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Keratoconus Management: Navigating Patient Options

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INTRODUCTION

Keratoconus (KC) is a condition which results in progressive corneal thinning. It was first discovered by Dr. John Nottingham in 1854 who described it as "conical cornea" due to the outward bowing appearance caused by the condition.[1] The prevalence of KC is between 0.2 and 4,790 per 100,000 people. KC does not have a gender predilection. It is believed to appear more commonly in South Asian and Middle Eastern populations.

Keratoconus typically begins in the second and third decades of life although it can develop at any time. The clinical symptoms of the condition include blurred and distorted vision. Patients may present with higher-order aberrations (HOA)–the most characteristic of which is coma –resulting in blurred and double vision. The common signs of KC include corneal protrusion and thinning, prominent corneal nerves, Fleischer ring, Vogt's striae, and scissors reflex on retinoscopy[2]. The most frequently encountered phenotype is oval cones in the central cornea. The primary diagnostic tool for KC is corneal topography, although pachymetry, including epithelial mapping and corneal tomography, are often performed in conjunction with each other as they aid with early detection and the monitoring of KC progression.

Advancements in clinicians' knowledge of KC and expertise in its treatment, have led to novel therapies. Stopping disease progression is now possible and improving patients' quality of vision is feasible in many cases.

Preventive measures halting progression and management of mild and moderate forms of KC are reviewed. Treatment of severe KC will also be briefly reviewed.

MANAGEMENT

Current KN management options are based on three pillars: prevention, progression and precision. Treatment should be based on the patient's primary complaint and treatment objectives. It should be specific to the individual and penetrating keratoplasty (PKP) or deep anterior lamellar keratoplasty (DALK) should be considered only in advanced cases due to their surgical risks and the increased risk of corneal graft rejection in young patients.[3] Surgical options should be assessed based on these considerations: i) Does progression of KC need to be arrested? ii) Does the corneal shape need to be significantly modified to improve corrected distance visual acuity (CDVA)? iii) Does the patient's quality of vision need to be enhanced? Various clinical parameters in combination with clinical history are used to answer these questions and provide the optimal case management option.

Scheimpflug imaging and epithelial optical coherence tomography (OCT) mapping are essential in the evaluation and surgical planning of KC eyes. The Pentacam® (Oculus Optikgeraete GmbH [Wetzlar, Germany]) is preferred due to its proven accuracy and repeatability, although various other systems may be used based on surgeon preference[2,4]. In addition to a complete ocular examination, the parameters examined are pachymetry (microns, µm), keratometry (Diopters, D) and corrected distance visual acuity (CDVA). KC is categorized based on severity: mild (>440 µm, <55 D, >20/25 CDVA), moderate (>440 µm, <55 D, >20/50 CDVA) and severe (<440 µm, >55 D, <20/25 CDVA). This classification corresponds approximately to Stages I, II and III of the ABCD parameters on the Pentacam. Progression is monitored using the ABCD progression display and Belin-Ambrosio enhanced ectasia total deviation display (BAD). The Pentacam uses an anterior and posterior curvature 3 mm from the thinnest corneal pachymetry and CDVA.[5] The BAD incorporates anterior and posterior radius of curvature,

as well as corneal thickness at the thinnest point.[4] Both systems offer reliable methods to monitor KC progression.[2,4,5]

PREVENTION

The early detection of KC is challenging as patients may present with non-specific refractive symptoms. Formal corneal measurements may be the only method for early diagnosis. The BAD (D-index) has a high sensitivity and specificity for detecting subclinical and clinical KC.[4] Advances in machine learning have the potential to further improve the accuracy of early KC detection.[6] Early detection of KC may also be improved by knowledge of modifiable and non-modifiable risk factors. KC has a strong hereditary component: there is a 15 to 67 times greater risk of KC in patients with affected relatives.[2] Patients with obstructive sleep apnea are also at increased risk.[7] The primary modifiable risk factor for KC is eye-rubbing, which increases both the likelihood of disease development and its progression (**Table 1**).[8] Atopic conditions such as allergy, asthma and eczema can lead to eye rubbing. Therefore, regular use of antihistamines when indicated, as well as patient counselling to completely avoid eye rubbing is recommended.

PROGRESSION

Corneal collagen cross-linking (CXL) is a proven treatment modality for halting the progression of KC as it alters corneal biomechanics through covalent bonds formation, without impacting corneal translucency.[9] In fact, there are few, if any, conditions in medicine where a treatment has such a dramatic impact on the arresting of a disease. CXL can be used for patients with mild and moderate, and in some cases, advanced, KC (**Table 1**). The Dresden protocol is the standard approach. It utilizes riboflavin 0.1% and ultraviolet-A light.[2] The epi-off protocol is preferred as riboflavin has limited corneal penetration due to its macromolecule structure. Epi-on protocol may be used in pediatric populations as children are more sensitive to the effect of epithelial debridement. CXL slightly improves uncorrected distance visual acuity (UDVA) and CDVA, reduces higher order aberrations, and may improve topographic/tomographic parameters (**Table 2**).[10–12] CXL alone does not significantly impact the mean sphere and magnitude of astigmatism. Corneal pachymetry becomes more compact at 6 months, and reverts to pre-CXL levels by 12 months.[13] CXL is contraindicated in patients with <400 µm central corneal thickness as it may damage the endothelium due to toxicity.[14] However, recent studies dispute this notion.[15] Patient counselling regarding the avoidance of eye rubbing, and the performance of CXL, are crucial in preventing KC progression as it may worsen the condition.[2]

PRECISION

While the objective for the majority of patients with KC is to halt the progression of disease. Fortunately, surgeons are now able to offer patients treatments proven to not only stop, but also improve, UDVA and CDVA, reduce refractive parameters, and allow for better spectacle or contact lens fitting, thus improving the patient's overall visual experience. CXL combined with treatments such as topography and wavefront-guided excimer laser, intracorneal ring segments (ICRS), and toric phakic lenses, have the potential to improve visual acuity, enhance topography/tomography parameters, and reduce higher-order aberrations. Various types of precision treatments can be combined to achieve optimal patient outcomes, depending on KC severity (**Table 1**). It is important to note that, in addition to these treatments, scleral contact lenses still have a role to play.

