CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.2549679

Available online at: http://www.iajps.com ***Review Article***

KERATOCONUS PATHOGENESIS AND THE RECENT ACHIEVEMENTS IN THERAPEUTIC OPTIONS OF THE DISEASE: A LITERATURE REVIEW

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Abstract:

Centuries after the most primitive descriptions of keratoconus, much about the etiology and pathogenesis of it remains a mystery. Considerable strides have been made in early discovery of the disease, as well as towards providing best possible optical and surgical correction to improve vision quality in affected patients. Scientific interest in the condition is bound to remain high in the predictable future for two major reasons. First, the impending threat of iatrogenic ectasia or unmasking of subclinical keratoconus dangles like the sword over all refractive surgeons. Secondly, recent achievements have extended the therapeutic options and exposed the potential for further innovations. Hopefully, this will also translate into safer and more effective treatments for patients.

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Please cite this article in press Eman Mohammed Alonazi et al., ***Keratoconus Pathogenesis and The Recent Achievements In Therapeutic Options Of The Disease: A Literature Review.,*** *Indo Am. J. P. Sci, 2019; 06(01)*

INTRODUCTION:

Conical cornea was describable three centuries ago. John Nottingham provided the first wide-ranging understanding of keratoconus (KC) throughout his article published in 1854. In the last two decades, the sophisticated tools for mapping the cornea contours and advances in treatment of the KC have resulted in an awesome awareness in KC and evolution of scientific writing on that issue (Rabinowitz, 1998).

Keratoconus is a progressive, essentially bilateral, symmetric disorder, though presentation may be markedly asymmetric associated with structural changes in the organization of central or paracentral corneal stroma. Patients tend to develop corneal thinning (ectasia) that leads to myopic shift and irregular astigmatism with visual impairment and corneal bulging if untreated. Disease onset is usually at youth or adolescence with a gradual progression over the first few decades. Pediatric keratoconus is more aggressive than adult keratoconus, and therapeutic approaches differ because of the structural and behavioral differences between children and adults (Kankariya et al., 2013).

CORNEAL STRUCTURE:

The avascular cornea consists of five layers: stratified epithelium and its basement membrane, Bowman's layer (BL), stroma, Descemet's membrane (DM) and endothelium. The epithelium, BL, DM, and stroma are strongly implicated in the pathogenesis of KC. The human corneal epithelium is about 50 microns thick and its basement membrane consists mainly of collagen type IV, laminin and entactin; and the major proteoglycan is perlecan. Bowman's layer is an ill-defined layer that separates the epithelial basement membrane from the stroma. It is 8-12 microns thick and its collagen fibrils interlace into the stroma. The stroma that comprises the bulk of the cornea is around 500 microns thick and consists of an extremely structured network of collagen fibrils and extracellular matrix. However, type I corresponds to 75% of the amount present in the cornea, although cornea also contains collagen types III, V, and VI regularly interwoven into lamellae, and collagen type XII in epithelium basement membrane and sub-epithelial stroma. The major stromal proteoglycans are decorin, biglycan, lumican, keratocan and osteoglycin/mimecan. In KC there are diminished amounts of types I, III, V, and XII collagen, as well as lumican and keratocan proteins (Klyce, 2009).

EPIDEMIOLOGY:

Epidemiology of KC is derived mostly from hospital-based data. The reported incidence ranges between 50 and 230 per 100,000, and the estimated prevalence is 54.5:100,000 per year across different populations. KC occurs in all ethnic groups with no gender preponderance. However, investigations of hormonal differences note that the disease develops earlier and involves more rapid progression in males than females suggesting androgenic dependence (Millodot et al., 2011).

Studies reported a significantly higher incidence and prevalence in Asians compared with whites, suggesting the influence of ethnicity and genetics on the disease. (Hashemi et al., 2013) further reported that in Iran, non-Persian populations (such as Arabs, Turks and Kurds) had three times the prevalence of Persian ethnic populations.

