)	0.20
Family history of Keratoconus	20.8%	3%	8.4(4.71–14.96)	<0.001
Eye rubbing	82.8%	51.6%	4.33(3.21–5.85)	<0.001

	Keratoconus group (n = 461)	Control group (n = 461)	Odds Ratio (95% CI)	*P* value
Eye rubbing frequency ♦ **Never** ♦ **Rarely** ♦ **Sometimes** ♦ **Often** ♦ **Always**	 17,8% 24.1% 24.3% 24.3% 9.5%	 48.4% 21.3% 23% 6.3% 1.1%	 1 3.08(2.13–4.48) 2.87(1.99–4.15) 10.5(6.5–62.44) 23.93(9.17–63.44)	
Sun exposure			1(0.99–1.00)	0.90
Vernal keratoconjunctivits (VKC)	24.9%	3.7%	8.67(5.12–14.72)	<0.001
Allergy	15.8%	8.2%	2.09(1.38–3.17)	0.001
Asthma	4.4%	1.1%	3.92(1.45–10.60)	0.006
Eczema	2.4%	0.9%	2.79(0.88–8.84)	0.12
Thyroid	4.1%	5.6%	0.72(0.39–1.32)	0.36
Hypertension	3%	1.3%	2.38(0.91–6.24)	0.07
Dyslipidemia	3.3%	3%	1.07(0.5–2.51)	0.50
Down syndrome	0.2%	0	2(1.88–2.14)	0.50
Anaemia	2.2%	1.3%	1.68(0.61–4.67)	0.23

This prospective case-control study was completed in Iran and consisted of 992 patients [180]

Odds ratios represent the odds that a specific outcome will occur given a particular exposure compared to the odds of the outcome occurring in the absence of the exposure [192].

- OR = 1 means that the exposure does not affect the odds of the outcome occurring
- OR > 1 means that the exposure is associated with higher odds of the outcome occurring
- OR < 1 means that the exposure is associated with lower odds of the outcome occurring

Confidence intervals are used to estimate the precision of the odds ratios, large CIs indicate low precision and small CIs high precision. *P* values indicates whether the findings are statistically significant. From the table it can be seen that eye rubbing (always) has an OR 23.93 CI (917–62.44) and p <0.001 indicating that at least according to this study, it is associated with higher odds of keratoconus occurring due to always rubbing one's eyes. The p value indicates that this finding is statistically significant.

HISTOPATHOLOGY

Rabinowitz recognised that keratoconic corneas have a TRIAD of features [165]. These features are:

- Thinning of corneal stroma
- Breaks in Bowman's layer with fibrotic tissue filling the breaks
- Deposition of iron in basal epithelium

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 [165]. Basal cell density is also decreased in comparison to normal corneas. Bowman's layer often shows breakages, which are filled with collagen from the stroma forming Z-shaped interruptions, due to collagen bundles separation [165]. In the stroma, a decrease in the number of lamellae and keratocytes, degradation of fibroblasts, changes in the gross organisation of the lamellae, uneven distribution of collagen fibrillar mass and inter- and intra-lamellae particularly around the

apex of the cone, have been observed [165]. 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 in the more advanced the disease states [163]. Descemet's membrane is usually unaffected, except in cases of advanced disease where rupture of this tissue results in corneal hydrops. The endothelium is also generally unaffected by the disease, although pleomorphism and elongation of endothelial cells pointing towards the cone have been reported [163, 165]. It has also been demonstrated that corneal nerves in keratoconics have thicker fibre bundles, reduced density and sub-epithelial plexuses compared to normal subjects [163].

Mathew et al., 2011, 2015 believes that keratoconus is a disease of the anterior cornea and that a cascade of events leads to the development of ectasia. The events are accompanied by a co-existing "unknown" stromal weakening factor and include [193, 194]:

- Loss of anterior stromal tissue and or,
- Annular severance of corneal lamellae with tissue loss

Mathew et al., 2011, 2015 also stated that specific changes occur in the corneal collagen and keratocytes in keratoconus including [193, 194]:

- Interfibrillar collagen spacing similar to that of the normal cornea but intermolecular collagen spacing is significantly lower, which is probably due to changes to the cross links between fibrils
- Orientation of collagen fibrils is at 20/160° mainly in the apex of the cone caused by slippage of lamellae. Peripheral collagen fibrils maintain their normal 90/180° orientation
- Collagen mass is lost, which is more severe in apex of cone
- There is little or no lamellar interweaving and less insertion of the lamellae into Bowman's layers and deeper stroma, which causes mechanical weakness of the cornea
- Total collagen content of the cornea is not altered
- Keratocytes in keratoconus undergo increased apoptosis, probably due to the release of cytokines by damaged epithelial cells in response to wounding
- Corneal keratocyte density is decreased in keratoconus, atopy, eye rubbing contact lens wear and dry eye

Finally, histopathological evidence suggests that scarring in keratoconus occurs due to anterior stromal disease, specifically the anterior limiting membrane (ALM) and is unlikely due to contact lens wear alone [194].

DIAGNOSIS

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. It can therefore go unnoticed by the patient and practitioner unless specific tests (i.e., corneal topography) are undertaken for diagnosis [163]. 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. Near visual acuity, is generally found to be better than what would be expected from the refraction, distance visual acuity and age of the patient [165]. The appearance of "scissor" shadows, while performing retinoscopy, suggests the development of irregular astigmatism [165, 184]. Through retinoscopy it is possible to estimate the location of the cone's apex as well as its diameter and estimate the corrected visual acuity achievable with spectacles. Retinoscopy performs well in discriminating normal corneas from keratoconic corneas, but it does not perform well in the classification of keratoconus [184, 195]. The Charleux oil drop, that is observed by backlighting the mydriatric pupil, also poses a warning sign [165, 184]. 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 and is also a common sign preceding ectasia [165]. 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. 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 [165, 184] [196]. Another characteristic sign is the presence of Vogt's striae, 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, or by gas permeable contact lens wear [165, 167, 184]. The increased visibility of corneal nerves and observation of superficial and deep corneal opacities are also common signs, which can be present at different severity stages of the disease [165, 167, 184]. 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 [165, 167, 184]. Breaks in Descemet's membrane have been described in severe keratoconus causing acute stromal oedema, known as Hydrops. Hydrops presents as sudden vision loss with significant pain [197]. The most common signs observed in keratoconus patients are [184]:

- Fleischer's ring seen in 98% of patients
- Vogt's striae seen in 60% of patients
- Corneal scarring seen in 52% of patients