Wavefront-guided and topography-guided photorefractive keratectomy (WF-PRK and TG-PRK, respectively) can be combined with CXL for the treatment of mild cases of KC with a mild level of astigmatism (**Table 1**). WF-PRK and TG-PRK utilize the excimer laser to modify the shape of the cornea by removing a section of the stroma. It can improve CDVA (more so than UDVA), manifest refraction, amount of astigmatism, and higher order aberrations, primarily coma.[9] It is important to be aware of the risk of corneal haze formation following WF-PRK, although it is reduced with the application of mitomycin C.

Intracorneal ring segments (ICRS) reshape the cornea through polymethacrylate stromal implants. They are a favourable treatment option for moderate KC when combined with CXL and phototherapeutic keratectomy (PTK).[2] The combination of these three methods is effective and safe in improving visual acuity and clinical parameters, and reducing higher-order aberrations (**Table 2**).[16] However, it is important to keep in mind that ICRS can only be applied in transparent corneas with minimal thickness of 450 µm.

Toric intraocular lens (IOL) implants can correct astigmatism in phakic and pseudo-phakic patients. The ideal patient population is those who are intolerant to contact -lenses, and have mild-to-moderate KC and high-levels of regular astigmatism. Toric phakic IOLs can significantly improve visual acuity in KC patients who are stable, either due to their relatively young age or to previous CXL. They are contraindicated in patients with progressive KC or significant irregular astigmatism with poor CDVA.[2]

The treatments cited above focus on mild-to-moderate KC. Approximately 10%-20% of patients with KC have a severe presentation requiring keratoplasty.[2] In such cases, the most common procedures are PKP, where the full thickness cornea is replaced, and DALK, which involves selective transplantation of the anterior corneal stroma. DALK is associated with faster visual recovery, lower rates of graft rejection, and lesser endothelial cell loss, although patients with PKP may achieve better final visual acuity.[2,17] Several novel treatments are being investigated, including Bowman layer transplantation (BLT),[18] intrastromal stem cells transplantation[19] and corneal allogenic intrastromal ring segment (CAIRS).[20] These treatment modalities along with scleral contact lenses offer hope in preventing or delaying the need for invasive cornea surgery in patients with severe KC.

CONCLUSION

Multiple advances in the treatment of keratoconus currently are available and should be individualized to each patient, based on three principles: condition progression, whether or not the shape of cornea needs to be modified and whether or not the quality of vision requires improvement. Patient counselling regarding the avoidance of eye-rubbing, as well as performing corneal cross-linking, can prevent progression. The shape of the cornea can be altered with ICRS and TG-PRK, and combining these treatments can produce positive results for patients with mild and moderate KC. Patients with mild-to-moderate KC and severe correctable "regular-ish" astigmatism who are intolerant of contact lenses may benefit from Toric IOLs. Patients with severe KC having failed a trial of scleral contact lens wear, may require PKP and DALK, although non-invasive therapies that delay invasive treatment may be available in the future.

<table>
<tr><th></th><th>Mild[a]</th><th>Moderate[b]</th><th>Severe[c]</th></tr>
<tr><td>Eye-rubbing</td><td colspan="3">Stops progression</td></tr>
<tr><td>Cross-linking</td><td colspan="2">Stops progression</td><td rowspan="4">Penetrating Keratoplasty
DALK

BLT

Intrastromal stem cells transplantation</td></tr>
<tr><td>WG and TG-PRK/CXL
(Wavefront-guided and topography-guided photorefractive keratectomy)</td><td>Improves UDVA to functional level</td><td></td></tr>
<tr><td>ICRS/PTK/CXL</td><td></td><td>Improves UDVA to functional level</td></tr>
<tr><td>Toric ICL</td><td>Improves UDVA to functional level</td><td></td></tr>
</table>

Table 1. Treatment modalities for patients with mild, moderate and severe keratoconus.

[a]Pachymetry >440 µm, keratometry <55 D, CDVA >20/25
[b]Pachymetry >440 µm, keratometry <55 D, CDVA >20/50
[c]Pachymetry <440 µm microns, keratometry >55 D or CDVA <20/50

WG: wavefront guided, **TG-PRK:** topography guided photorefractive keratectomy, **CXL:** crosslinking, **ICRS:** intrastromal corneal ring segment, **PTK:** phototherapeutic keratectomy, **ICL:** implantable collamer lens, **UCDA:** uncorrected distance acuity, **DALK:** deep anterior lamellar keratoplasty, **BLT:** Bowman's layer transplantation.

	CXL	WG-PRK/CXL	ICRS/PTK/CXL
UDVA/CDVA	↑ ↔	↑↑	↑↑
Topographic/Tomographic parameters	↑↓	↓MR[a] ↓Cylinder Δ cornea	↓MR[a] ↓Cylinder Δ cornea
Higher-order aberrations/ Coma	↓	↓↓	↓↓

Table 2. Utility of corneal crosslinking (**CXL**), wave-front guided (**WG**) and topography-guided photorefractive keratectomy (**TG-PRK**) and intrastromal corneal ring segment (**ICRS**) for various visual parameters in patients with keratoconus.

[a]Mean refractive indices
Δ: Change

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