Epidemiologic reports document a wide prevalence range explained by differences in geographical situation, populations studied, and diagnostic criteria used in the investigations. Authors have suggested that differences in exposure to ultraviolet light, according to latitude in the terrestrial globe could explain differences in prevalence (Jonas et al., 2009).

The onset of KC is generally during puberty, which may progress until the third or fourth decade of life, when the corneal shape generally becomes stable. Rarely, it may be congenital (Nielsen et al., 2007).

AETIOLOGY AND PATHOPHYSIOLOGY:

Keratoconus is likely to be a multifactorial, multigenic disorder with complex inheritance patterns, probably triggered by environmental factors: a 'two-hit' hypothesis. As many pro-inflammatory molecules have been associated with KC, a genetic predisposition to abnormalities of any of these inflammatory components triggered by external factors (contact lenses, eye rubbing, or exposure to ultraviolet light) may constitute the disease. As recently proposed, epigenetics (changes in gene expression) seems to have an important role in this complex disease etiology. Considering all these concepts, the pathophysiologic components of KC can be largely classified into the following: imbalance of pro-inflammatory and anti-inflammatory mediators, imbalance of the enzymes that degrade extracellular matrix and their corresponding inhibitors, oxidative stress, cellular hypersensitivity and changes of the stromal composition. These events occur simultaneously and causality between them may occur (Lema and Duran, 2005).

Recent studies found evidence of inflammatory markers, and cytokines in the tears of patients with KC. According to cell cultures of keratocytes from normal corneas and that with KC, Pouliquen and colleagues suggested that cytokines, IL-1, tumor necrosis factor-α (TNF-α), TGFβ, IL-6, IL-8, and PDGF, may regulate a protease cascade concerning the plasmin system (including: tissue plasminogen activator (t-PA), urokinase-type plasminogen activator (u-PA), and plasminogen activator inhibitor), cyclooxygenase, and metalloproteinases (MMPs). t-PA converts plasminogen to plasmin, which causes fibrinolysis. However, plasmin activates collagenases and it is related to fibroblast collagen synthesis inhibition by PGE2 (Bauman et al 2010). Cyclooxygenase, which converts arachidonic acid into prostaglandin E2 (PGE2) was significantly increased in keratocytes from KC (a 10-fold increase in the maximum reaction rate (Vmax)), and hence basal PGE2 level was 10 times greater than in keratocytes from normal corneas. In addition, the ketatoconic cells exhibited a very strong effect of t-PA and u-PA on the secretion of PGE2. PGE2 has antifibrotic effects via inhibition of major pathobiologic functions of fibroblasts including chemotaxis, proliferation, collagen formation, and differentiation to myofibroblasts (Jun et al., 2011).

Tear film proteomics showed decreased levels of lactoferrin, and secretory IgA in KC compared with control tears. Lactoferrin and IgA seem to have the greatest effect on KC because of their immunomodulatory, antimicrobial and anti-inflammatory roles (lactoferrin inhibits IL-1, IL-2, IL-6, and TNF-α; IgA inhibits the immune response). Decreased levels of lactoferrin, IgA, ZAG (zinc- α2-glycoprotein), and IGKC (immunoglobulin κ-chain) have also been noticed in tears of keratoconic eyes (Acera et al., 2011, Balasubramanian et al., 2012).

The mechanical effect may have a role, causing an increase in both corneal temperature (secondary to friction with the conjunctiva) and intraocular pressure. (McMonnies et al., 2012). In 2013, it was stated that eye rubbing increased the level of tear MMP-13, IL-6, and TNF-α in both normal and keratoconic eyes. Consequently, persistent eye rubbing might cause a sustained increase in the levels and activity of these cytokines (Balasubramanian et al., 2013).