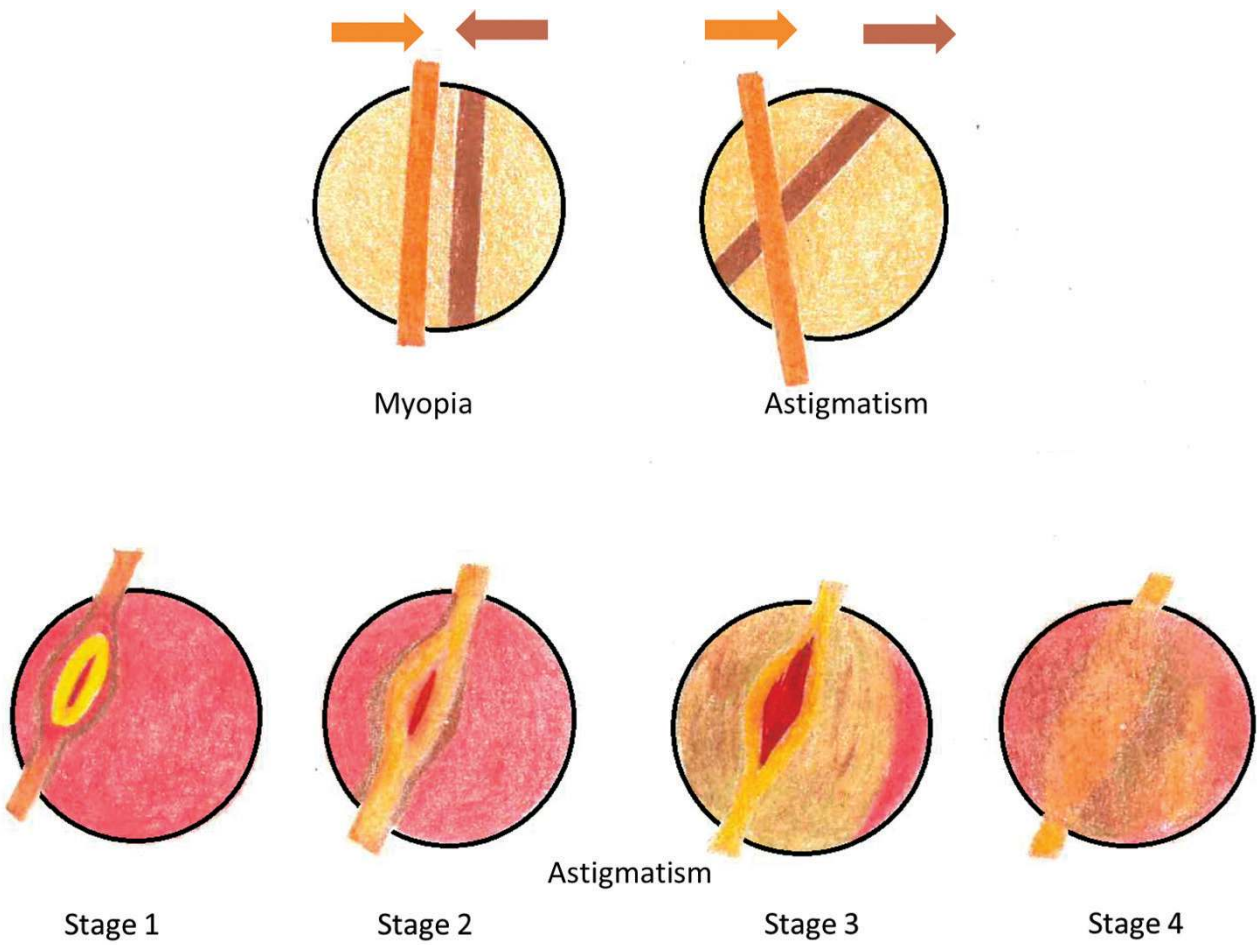

Figure 43: Retinoscopy and the red-reflex in keratoconus

In myopia an against movement is seen with streak retinoscopy and a with movement in hyperopia. In astigmatism the direction of the light reflex movement is different to that of the beam. In keratoconus no homogenous light shadow movement is visible – "scissors" or "fish mouth" reflex Adapted from Naderan, 2018. [195]

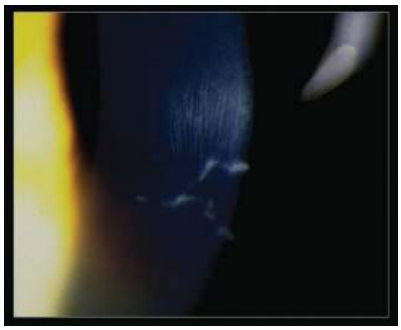

Figure 44: Vertical striae in keratoconus

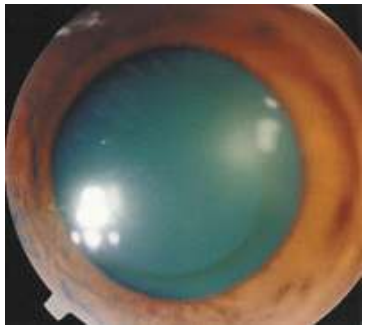

Figure 45: Fleischer's ring in keratoconus

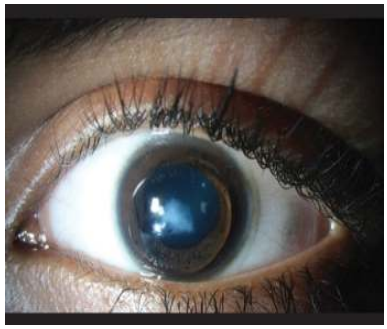

Figure 46: Corneal scarring due to hydrops in keratoconus

This patient uses a soft piggy back system with the RGP corneal lens on top of the soft lens

Using corneal topography Rabinowitz claims a 98% sensitivity and 99.5% specificity in diagnosis of keratoconus using the following criteria [165] [168]:

Corneal Curvature

Central curvatures steeper than 47.2D

Corneal Slope or Eccentricity

Corneal slope of more than 1.2D, usually steeper inferiorly

Corneal Shape

Skewing of the radial axis of astigmatism by more than 21°

Corneal Regularity

Increased areas of power surrounded by concentric areas of decreasing power

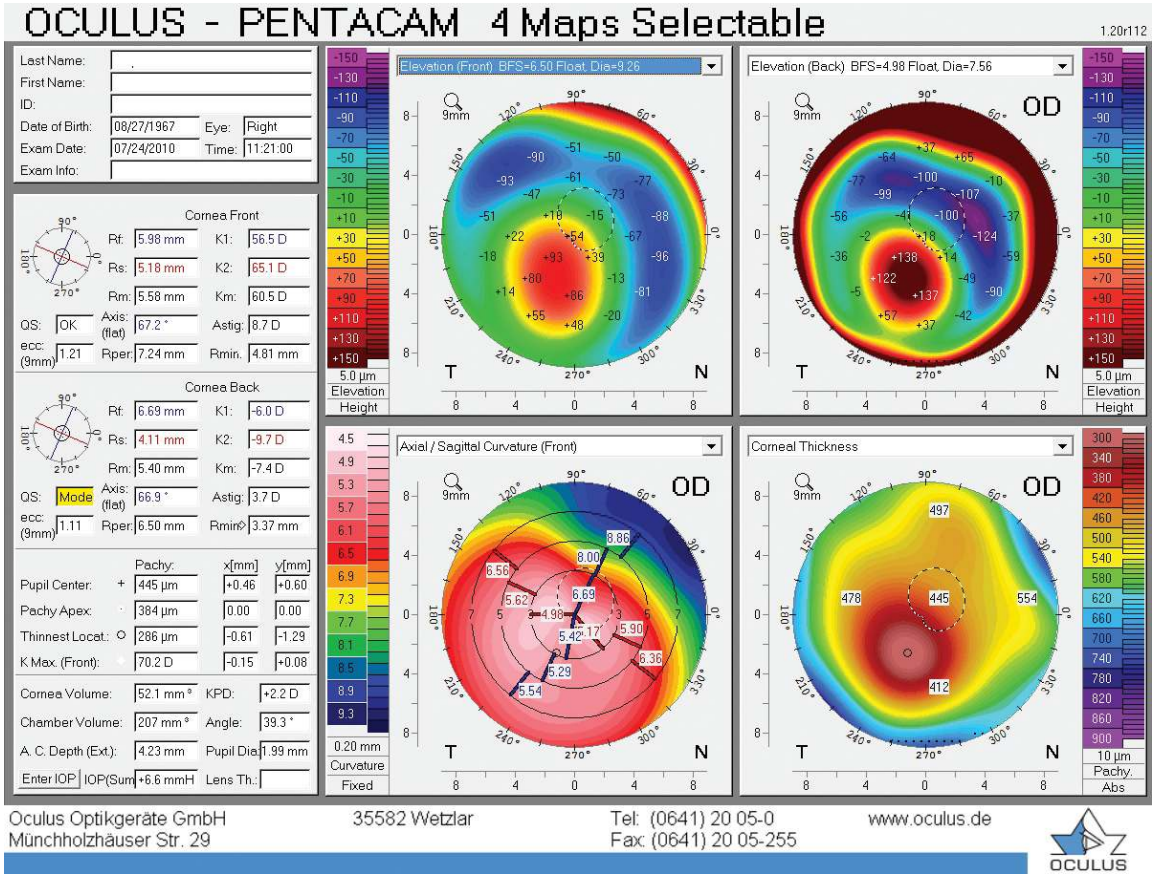

Figure 47: Pentacam scan of stage 3–4 keratoconus

Subjective Complaints of Keratoconus

Table 34: Symptoms associated with keratoconus modified from Naderan, et al., 2015

Visual symptoms	Keratoconus group	Control group
Blurred vision	38.8%	4.8%
Poor visual acuity with spectacles	30.4%	9.1%
Itchy eyes	18.4%	1.3%
Frequent changes of spectacles	17.4%	10.8%
Pain	10.6%	1.5%
Foreign body sensation	6,3%	1.5%
Diplopia	5.6%	0.9%
Contact lens intolerance	4.5%	3.0%
Tearing	4.3%	0.2%
Redness	4.3%	0%
Photophobia	4.1%	0%

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DIAGNOSIS: INDEX-BASED SYSTEMS

Keratoconus detection at an early stage of disease development has become increasingly important to [163]:

- Prevent iatrogenic ectasia
- Provide early intervention by corneal crosslinking

Index-based systems available on corneal topography systems, OCT, aberrometry and Scheimpflug systems are useful but not failsafe. Take care with Scheimplug systems when interpreting posterior surface data (shape and aberration), there is not enough information to make a clinical based diagnosis on this alone. Index based systems include many of the following indexes, which may vary between different corneal analyses systems. Abnormal values are normally flagged in yellow or red [198, 199].