Intercellular adhesion molecule 1 (ICAM-1), vascular adhesion molecule 1 (VCAM-1), IL-6, and MMP-9 were overexpressed by 2–40 times, while anti-inflammatory marker IL-10 was expressed 8 times less in keratoconic eyes wearing contact lenses compared with normal myopic ones. A relative increased levels of cathepsin B and decreased levels of α-fibrinogen, cystatin SN, and cystatin S were noticed in the tears of patients with KC, denoting that tear proteins differentially expressed in KC including increased proteases and decreased protease inhibitors. Cystatins are inhibitors of cysteine proteases (thiol proteases), which degrade proteins. In concordance with findings by (Balasubramanian et al., 2013) in tears, lysosomal cathepsin B and cathepsin G have been increased in keratocytes of keratoconic corneas, compared with normal tissue. Jun and colleagues studied T-helper 1 cell cytokines (IL-12, IFN-γ, and TNF-α), T-helper 2 cell cytokines (IL-4, IL-10, and IL-13), and T-helper 17 cell cytokines (IL-17) in serum and tears of subjects with KC. The affected corneas had higher levels of IL-1α, IGF-1 (insulin-like growth factor 1), TNF-α, and TGF-B1 (TGFβ-1) than normal corneas, and lower levels of B-NGF (β-nerve growth factor). It is well established that IL-1α and TNF-α induce keratocytes apoptosis, and may develop collagen turnover. Neutrophil-to-lymphocyte ratio (NLR), represents a prospective predictor of systemic inflammation. Karaca and colleagues noticed that there was a positive correspondence between NLR and progressive KC, and accordingly concluded the relationship between the progressive KC and increased systemic inflammation (Davidson et al., 2014).

MMPs, a cluster of endopeptidases that contain gelatinases (MMP-2 and -9), collagenases (MMP-1, -8, and -13), stromelysins (MMP-3 and -10), and matrilysins (MMP-7 and -26) synthesized by corneal epithelium and stromal cells, have been suspected to have a major role in KC (Mackiewicz et al., 2006).

It was noticed that the decreased collagen amount and increased its solubility in keratoconic eyes due to significantly more collagenase and gelatinase activities. Recently, LOX (lysyl oxidase) is an amine oxidase that oxidates peptidyl lysine and hydroxylysine molecules in collagen and lysine present in elastin, generating peptidyl-aminoadipic-δ-semialdehydes. These can instinctively combine with nearby aldehydes or epsilon amino groups of peptidyl lysine, creating covalent unions that stabilize collagen and elastin fibers making them insoluble.136 In 63% of cases of KC, LOX distribution and activity have been markedly decreased 2.5 times lower than that of control cases (Pannebaker et al., 2010).

Notably, cornea neutralizes free radicals and oxidants (ROS/RNS) resulted from cellular metabolism and ultraviolet light exposure by potent enzymes such as

superoxide dismutase 1 (SOD 1), glutathione peroxidase, nicotinamide adenine dinucleotide phosphate, and catalase, plus antioxidant molecules (a-tocopherol, ascorbate, ferritin, and proteoglycans). Catalase is the major pathway through which the cells dispose of excess hydrogen peroxide (Cheung et al., 2014, Cheung et al., 2013). Lack of these molecules increases the levels of ROS and RNS damaging the DNA and the mitochondrial respiratory chain, denaturating proteins, causing lipid peroxidation, which further generation of free radicals. Keratoconic corneas have decreased glutathione content and total antioxidant capacity. Furthermore, in vitro studies of KC have shown that IL-1α decreased the synthesis of the SOD (Lema et al., 2009a, Lema et al., 2009b).

Previous studies demonstrated that keratocytes from keratoconic eyes have fourfold increase of IL-1 receptors, than normal keratocytes. It was hypothesized that keratoconic keratocytes had increased sensitivity to IL-1 released from the corneal epithelium. Interleukin-1 induces keratocyte death in vitro and depresses chemotaxis, and it can upregulate keratinocyte and hepatocyte growth factors (HGF). It can also regulate the expression of keratocyte metalloproteinases, collagenase and complement factors along with production of IL-6 in keratocytes. This hypothesis interpretes the incidence of KC in relation to eye rubbing, contact lens wear, and atopy, if it is supposed that epithelial microtrauma leads to an increased release of IL-1 (Wojcik et al., 2014a, Wojcik et al., 2014b).

GENETICS:

Habitually keratoconus is an isolated disorder; however, associations with vernal keratoconjunctivitis, atopy, Down syndrome, retinitis pigmentosa, Leber congenital amaurosis, hard contact lens wear, mitral valve prolapse and connective tissue disorders, such as Marfan and Ehlers–Danlos syndromes, have been reported but a cause and effect link is often difficult to set up. Some associations may spot towards a common genetic cause; others may cause corneal ectasia by repeated mechanical trauma. The central corneal thickness (CCT) may be a genetic trait as proved by a recent genome analyses that identified multiple loci which confer vulnerability to low CCT and keratoconus (Gordon-Shaag et al., 2015). Genetic heterogeneity rather than a single gene is responsible for KC. Exclusively; two small nuclear polymorphisms were identified risky for KC: FOXO1and FNDC3B. FOXO1 regulates the TGF-β pathway, which is involved in the pathogenesis of KC. Moreover, unaffected relatives of KC patients may have abnormal videokeratography indices. As a result these relatives may undergo a silent subclinical KC. Additionally; evidence for genetics comes from population based studies as KC is more frequent in definite ethnicities than in others (Rabinowitz, 2003).

Genetics also explain the autosomal dominant inheritance found in certain families, and among monozygotic twins. On the other hand, consanguinity has been linked with a higher risk of keratoconus. The huge number of loci more than simple Mendelian genetics is involved in keratoconus. Furthermore, (Adachi et al., 2002) described HLA-A26, B40 and DR9 antigens to be more frequent in pediatric keratoconus compared to adults. Therefore, HLA haplotype could provide a familial marker for keratoconus. Also, genetic allergic conjunctival diseases and consequent eye rubbing has been associated with KC progression (Caputo et al., 2016).

Even with the meticulous genetic research in keratoconus over the past decades, only few genes have been reported: VSX1 (locus 20p11.2) (visual system homeobox 1), miR-184 microRNA, and DOCK9 (locus 13q32) (dedicator of cytokinese 9). Since the primary report in 2002, mutations in VSX1 have been associated with keratoconus and other corneal dystrophies (Abu-Amero et al., 2011). Recently, a mutation altering the miR-184 region was recorded in a family with keratoconus and anterior polar cataract as miR-184 has been reported to be highly expressed in the cornea and lens. DOCK9 (Dedicator of cytokinesis 9) is a powerful candidate gene for keratoconus as mutations in it were reported through sequencing candidate genes in a linkage locus, (13q32) that was reported to segregate under an autosomal dominant manner by (Gajecka et al., 2009) in Ecuadorian family.

Several genes with recorded mutations such as SOD1 (locus 21q22.11) which regulates the expression of superoxide dismutase (SOD) and LOX (locus 5q23.2), gene encoding lysyl oxidase (LOX) enzyme, have also been related to keratoconus.57 Single-nucleotide polymorphisms in the hepatocyte growth factor (HGF) gene and has been associated with keratoconus suggesting the impending contribution of inflammatory pathway. In KC, the genes encoding collagens type I, III, IV, V, VI, VII, and VIII have been identified as new markers on the telomere of chromosome (Nowak and Gajecka, 2011).

HISTOPATHOLOGY:

A triad of the classical histopathology of keratoconus comprises of thin corneal stroma, breaks in Bowman's layer, and iron deposition in the basal

layers of the corneal epithelium. These details are obviously appreciated by electron microscopy. Gross histopathologic analysis of keratoconic corneas undergoing penetrating keratoplasty has discovered two types of cone morphology: "nipple"- type cones, located centrally, and "oval"-(sagging) type, located inferiorly or inferotemporally. These types of cones often can be distinguished on slit-lamp examination or anterior corneal topography (Hayes et al., 2012).

CLINICAL FEATURES:

A typical keratoconic patient presents in the teens or early twenties with blurred vision with frequent changes in refractive error. The thin cornea induces irregular astigmatism, myopia, and protrusion, causing mild to severe visual impairment. Symptoms vary according to the stage of the progression. In early KC there may be no symptoms, and only noted by the ophthalmologist basically because the patient cannot be refracted to a clear 20/20 corrected vision. In advanced KC there is considerable vision impairment accompanied by intense visual loss however, patients luckily never become totally blind from KC (Ertan and Muftuoglu, 2008).