- ISV – Index of surface variance
- IVA – Index of vertical asymmetry, abnormal value 0.28
- KI – Keratoconus index, abnormal > 1.07
- CKI – Centre keratoconus index, abnormal value 1.03
- IHA – Index of height asymmetry, abnormal value 19
- IHD – Index of height decentration, abnormal value 0.014
- Rmin – Minimum axial/sagital curvature, abnormal value < 6.71
- TKC – Topographical KC classification

Table 35: Index based systems for keratoconus detection, modified from Romero-Jiménez et al. [163]

Paper	Index	Cut-off point- higher values is diagnostic of keratoconus	Description
Rabinowitz and Mc Donnel, 1989 [200]	K-Value I-S – Value – Inferior-superior asymmetry	47.2D 1.4	Diagnosis is performed based on the central keratometry I-V value. It consists of averaging keratometric values obtained at various points of the superior hemicornea and subtracting them from the mean of the points corresponding to the inferior hemicornea
Maeda and Klyce [201]	KPI – keratoconus prediction index KCI% - Klyce/Madea keratoconus index – composite index	By using a cut-off value of KPI = 0.3, this index achieves a sensitivity of 68% with a specificity of 99%. 0%	KPI is derived from 8 quantitative keratography indexes. KCI% is derived from KPI and 4 other indexes
Smolek and Klyce, 1997 [202]	KSI – keratoconus severity index	0.25	Keratoconus detection and level of severity is assessed
Schiegerling and Greivenkamp, 1996 [203]	Z3 – Zernike polynomial	0.00233	Diagnosis is performed on topography height data modified into Zernike polynomials
Rabinowitz and Rasheed, 1999 [204]	KISA% - KISA% = K x (I-S) x AST x SRAX x 0.3	– KISA% < 60: normal cornea – 60 < KISA% < 100: early keratoconus with no clinical signs – KISA% > 100: keratoconus.	Diagnosis is derived from K-readings, I-S value, AST (astigmatism), and SRAX (skewed radial axes)
Mc Mahon et al., 2006 [205]	KSS – keratoconus severity score	0.5	Diagnosis based on slit-lamp findings, corneal topography, corneal power, HOA and wave front root mean square error
Mahmoud et al., 2008 [206]	CLMI – cone location and magnitude index	>0.45	Diagnosis is based in detecting the presence or absence of keratoconic patterns and determining the location and magnitude of the curvature of the cone

Diagnosis Summary [163, 172]

- Both changes on the posterior corneal surface and alteration in the corneal thickness progression are necessary to diagnose early stages of keratoconus
- Pachymetry is the least reliable indicator to diagnose keratoconus. Keratoconus can be present in corneas with normal central thickness
- ORA corneal biomechanic metrics, CH – corneal hysteresis and CRF – corneal resistance factor, are reduced in keratoconus. Low CH and CRF in keratoconus are due to the reduced ability of the cornea to dissipate energy, a function of both viscosity and elasticity [207]
- Tomography (Scheimpflug and OCT) and slit-lamp examination are currently the best and most widely available test to diagnose early keratoconus [208]
- Currently a "gold standard" classification for keratoconus is not available
- The often used Amsler-Krumeich classification [209, 210] system is limited, additional information including visual performance (BVA) correlated with corneal topometric and tomographic parameters may improve the classification and diagnosis of keratoconus

CLASSIFICATION

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

By corneal power [165]:

- ***Mild*** < 45D
- ***Moderate*** 45–52D
- ***Advanced*** 52–65D
- ***Severe*** > 62D

By corneal Thickness [165]:

- ***Normal:*** 543
- ***Early:*** 506
- ***Moderate:*** 473
- ***Advanced:*** 446

By morphology [163]:

- ***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. Contact lens correction is relatively easy
- ***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
- ***Globus.*** The cone is located throughout 75% of the cornea. Contact lens correction is a difficult and challenging

By disease evolution [163]:

- Stage 1. Fruste or subclinical form, diagnosed by corneal topography, visual acuity ≈ 6/6 achievable with spectacle correction
- Stage 2. Early form, mild corneal thinning, corneal scarring absent
- Stage 3. Moderate form, corneal scarring and opacities absent, Vogt striae, Fleischers ring, visual acuity < 6/6 with spectacles, but 6/6 with RGP correction, irregular astigmatism between 2.00–8.00D, significant corneal thinning

- Stage 4. Severe form, corneal steepening > 55.00D, corneal scarring, visual acuity <6/7.5 with contact lens correction, severe corneal thinning and Munson's sign

Table 36: Adapted Amsler-Krumeich classification of keratoconus [211, 212]

	Best corrected spectacle visual acuity	Index of surface variance (ISV)	Keratoconus index (KI)	Other indices	Minimum radius of curvature (Rmin in mm)	Retinoscopy signs	Slit lamp observations
Pre-stage	20/20–20/15	<30	1.04–1.07	All four are normal	7.8–6.7	No scissors of fish mouth reflex	Clear cornea
Level 1	20/25–20/15	30–55	1.07–1.15	Possibly one value within abnormal range	7.5–6.5	Distorted reflex, scissors or fish mouth reflex	Clear cornea, Fleischer's ring at the apex base. Decrease in cornea thickness measurable but not observable
Level 2	20/60–20/20	55–90	1.10–1.25	Possibly one value within abnormal range	6.9–5.3	Clear scissors or fish mouth reflex, difficult to perform retinoscopy	Often cornea still clear, apex slightly thinner and decentred. Partial or circular Fleischer's ring and Vogt striae visible
Level 3	20/125–20/30	90–150	1.15–1.45	At least one value within abnormal range	6.6–4.8	Distinct scissors or fish mouth reflex, nearly impossible to perform retinoscopy	Apex thinner, decentred, and often slightly cloudy. Mostly circular Fleischer's ring and Vogt striae clearly visible. Munson's sign may be apparent
Level 4	<20/400–20/100	>150	>1.50	At least one value in the abnormal range	<5.00	Retinoscopy impossible to perform	Corneal scarred and opaque at the apex. Munson's sign clearly visible

CORNEAL BIOMECHANICS

The human cornea is a viscoelastic tissue that responds to the presence of any force. This response is not only dependent on the magnitude of the force, but also on the velocity of the force application. As a viscoelastic element, two main properties can be identified in corneal tissue; static resistance or elasticity and viscous resistance or damping [213, 214]. The first property describes the proportionality between the magnitude of tissue deformation and the applied force. The second property represents the dependence on time of the relationship between deformation and applied force. These properties describing the viscoelasticity of the cornea are in relation with its biomechanical behavior [213–215]. Many studies have been conducted in an attempt to characterise corneal biomechanics, but to do it *in vivo* is not an easy task. However, Luce presented in 2005 a non-invasive device for characterising the corneal biomechanics in vivo, the ocular response analyzer or ORA (Reichert) [216]. This instrument uses a dynamic bidirectional applanation process to provide a new two measurements of corneal biomechanics; CH (corneal hysteresis) and the CRF (corneal resistance factor). A reduction in the ORA metrics (CH and CRF) was found in keratoconic corneas indicating changes in its biomechanical properties [214, 215]. These biomechanical changes seem to be the consequence of changes occurring in the collagen lamellar structures of keratoconic corneas, probably distortion

of the orthogonal lamellar matrix. Compared with normal patients, both CH and CRF decrease in KC corneas indicating mechanical softening of the stroma. Low CH and CRF in keratoconus is due to the reduced ability of the cornea to dissipate energy, a function of both viscosity and elasticity. However, when comparing these biomechanical metrics, it is clear that a wide substantial overlap exists between normal corneas and keratoconic corneas. Therefore, these metrics have not been as effective in identifying keratoconus as first anticipated. Furthermore, the exact correlation between these metrics and the established mechanical properties of the tissues are still unknown [214, 215]. The ORA needs to be complemented with other diagnostic imaging tools to obtain a reliable diagnosis of keratoconus. According to Reichert, CH represents ocular resistance due to the combined effects of CCT (central corneal thickness), ocular rigidity and the cornea's elastic properties. CRF is dominated by the viscous and elastic properties of the cornea and appears to be an indicator of the overall resistance of the cornea. However, unlike true corneal properties such as CCT and Young's modulus, which are invariant to the measurement technique, CH and CRF are specific responses to the ORA measurement process. Therefore, they should not be considered corneal properties until proven otherwise [217, 218]. Other instruments, such as the Corvis ST (Oculus) also measure biomechanical properties and studies are continuing to determine the diagnostic value of these instruments.

DIFFERENTIAL DIAGNOSIS

Pellucid Marginal Degeneration [219]

Pellucid marginal degeneration is characterised by a peripheral band of thinning of the inferior cornea from the 4 to the 8 o'clock position. There is 1–2-mm uninvolved area between the thinning and the limbus. The corneal protrusion is mostly marked above the area of thinning and the thickness of the central cornea is usually normal. Like keratoconus, pellucid marginal degeneration is a progressive disorder affecting both eyes, although eyes may be asymmetrically affected. In moderate cases, it can easily be differentiated from keratoconus by slit-lamp evaluation because of the classical location of the thinning. In early cases, the cornea may look relatively normal and in advanced cases it may be difficult to distinguish from keratoconus, because the thinning may involve most if not all of the inferior cornea. In both instances, corneal topography is very useful to make the distinction. The corneal topography has a classical "butterfly" appearance, demonstrating large amounts of against-the-rule astigmatism as measured by simulated keratometry.

Because of the large amounts of against-the-rule astigmatism, patients with pellucid marginal degeneration are much more difficult to fit with RGP contact lenses than patients with keratoconus, although spherical or aspheric contact lenses with large overall diameter should initially be attempted in early-to-moderate cases.

KERATOGLOBUS [220]

Keratoglobus is a rare disorder, in which the entire cornea is thinned most markedly near the corneal limbus, in contrast to the localised thinning centrally or para-centrally in keratoconus. The cornea may be thinned to as little as 20% of normal thickness and it assumes a globular shape. In advanced keratoconus, the entire cornea can also be thinned and globular-shaped, making it difficult to distinguish these two entities. However, even in very advanced keratoconus there may be a small area of uninvolved cornea superiorly that approaches normal corneal thickness. Keratoglobus is bilateral, but it is usually present from birth and tends to be non-progressive. It can be distinguished from megalocornea and congenital glaucoma because the cornea is usually of normal diameter. It is a recessive genetic disorder and is often associated with blue sclera and other systemic features, in contrast to keratoconus, which is most commonly an isolated disorder.

In contrast to keratoconus, the corneas in keratoglobus are prone to corneal rupture from even minimal trauma. Thus, hard contact lenses are contraindicated, and protective spectacles should be strongly encouraged.

Posterior Keratoconus [221]

Posterior keratoconus is a rare, sporadic, usually unilateral and non-progressive corneal condition first described by T. Harrison Butler in 1930 as a "small basin-like depression" in the posterior surface of the cornea. Also known as keratoconus posticus, it is characterised by thinning of the posterior cornea without ectasia of the anterior cornea. It presents as a corneal opacity and is generally considered a developmental abnormality. However, it can also be acquired after ocular trauma. The histopathology of the abnormal cornea includes disorganisation of the basal epithelium and basement membrane, fibrous replacement of Bowman layer, thinned stroma with scarring and irregular arrangements of central collagen lamellae and variable structural changes in Descemet membrane. Topographic analysis of the cornea, has further shown that there are in fact anterior surface changes in posterior keratoconus, including central steepening in the area overlying the posterior corneal depression, with gradual paracentral flattening. Treatment is usually not necessary.

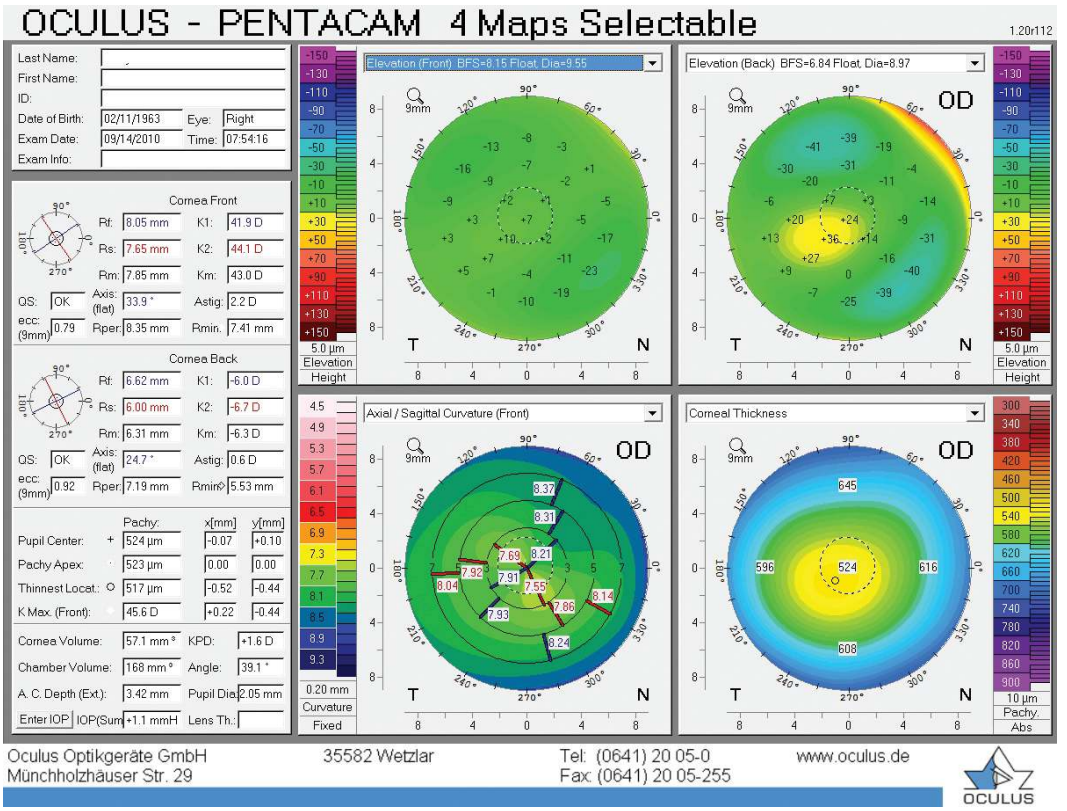

Figure 48: Pentacam scan of posterior ectasia

MANAGEMENT OF KERATOCONUS [163, 165, 172, 222]

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 keratoctomy, laser in situ keratomileusis) intraocular lens implants or a combination of these.

Spectacles [163, 172]

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.

Contact Lenses [88, 163, 172]

The first to describe the use of contact lenses to manage keratoconus was Adolf Fick in 1888. Since then, contact lens wear has represented the most common and successful treatment option for early to moderate cases of keratoconus. 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. High levels of irregular astigmatism cannot normally be corrected with other contact lens types. Frustre and early forms of keratoconus can be, in some cases, successfully corrected with hydrogel contact lenses. Several bespoke soft contact lens designs for keratoconus are currently available. 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.

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. The apical touch fitting technique is characterised 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. This technique provides good visual acuity. However, an increase in corneal scarring has been documented. 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. This technique has also been associated with good visual acuity. Previous studies have not found differences in contact lens wearing comfort between apical touch and apical clearance fittings techniques. Furthermore, although corneal scarring might occur with apical touch compared to three-point touch fittings, no randomised clinical trial that I am aware off has been carried out to assess which of these two fitting philosophies perform best.

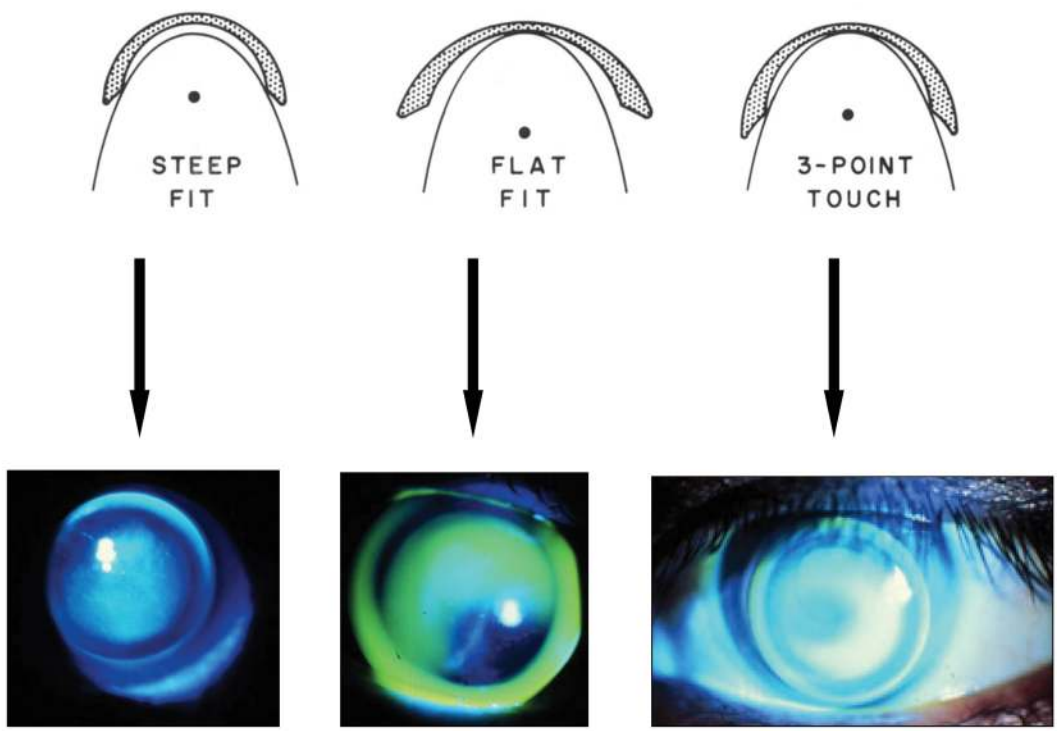

Figure 49: Steep, flat and three-point touch fitting of corneal RGPs in keratoconus