Regarding detectable clinical signs by slit-lamp examination of the cornea, in moderate to severe KC the signs may be: thin stroma (centrally or paracentrally, most frequently inferiorly or inferotemporally; conical protrusion; a partial or complete iron line surrounding the cone (Fleischer's ring); and fine vertical lines in the deep stroma and Descemet's membrane that parallel the axis of the cone and disappear momentarily on mild digital pressure (Vogt's striae). Other associated signs may include epithelial nebulae, anterior stromal scars, enlarged corneal nerves, and increase intensity of the corneal endothelial reflex and subepithelial fibrillary lines (Kok et al., 2012).

Munson's sign and Rizzuti's sign are also valuable adjunctive external signs linked with keratoconus. Munson's sign is a V-shaped conformation of the lower lid shaped by the ectatic cornea in down gaze. Rizzuti's sign is a sharply focused beam of light near the nasal limbus, formed by lateral illumination of the cornea in advanced keratoconus. On slit-lamp examination, the conjunctiva may be injected with diffuse stromal opacity in the cornea that is referred to as "hydrops," which is caused by breaks in Descemet's membrane that allow stromal imbibitions of aqueous throughout them causing painful edema and redness that may persist for weeks or months then diminishes gradually, followed by corneal scarring. In such condition it is useful to dilate the pupil. To confirm the diagnosis in suspicious cases, retroillumination techniques and scissoring of the retinoscopic reflex or the "Charleux" oil droplet sign are extremely useful (Eghrari et al., 2015).

DIAGNOSIS:

In suspected keratoconus with normal cornea, measuring the anterior topography of the central and paracentral cornea is extremely useful to confirm the diagnosis. In its most observable form, clinically evident KC is seldom suspicious. Several procedures are now on hand for measuring anterior corneal topography ranging from simple low-cost devices, such as handheld keratoscopes (placid disks), to costly sophisticated devices, such as computer-assisted videokeratoscopes.

Placido disk studies

In 1938 Marc Amsler, was the first to describe early corneal topographic changes in keratoconus. By means of a photographic placid disk Klein keratoscope, early KC is characterized by a downward deviation of the horizontal axis of the Placido disk reflection (Maeda et al., 1994).

Photokeratoscopy

The photokeratoscope produces a topographic trace of 55–80% of the total corneal contour, but it provides nothing about the central 3 mm of the cornea. Until now, nine-ring photokeratoscopes, such as the Corneascope (Kera Corporation, Santa Clara, CA), were generally used as by it, early KC is depicted by compression of the mires inferiorly or inferotemporally (Maeda et al., 1995).

Keratometry

The ophthalmometer (keratometer), (Javal-Schiotz or Bausch and Lomb type) gives information about only 2–3 points approximately 3 mm apart, can distinguish keratoconus by screening deformation of its mires or central or inferior steepening. Whereas steep corneas may imply keratoconus, there are steep non keratoconic corneas with high degrees of regular astigmatism. In opposition, there are keratoconic patients with normal central corneal curvatures but have irregular astigmatism or inferior steepening only (Maguire et al., 1987a, Maguire et al., 1987b). The Orbscan (Bausch and Lomb, Rochester, NY, USA) utilized slit scan to supply wide-field pachymetry plus anterior and posterior elevation as well as keratometry maps. Afterward iteration, the Orbscan II, combines slit scan with Placido- topography analysis showing to be more sensitive than former devices for keratoconus detection. To discriminate keratoconus suspects from normal subjects, maximum posterior elevation in comparison to the best fit sphere (BFS), irregularity in the central 3 mm

and 5 mm zones as well as pachymetry have been found to be helpful (Pinero et al., 2010a, Pinero et al., 2010b).