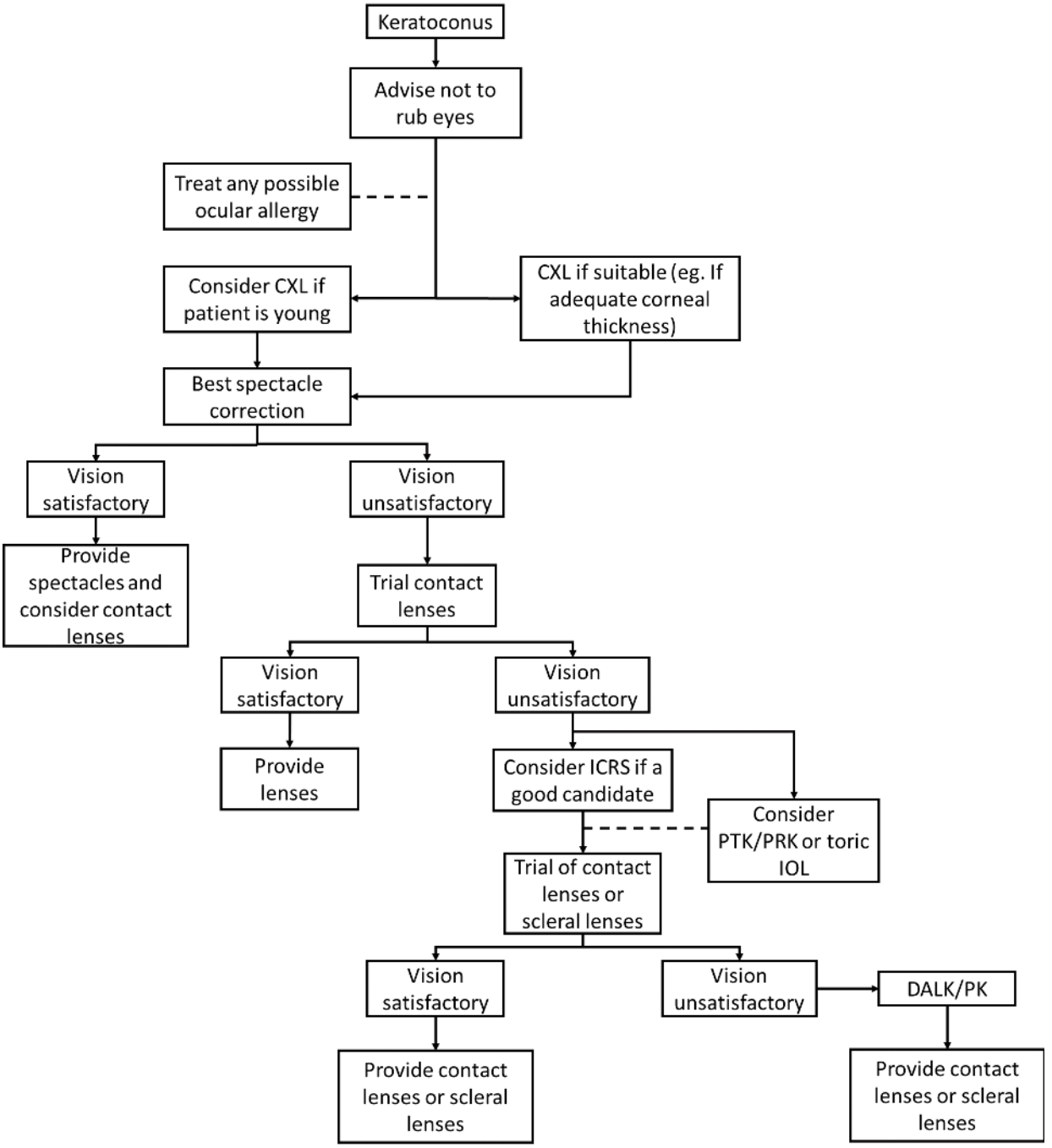

Figure 50: Flow diagram of keratoconus management [172]

Suggested Approach to Contact Lens Fitting

The "first definite apical clearance technique" from the CLEK study works well and is not dependent on the design of the lens [166]. It can be used with most designs although each manufacturer will have their own preferred system, which should be used with their products. Although I use the FDACL system I will usually ensure that the final lens bears minimally or has "feather" touch rather than bearing excessively on the cone. The treatment goal is to maximise visual acuity and comfort while preventing corneal scarring.

- Select first trial lens based on average K-readings (topography preferred)
- Evaluate the fluorescein pattern and establish definite apical clearance pattern (FDACL)

- The final lens selected is usually 3.00D flatter than FDACL
- Over refraction. Be aware that small changes in base curve can lead to quite large and unexpected changes in the refraction or lens power. The rule of thumb regarding base curve and lens power can be modified to 0.05 mm = 0.50D change with lenses steeper than 6.90 mm [88]
- Final lens selection depends on:
  - Amount of tamponade or touch required to maximise VA
  - Comfort
  - Corneal scarring and other signs

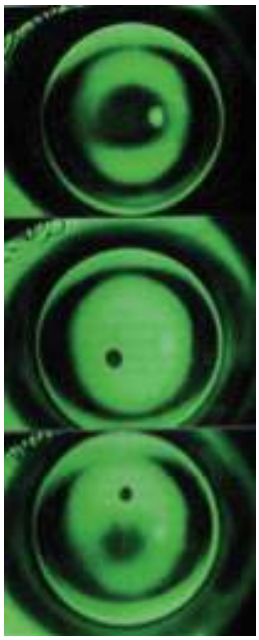

Figure 51: FDACL technique

Apical clearance vs central or feather touch:

- Feather touch is my first choice for mild to moderate keratoconus, slight tamponade usually results in good acuity. Complications of feather touch include corneal abrasion and punctate staining
- Feather touch is useful in fitting sagging cones, typically larger diameters and optic zones are used in these cases
- According to the CLEK study apical clearance is a viable option when fitting keratoconics. However, complications include transient punctate staining, epithelial contact lens imprint and steepening of the flatter corneal meridian [166]
- Apical clearance is useful in cases of persistent staining and to prevent scarring
- Apical clearance works well for central nipple cones, typically small optic zones and diameters are used in these cases
- With apical clearance 6/6 endpoints may be difficult to attain

Many contact lens practitioners fit RGPs flat which feels great when the patient wears the lenses but often results in corneal abrasions, central scarring and loss of vision. Refitting these patients with appropriate RGPs is difficult and patients will often complain that the previous flat lenses were more comfortable, and their vision was better. Therefore, is it important to follow keratoconus patients regularly in order to adjust the fit avoiding flat lenses and their complications.

The Use of Soft Contact Lenses in Keratoconus [223]

Many clinicians believe that keratoconus and irregular astigmatism should and can only be corrected using RGP lenses. RGP lenses indeed offer significant visual improvement by their outstanding ability to correct irregular astigmatism. However, patients often find that the enhanced visual acuity comes at a price, physical discomfort. Discomfort with RGP contact lenses may derive from chronic epithelial erosions and/or recurrent corneal abrasions, increased inferior edge lift and/or lens displacement and back surface lens deposits, lens adherence and solution sensitivity issues [224]. Many patients simply cannot tolerate RGP lenses and they often stop wearing the lenses accepting the poor visual acuity rather than having the chronic discomfort.

Clinicians have observed over the years that thicker spherical soft lenses, or those manufactured in materials that are stiffer compared to HEMA-based hydrogels (like the CSI lens of the past, or the higher-modulus first-generation silicone hydrogels), has the ability to mask small amounts of corneal astigmatism. However, significant amounts of irregular astigmatism and/or keratoconus proved to be much more difficult to correct with these lenses. Toric soft lenses improves the situation somewhat, but visual results are variable, generally poor except in the earliest stages of keratoconus. Keratoconic corneas are generally steeper than normal corneas, making it difficult to fit conventional soft lenses, which have limited BC parameters. This is especially the case with disposable lenses, which limits their usefulness in keratoconus even as piggy back lenses due to edge fluting. Given all these limitations, soft lenses are still a viable option for certain keratoconics. Soft toric lenses work quite well in pellucid marginal degeneration. It seems that, if the right combination of factors such as corneal thickness, curvature and degree of irregular astigmatism exist, one should at least try to fit a soft lens in patients who cannot tolerate RGP lenses.

The approach I use, involves the selection of a silicone hydrogel spherical or toric disposable lens with a power close to the patient's refractive error. If the lens fit is adequate (good movement, centration and no fluting) I will leave it to settle for at least 20 minutes after which a sphero-cylindrical over refraction is done provided the lens orientation is stable. If the trial lens is spherical, it is a simple matter of adding the over refraction value to the trail lens power and either a toric or spherical lens can be fitted. If a toric trial was used and the over refraction includes significant cylinder a calculator can be used to determine the resultant lens prescription (ToriTrack® Calculator – Crossed Cylinder Calculator, available at www.coopervision.com). I prefer using my trial frame and vertometer to calculate this resultant prescription. Simply place the trial contact lens prescription in the trial frame and add the over refraction value on top. In the example depicted below, a trial lens of -2.00/-1.75x60 was used and the over refraction was plano/-1.50x90. The resultant lens power was read on the vertometer as -2.25/-2.75x73. With the addition of extended ranges in disposable toric lenses, it is now possible to order disposable lenses with cylindrical power up to -5.25 in nearly any axis. Finally, remember to compensate for any rotation using the CAAS and LARS rules.

Figure 52: Using a trial frame and lensmeter to calculate a crossed cylinder resultant prescription

Bespoke Soft Lens Designs for Keratoconus

Soft K and Soflex Toric LITE [225]

The Soft K Sphere and Toric designs were developed by Israel-based Soflex and are currently distributed by *The Contact Lens Laboratory of South Africa*. Soft K is a silicone hydrogel lens designed for managing keratoconus, irregular astigmatism and even post-surgical corneas. It is a daily wear lens that can be replaced on a quarterly schedule.

The Soft K lens is manufactured in the Definitive material (Contamac, Inc), which has a 74% water content and a Dk of 60. The diameter is standardised at 14.2 mm, and sphere powers correct +10.00D to –20.00D, with cylindrical correction up to –7.00D at any axis. Base curves range from 7.0 mm to 8.2 mm in 0.3 mm steps. It is also available in a reverse geometry design. An important element in fitting this lens is to be patient and allow adequate settling time prior to assessing lens movement, as initial tearing can make lenses look falsely loose. After selecting and applying the initial trial lens, a good 10 minutes is necessary before these measurements are be made.

For a keratoconic or prolate corneal topography (including PMD), start with the 7.6 mm base curve. For post-surgical or oblate corneas, start with the 7.9 mm base curve. Make base curve changes only after the appropriate settling period, go steeper if movement is excessive and flatter if there is inadequate or no movement. Once the best physical fit has been achieved, and after an additional 20 minutes has elapsed (for a total on-eye settling time of 30 minutes), determine lens power.

Perform a spherical over-refraction initially. If good functional vision is found (6/12 or better), adjust the over refraction using vertex compensation if greater than ±4.00D and order the lens. Unless the vision is severely compromised, delay ordering a toric lens initially and ask the patient to wear the spherical Soft K lens for two weeks. During this period, there may be alterations in the corneal shape, due to the controlled thickness of the central optical zone, which may reduce the eventual need for a toric. If, after two weeks, the cylindrical correction is still significant in magnitude and improves visual acuity, order the Soft K Toric lens with the compensated and vertexed over refraction factored into the diagnostic lens power. The toric lens should be ordered only if there is at least a two-line increase in acuity with its use.

The Soflex Toric LITE lens is a prism ballasted soft lens available in sphere powers from -20.00 - +20.00D in 0.25D steps with cylindrical power up to -15.00 at any axis. Base curves range from 8.10, 8.40. 8.70, 9.00, 9.30 and 9.60 mm and diameters in 13.50, 14.50 and 15.00 mm. Replacement schedule is yearly, and the lens is available in 58% water Filcon 2 material.

KeraSoft IC [226]

The KeraSoft IC lens was developed in the United Kingdom by UltraVision CLPL and is distributed by *The Contact Lens Laboratory of South Africa*. This lens can be employed for managing keratoconus (all stages), PMD, post-corneal surgery including post-LASIK ectasia and other irregular astigmatic conditions.

KeraSoft IC has an aspheric design and is manufactured in the Definitive material. It is designed for quarterly replacement. Fitting involves an eight-lens diagnostic set with the standard 14.5 mm diameter (it can also be ordered in 14.0 mm, 15.0 mm, and 15.5 mm), plano power and base curves ranging from 7.80 mm to 8.60 mm (the full base curve range is 7.40 mm to 9.40 mm in 0.2 mm steps). Most lenses in the set have a standard periphery (also available in peripheries ranging from Steep 1 to Steep 4 and from Flat 1 to Flat 4), but the flatter base curves also include lenses with flat and steep peripheries for unusual fitting circumstances. It is a small set, but one that I find very useful in its intelligent design. Sphere powers can be ordered from +20.00D to –20.00D, with cylinder powers from –0.50D to –12.00D in 0.25D increments in axes from 1º to 180º in 1º increments.

The KeraSoft IC fitting process follows a rigid protocol known as the MoRoCCo VA system. Initial lens design for keratoconus, involves first looking at a patient's corneal shape, which can vary from steep central cones to low decentred cones that require different base curves also depending on the severity of the cone. PMD corneas often require flatter base curves and may require additional peripheral modification of the flat superior zone and steep inferior zone. Post-surgical corneas will often need steeper peripheries. Using the Corneal Shape Recognition and Corneal Profile Charts supplied by the manufacturer enables selection of the initial trial lens for evaluation.

The MoRoCCo VA system is then employed for the fitting assessment as follows:

- **Mo (Movement)** Up to 2 mm of movement is acceptable as long as the patient is comfortable. Change the base curve radius if movement is greater than this, if movement is less than 1 mm, or if the patient is uncomfortable. Note: Be prepared to see much more movement with all these soft keratoconus lenses than you see with traditional soft lenses. Increased patient comfort comes with adaptation as well, and patient education is therefore important
- **Ro (Rotation)** To assess rotation, use the vertical laser mark, which should be at 6 o'clock and stable, with up to 10º of acceptable rotation. Be sure to compensation for rotation. A slightly flatter base curve may improve the stability, but unstable rotation results from a flat fit. Stable but greater than 10º of rotation implies a tight fit, in which case the base curve radius should be flattened
- **C (Centration)** Centration should be good, but a minimal amount of decentration is acceptable if acuity is stable and clear. If vision improves immediately after the blink, then the fit is tight. Lateral decentration with a drop on up gaze indicates a flat fit
- **Co (Comfort)** Comfort should be good. if there is persistent edge awareness, try a steeper base curve radius. If there is discomfort and the lens is stationary, then the lens is likely tight
- **VA (Visual Acuity)** Visual acuity should be stable, with no fluctuation between blinks. Vision that is worse after the blink is likely due to a flat fit. If it is clearer after the blink, then it is likely a steep fit. If good acuity cannot be achieved after the above adjustments, it may be due to a very flat peripheral cornea. Peripheral modification may be needed in such cases, or the lens design discontinued in favour of other lens options

The periphery of the KeraSoft IC lens can be steepened or flattened independently of the base curve. This customisable process is known as Sector Management Control (SMC). Up to two sectors in the periphery can be modified when necessary, such as with post-graft corneas that requires flatter base curves but needs peripheral steepening. Also, low cones and PMD corneas may require SMC steepening of the inferior sector and possibly flattening of the superior sector. Lens Sector Angles (quadrants) are designated and specified as either STD (Standard), STP (Steep) 1 through 4, or FLT (Flat) 1 through 4 (up to four steps of change are available).

Flexlens Tri-Curve Keratoconus [227]

The Flexlens Tri-Curve Keratoconus (X-Cel Contacts) lens is a hydrogel lens that has been available for several years, featuring significantly increased thickness to control the irregular corneal astigmatism caused by keratoconus. This lens can be imported directly from *X-Cel Contacts*. It is available in both 49% or 59% hioxifilcon, in 55% methafilcon, and more recently in the Definitive silicone hydrogel material, which is the material of choice to offset the reduced oxygen transmission associated with thick hydrogels. The center thickness ranges from 0.40 mm to 0.65 mm, and the lens incorporates two peripheral curves. A flat secondary curve of 1.2 mm to 1.8 mm and a peripheral curve of 2.2 mm to 2.8 mm is used to aid lens alignment. Other standard parameters include diameters from 8.0 mm to 16.0 mm in 0.1 mm steps, base curves from 5.0 mm to 11.0 mm in 0.1 mm steps and sphere powers from +50.00D to –50.00D. The diagnostic set parameters include base curves of 6.0 mm to 8.7 mm in 0.3 mm steps, diameters of 14.0 mm and 14.5 mm, power of –3.00D and centre thickness of 0.45 mm.

Toric powers, unfortunately, have not yet been offered with this lens design. Keratoconus patients who have moderate amounts of irregular astigmatism, may do well with this design, but those who have significant residual astigmatism would need the Flexlens Piggyback design instead, which is a soft lens with a cut-out section to accommodate an RGP lens.

The gains in patient comfort with customised soft lenses are well worth the additional chair time spent in fitting these lenses. Good lens movement and the use of silicone hydrogel materials can help provide irregular corneas with improved metabolism and reduce the risks of vascularisation. Because of the increased thickness of these materials be prepared to see more movement than with other types of soft contact lenses. About 0.75 mm to 1 mm of movement is desirable. Greater amounts may result in increased lens awareness. However, this does improve with adaptation.

Alden NovaKone [228]

The NovaKone (Alden Optical) lens, is a relatively new addition to this lens category that uses increased thickness as a lens parameter to compensate for corneal irregularity. In South Africa, it is available from *Danker lenses*. The central zone of this soft lens can neutralise irregular corneal astigmatism, much like an RGP lens would, due to its significantly increased thickness. It has an advantage in that it can correct residual astigmatism by incorporating astigmatic correction on the front surface of the lens. Rotational stability for the toric application comes from Alden's Dual Elliptical Stabilisation design.

The lens is manufactured in the 54% water hioxifilcon D material and comes in a standard 15.0 mm diameter. It can be replaced quarterly. The 18-lens diagnostic set contains a wide range of base curves (from 6.6 mm to 8.6 mm in 0.4 mm steps) and fitting curves (including flatter curves for the corneal regions outside of the cone). The following table lists the complete parameter range. These lenses have significant amounts of minus lens power and varying thicknesses.