Computer-assisted videokeratoscopy

Long-ago, computer-assisted videokeratoscopes have been rapidly approved clinically. It was first introduced in the 1980s. Several devices are now offered, most using placido disk ideology, although other technologies are quickly up-and-coming. Keratoconus prediction index from the Klyce–Maeda group, the KISA index by the Rabinowitz group and the Topographic Modeling System (TMS-1, Computed Anatomy, New York, NY) are some of the popular ones (Rabinowitz and McDonnell, 1989). They consist of a placido disk-type nose cone, capturing the placido disk image into a computer-based system, which can quickly evaluate data perfectly and reproducibly. Both the central and paracentral cornea can be measured in one session. This technology, which uses spherically biased algorithms (sagittal topography), has been shown to be greatly accurate and reproducible in the central two thirds of human corneas. Topographic data points using 256 radial lines scanning across 25 rings in polar coordinates are examined and approximately 7,000 data points are produced. A three-dimensional corneal mapping, including dimensions of anterior and posterior corneal surfaces, pachymetry, as well as anterior chamber angle characterization allows easy appreciation of the corneal curvature.

Modern attention has focused on understanding of corneal biomechanics in keratoconus using tools such as the Ocular Response Analyzer (Reichert Inc, Depew, NY, USA). Relative to controls, keratoconic eyes have been found to have too much higher aberrations and lesser values of corneal hysteresis and resistance factor.

Videokeratographic pseudokeratoconus represents a source of confusion in assigning minimal topographic criteria for keratoconus as videokeratography patterns simulates keratoconus. The most common cause is contact lens wear (both hard and soft), which induces inferior steepening that may be indistinguishable from keratoconus. Videokeratographic pseudokeratoconus may also result from technical mistakes during videocapturing, such as inferior eyeball compression, malalignment of the eye with inferior or superior rotation of the globe, and incomplete digitization of mires, forming of dry spots, which simulates inferior steepening. Early pellucid marginal degeneration, inflammatory corneal thinning, and prior ocular surgeries can all induce patterns simulating keratoconus by videokeratography (Quisling et al., 2006).

DIFFERENTIAL DIAGNOSIS:

It is essential to differentiate KC from other ectatic dystrophies and thinning disorders, such as, pellucid marginal degeneration, Terrien's marginal degeneration, and keratoglobus. Pellucid marginal degeneration is characterized by a peripheral thin band of the inferior cornea from the 4 to the 8 o'clock position. There is 1–2-mm unaffected area between the thinning and the limbus making the corneal protrusion most obvious above the area of thinning, and the central cornea is usually normal. Keratoglobus is a rare nonprogressive bilateral disorder that usually present from birth in which the whole cornea is thinned to as little as 20% of normal thickness, most distinctly near the corneal limbus. assuming a globular shape (Sykakis et al., 2012).

MANAGEMENT:

Optical correction (**Spectacles and contact lenses)**

In early KC, the refractive error can be managed by spectacle use. Later on, the consequent irregular astigmatism results in suboptimal visual acuity with spectacles, necessitating contact lenses use. Contact lenses are the mainstay and represent the treatment of choice in 90% of patients. Soft or soft toric contact lenses made from hydrogel or silicone hydrogel may be satisfactory for clear vision. Different lenses can be convenient depending on the type, site, and the size of the cone. However, rigid gas permeable lenses are the major contact lens type in keratoconus. Moderate keratoconus necessitates application of intralimbal rigid gas permeable lenses or miniscleral lenses. Very advanced cases with large, decentered cones, dry eye, or embarrassment with usual lenses may be corrected with the application of scleral lenses. Other options include piggyback lenses and hybrid lenses (Barnett and Mannis, 2011).

Recently, lenses such as Rose K can be more comfortable and are more tolerable to the patient to wear over lengthy hours. These lenses offer patients more stable vision, support better corneal oxygenation, however, the risk of hypoxia still exists with difficult placing and removing technique. Patients may need special contact lenses to correct residual astigmatism after corneal grafting, cross-linking or ring implantation, but the fitting pattern can be different from that in untreated eyes. By means of the modern contact lenses now offered, patients with 20/40 spectacle correction may enjoy stable 20/20–20/25 contact lens correction for long periods. Frequent complications of lenses include lens embarrassment, induced corneal abrasion, apical

scarring and hypoxia induced neovascularization (McMahon et al., 2006a, McMahon et al., 2006b).