Table 37: NovaKone lens parameters [228]

NovaKone Toric Parameters	
Material	Benz G4X 54%, hioxifilcon D
Diameter (mm)	15.0 as standard, others available in 0.1 steps
Base curve (central) (mm)	5.4, 5.8, 6.2, 6.6, 7.0, 7.4, 7.8, 8.2, 8.6 as standard, others available as 0.1 mm steps
Fitting curve (paracentral) (mm)	8.2, 8.4, 8.6 as standard, others available in 0.1 mm steps
Sphere power	+30.00D to –30.00D in 0.25D steps
Cylinder power	Up to –10.00D in 0.25D steps
Axis	1º to 180º in 1º steps
IT Factor* (increased thickness)	0 = Standard thickness
	1, 2, 3, 4 incrementally thicker for higher levels of irregularity
** IT Factor is used to increase the lens thickness when irregularity is observed.*	

Thickness control with the NovaKone lens is critical to its success. This variable is controlled as the Index of Thickness (IT) factor, ranging from thinnest (level 0) to thickest (level 4) in incremental steps. Steeper curves for advanced cones with several IT factors are provided in the diagnostic set for correcting irregular astigmatism. Its effectiveness is evident not only by the level of visual acuity obtained through sphero-cylindrical over-refraction performed over the spherical test lenses, but more importantly by assessing the quality of the front surface of the lens with an "over-K or over -topography" measurement.

As long as, the quality of the over-K mires is good with a test lens (regardless of the amount of astigmatism measured), it implies that irregular astigmatism has been corrected by the test lens. Good visual acuity can usually be achieved via sphero-cylindrical over-refraction. This astigmatism correction is then incorporated into the rotationally stabilised toric lens design (compensate for toric rotation as you normally would do with any toric lens, assuming good lens movement and centration are observed). Two laser marks on the lens horizontal axis aid in toric rotational measurement. You may have to repeat this process with more than one IT factor to determine the best lens. It is not uncommon to find that higher IT factors can achieve better acuity with less additional toric refractive correction required. Having said that, however, you should still attempt to use the lowest IT factor thickness that produces a satisfactory visual outcome. This is to provide the most comfortable lens for the patient, as well as to facilitate oxygen transmission to the eye. High molecular weight fluorescein is used to evaluate the fit of the lens in a similar manner to a conventional mini- or semi-scleral lens.

Both practitioners and patients need to have realistic expectations, and both need to recognise that fitting these lenses requires additional time for on-eye assessments, with the likelihood that multiple visits are needed to achieve the final optimal outcome. Finally, bespoke soft keratoconus lens designs are expensive and therefore may not suit every patients budget.

Piggy Back and Hybrid Lenses

Piggyback lens systems date back to the early 1970s. First reported attempts at this combination lens fitting technique occurred in 1964 by David Westerhout with results published in 1973 [229]. He fitted five piggy back systems in keratoconic patients which resulted in improved wearing times (14 to 16 hours), better comfort and vision. Kok et al., 1993 found that in 80% of eyes, patients wore piggyback systems longer than 12 hours per day without discomfort. Decreased mechanical irritation and pressure on the weakened corneal apex allows keratoconic piggyback lens wearers longer wearing times without comfort difficulties [230].

Piggy backing consists of a RGP lens fitted on top of a soft lens (I have seen soft lenses fitted over RGP as well), older piggyback lens systems often resulted in corneal oedema and neovascularisation, due to hypoxia. With improved RGP and soft lens materials that offer higher Dk/t, piggyback lens systems have resurfaced as a viable option for keratoconic patients. Research shows that we can achieve the physiological corneal oxygen requirements necessary to reduce and prevent oedema with these higher-Dk combination lenses [231]. Silicone hydrogel disposable lenses are best suited for use in piggy back systems. However, limitations in lens parameters especially base curves, which are on the flat side for keratoconic eyes, can be problematic requiring a custom-made lens. In the past, the Acuvue Advance 8.30 base curve was well suited for piggy back systems, but this lens is no longer available in South Africa.

Plus-power soft lenses create a steeper anterior surface and minus-power soft lenses create a flatter anterior surface. Therefore, we could potentially achieve a successful fit by altering soft lens power [232]. A fit is successful when a well-centred RGP lens moves independently of the soft lens with each blink with acceptable visual acuity and absence of corneal compromise. Ideally, the RGP lens should achieve 0.75 to 1 mm of movement over the soft lens surface with each blink. If the RGP lens is too tight and moves less, the potential for central corneal oedema increases. The soft contact lens should move 0.25 to 0.50 mm with each blink. Additionally, stationary air bubbles trapped between the soft and RGP lens that can't be removed indicates a steep RGP lens fit, which should be addressed [233].

Improved subjective visual quality and objective visual acuity with a piggyback lens system is yet another advantage for keratoconic patients. The soft contact lens effectively masks some of the irregularity of the corneal surface. This enables the GP lens to more effectively correcting the remaining irregular astigmatism common in keratoconic eyes. Between 10 and 25% of keratoconic patients undergo a penetrating keratoplasty because of

lens intolerance, reduced vision and/or corneal compromise [234–236]. By increasing comfort, wearing time and vision while decreasing corneal compromise, a piggyback system may delay or prevent the need for a penetrating keratoplasty.

Despite the advantages with piggyback lens systems, many patients find the care and handling necessary to maintain the lenses inconvenient. In addition to the need for handling two different types of lenses for each eye, patients must use two different care systems to optimally disinfect each lens type. However, I frequently will advise patient to use a peroxide system such as AOSept® or Oxysept® for both the soft and RGP lenses, which simplifies matters.

The first hybrid contact lens was introduced in 1983 as the Saturn II. Due to design performance issues, the lens was re-designed and re-introduced by Sola/Barnes-Hind Inc. laboratories as the SoftPerm lens in 1985 [237]. The initial indications for this hybrid contact lens, included improving performance and comfort for the fitting of irregular corneas in comparison to rigid contact lenses. In addition, it was designed for managing regular astigmatism and spherical refractive error for cases, in which rigid contact lens adaptation could not be achieved.

Problems with the SoftPerm hybrid contact lens included low oxygen transmission of both the rigid and soft sections (14 Dk/t), lens breakage and splitting at the rigid/soft interface, lens adherence and flexure of the rigid lens portion [237]. In an attempt to improve the oxygenation of the cornea, I often fenestrated the lens. This did not alter the fit, and although the improvement in oxygenation was minimal and localised, it still improved matters somewhat.

In 2001, SynergEyes Inc. began research and development of a new hybrid contact lens that ultimately received FDA approval in 2005 as the SynergEyes hybrid contact lens. The SynergEyes hybrid lens differed from the SoftPerm design in the use of a high-Dk central GP material (Paragon HDS 100, Paragon Vision Sciences) and the development of a stronger junction between the rigid and soft portions of the lens that significantly reduced the incidence of splitting between the two sections. The soft skirt portion is a 27-percent water, non-ionic and group 1 material with a Dk/t of 9.3. In addition, the SynergEyes lens is available with adjustable soft skirt curves as well as multiple rigid base curves, allowing for more precise control of lens fitting characteristics [238].

The company initially developed and distributed four design variations of its hybrid lens technologies including the “A” design for fitting standard corneas, the “KC” design for fitting some cases of keratoconus and other highly prolate corneas, the “PS” design for fitting post-surgical corneas and other eyes that have oblate topographies, and the SynergEyes Multifocal design for fitting presbyopic eyes. SynergEyes also introduced the ClearKone and UltraHealth designs, which is intended to fit keratoconic and irregular corneas, as well as the Duette design for normal corneas. The ClearKone/UltraHealth design is fit with a vaulting method that allows for clearance over the apex of the cone while the reverse curves in the lens design appropriately return the lens onto the cornea for adequate tear flow [238].

Synergeyes lenses are supplied by *Danker Lenses* in South Africa. Appropriate fitting guides are available from Synergeyes which illustrates the unique fitting protocols for each of the Synergeyes products. One of the disadvantages with this lens is the cost and the fact that the lens replacement schedule is six monthly. In my practice, very few patients can afford to replace the lenses regularly and over wear them, which results in unnecessary complications. Only one other hybrid lens is available from *The Contact Lens Laboratory of South Africa* - EyeBrid Silicone hybrid contact lenses, which are manufactured by LCS, headquartered in Caen, France. LCS successfully introduced EyeBrid Silicone lenses into the French market in 2013. For normal regular corneas, the lenses are fit on flattest K, and for irregular corneas the base curve is selected by adding 0.2 mm to the mean K-reading.

Surgery [239]

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. 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 [235]. Another study in which keratoconus subjects were followed-up for 48 years reported that less than 20% of them required PKP intervention [236]. In a 7 year follow-up study of 2363 keratoconus subjects, 21.6% required PKP [234]. The risk factors increasing the likelihood of surgery in keratoconic are the presence of corneal scarring, visual acuity worse than 6/12 with contact lens correction, corneal keratometry steeper than 55D, corneal astigmatism >10 D, early age of keratoconus development and poor contact lens tolerance [163, 240].

Deep Lamellar Keratoplasty (DLK), in which superficial corneal layers are removed (Descement's layer and endothelium remain intact) and replaced with healthy donor tissue, has been employed in keratoconus management in recent years [241]. However, eyes undergoing PKP are more likely to achieve 6/6 vision than those undergoing DLK. 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 [242]. The existing limited evidence confirms reduced rejection and refractive astigmatism with DLK, but better visual outcomes with PKP [243]. Internationally agreed data sets and follow-up protocol are warranted.

Other corneal surgical procedures for the treatment of moderate keratoconus, include excimer laser-assisted anterior lamellar keratoplasty [244], epikeratoplasty and laser-assisted in situ keratomileusis [245]. Although laser refractive surgery procedures following PKP and DLK have been commonly used to correct high levels of surgery-induced astigmatism, a higher risk of ectasia has been reported following the use of these surgical techniques [246, 247].

Intra-corneal ring segments, a surgical technique originally developed for the treatment of low myopia, has been recently adapted for the treatment of keratoconus. The technique consists of 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 and prevent or, at least, delay the need for corneal graft. It is commonly used to treat mild to moderate cases of keratoconus, as normal corneal transparency and a minimum corneal thickness of 450 microns at the site of the incision are required. This surgical option has been associated with an improvement in uncorrected and best corrected visual acuity and a decrease in high- order corneal aberrations, especially coma [248–250].

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 the riboflavin, generating reactive oxygen species that induce covalent bonds between collagen fibrils in the corneal stroma [251]. The irradiation level at the corneal endothelium, lens and retina is significantly smaller than the damage threshold. It has been recommended not to perform this technique in corneas thinner than 400 μm as toxic reactions could take place in the corneal endothelium [188]. 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. This technique has been successfully used in combination with other surgery techniques, such as corneal ring segments [249]. 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 [251, 252].

COMPLICATIONS OF KERATOCONUS

Progression

Ectasia progression is defined by a consistent change in at least 2 of the following parameters [172]:

- Steepening of the anterior corneal surface
- Steepening of the posterior corneal surface
- Thinning and/or an increase in the rate of corneal thickness change from the periphery to the thinnest point

Although VA often decreases with progression, changes in uncorrected and corrected VA are not required to document progression.

"Forme Fruste" Keratoconus

In medicine, a "forme fruste" (French, "crude, or unfinished, form"; pl., formes frustes) is an atypical or attenuated manifestation of a disease or syndrome, with the implications of incompleteness, partial presence or aborted state [120]. In the late 1930s, Swiss ophthalmologist Marc Amsler (of Amsler Grid fame) coined the term "forme fruste" keratoconus to describe a subtle form of asymmetric corneal astigmatism that has topographical features that "mimic" those often seen in early forms of keratoconus, such as superior flattening and inferior steepening [253]. The condition was further described by Duke-Elder in the 1960s [254] and Klyce et al., 2009 [255]. "Forme fruste" keratoconus, can therefore be defined as a cornea that has no abnormal findings by both slit-lamp examination and corneal topography, with the fellow eye having clinical keratoconus. Unlike primary keratoconus, "forme fruste" keratoconus is characterised by the presence of stable asymmetrical astigmatism that is non-progressive, corneal thickness that is normal and stable and no slit lamp signs of keratoconus. "Forme fruste" keratoconus is usually diagnosed using corneal topography systems and depends on the attending clinician's judgement. This often leads to ambiguous findings and incorrect diagnosis. Therefore, the true diagnosis of "forme fruste" keratoconus should be made only through a historical profile of the patient that clearly documents the non-progressive nature of the asymmetric corneal astigmatism with no changes in corneal thickness [256].

Corneal Scarring

Corneal scarring in keratoconus is quite common, especially in patients wearing RGP lenses bearing on the cornea for visual correction. These scars often occur in the area of bearing or mechanical trauma from the lens causing abrasions or "hurricane staining". If left untreated the scars can form "proud nebulas" [257] or superficial fibroplastic nodules (SFN's), which represent chronic abrasions and buildup of scar tissue with each repetitive cycle of abrasion. SFN's represent quite a fitting challenge as the goal is to fit the RGP lens away from the heaped-up scar tissue in order to avoid recurrent abrasions. Semi-scleral or mini-scleral lenses are often used to refit these patients. SFN's can also be surgically removed [257, 258].

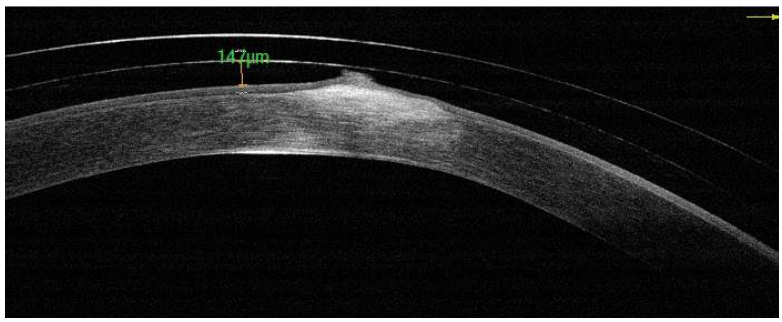

Figure 53: An AS-OCT scan of a "proud nebula" in keratoconic patient fitted with a mini-scleral lens

Acute Hydrops [197]

Corneal hydrops occurs due to tears in Descemet's membrane causing the edges to roll, thereby creating a gap in the membrane through, which aqueous from the anterior chamber percolates into the corneal stroma. Some sort of trauma, such as vigorous eye rubbing, may be the inciting factor. Continuous accumulation of the aqueous leads to the separation of the collagen lamellae and the formation of large fluid-filled stromal pockets within the cornea. Meanwhile, as a part of the reparative process the adjacent endothelium migrates over the defect causing a partial seal so that the seepage is prevented with subsequent resolution of stromal oedema. According to various studies the resolution of corneal oedema may occur any time between 5 and 36 weeks. Symptoms include; sudden onset of vision loss accompanied by pain and foreign body sensation as well as conjunctival injection with diffuse stromal opacity.

Medical therapy aims at providing symptomatic relief till spontaneous resolution occurs. It includes the use of topical lubricants, antibiotics (to prevent secondary infection), cycloplegics (to reduce pain and photophobia), hypertonic saline eye drops (help draw fluid), anti-glaucoma medications (to lessen the hydrodynamic force on the posterior cornea) and topical steroids or nonsteroidal anti-inflammatory drugs (NSAIDs). Sometimes a bandage contact lens may be used to provide pain relief until the edema subsides or until the patient is comfortable [197]

After resolution, depending on the location of the eventual scar, the final best corrected visual acuity (BCVA) can be as good/or better than that achieved by surgical intervention.

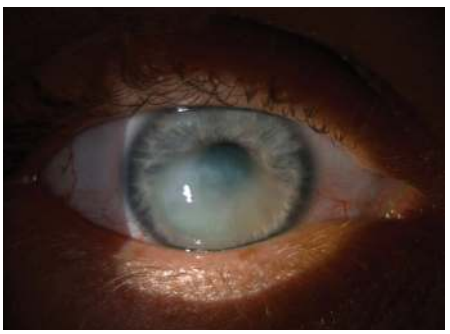

Figure 54: Corneal hydrops in a keratoconic patient

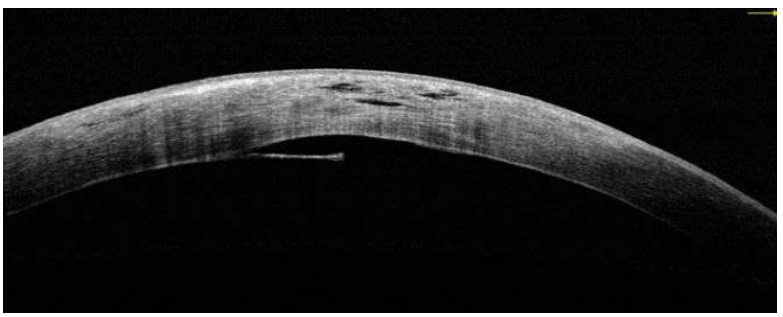

Figure 55: AS-OCT of corneal hydrops. Note the break in Descemets membrane and corneal stromal swelling

CONCLUSION

- Keratoconus affects mainly the anterior stroma, Bowman's membrane and corneal epithelium
- Currently there is no primary pathophysiological explanation for keratoconus. It is likely to involve environmental, biomechanical, biochemical and genetic disorders
- Most important risk factors include ocular allergy, mechanical factors such as eye rubbing, ethnic factors (Asian or Arabian decent), floppy lid syndrome, atopy and connective tissue disorders

- It is important to monitor progression. Progression is diagnosed when there is consistent change in at least two corneal (curvature, thickness, shape …)
- Most important goals of management are to halt progression and establish visual rehabilitation
- In cases of allergy, atopy or eye rubbing, patients must be treated with topical anti-allergic medication, topical lubricants and counselled not to rub their eyes
- There is no direct relationship between keratoconus and dry eye syndrome
- Contact lenses does not slow or halt progression of corneal ectasia and should not be fitted flat to "push the cone back"
- Pregnancy could contribute to accelerated progression of ectasia
- In acute hydrops, nonsurgical management should be attempted before surgery is considered