OPERATIONS AND THEIR INDICATIONS:

Collagen cross linking

Corneal collagen cross-linking (CXL) is a new invasive method for modifying the corneal stroma which has been approved by the Food and Drug Administration (FDA) to manage advanced keratoconus. Spoerl et al first experienced the effects of a combining of 0.1% topical riboflavin (vitamin B) as a photosensitizer and ultraviolet (UV) light at a wavelength of 370 nm for 30 minutes to crosslink corneal collagen in laboratory experiments. The "Dresden Protocol" is the universal protocol for standard CXL which includes debriding the entire corneal epithelium, then dripping riboflavin onto the anterior stroma. Consequent exposure to UV generates free radicals that crosslink adjacent collagen molecules and harden the cornea against additional ectasia. It is appropriate for minimum corneal thickness of 400 mm (Soeters et al., 2014a, Soeters et al., 2014b). However, a hypo-osmolar riboflavin solution is appropriate for thinner corneas as it causes artificial swelling of them, transepithelial crosslinking by diverse compounds planned to improve riboflavin penetration. Two other approaches for CXL are the epithelium-off and epithelium-on methods. The first one relies on the Dresden protocol and can lead to corneal stromal inflammation, opacity and pain (Theuring et al., 2015). The epithelium-on approach is a tailored technique in which no epithelial debridement is done but it should be avoided in dry eye or very thin corneas. Recently, accelerated CXL is used where the UV irradiation time is reduced by increasing the intensity of the irradiance to save time.55 CXL can be done alone or in combination with photorefractive keratectomy (PRK), laser assisted in situ keratomileusis (LASIK), Intacs, thermal keratoplasty, and orthokeratology for better results. A better technique in children is trans-epithelial cross-linking,"no touch" protocol, because of considerable decrease in treatment time and facility to carry out under topical anesthesia. The main aim was to decrease postoperative pain and infection. However, the epithelium prevents riboflavin and UVA light penetration (Ivarsen and Hjortdal, 2013).

Recorded complications of collagen crosslinking include bacterial, fungal, acanthamoeba, sterile keratitis and rarely corneal melting. Risks of typical cross-linking comprise abrasion-related discomfort, corneal haze, scars, blepharitis and mild photophobia. Epithelial stripping is complicated with severe pain, temporary visual loss, stromal haze and infections. Kymionis and colleagues reported significant endothelial cell loss after crosslinking in thin corneas. Furthermore; progression of KC after cross-linking is mainly linked to persistent eye rubbing and/or vernal keratoconjunctivitis (Wise et al., 2016).

Intrastromal corneal ring segment

Intrastromal corneal ring segments (ICRS) that are made of polymethyl methacrylate (PMMA) are fixed deep in the stroma to decrease the corneal curve. ICRS deal with myopia and keratoconus with different mechanisms. In myopia, they flatten the cornea improving vision, while in KC, ICRS decrease corneal distortion by flattening the steep area with favorable outcomes. ICRS implantation is indicated in severe reduction of visual quality, reduced vision with spectacle or lens correction, minimum age of 21 years, clear central corneas, minimum corneal thickness of 400 mm. Rings are contraindicated in central corneal scarring, or hydropsis. Four types of ICRS are offered for keratoconus: 1) Intacs (Addition technology Inc.) 2) Intacs SK (Addition technology Inc.) (Severe Keratoconus), 3) Ferrara Rings (Ferrara ophthalmics) and 4) Keraring (Mediphacos). Intacs and Ferrara rings are the most commercially available ICRS. Intacs is available in 150 arc length segments with a hexagonal cross-section and various sizes ranging from 0.210 to 0.450 mm which are chosen based on the amount and type of refractive errors. 80 For Intacs insertion, the canal can be created mechanically or with laser femtosecond at a depth of 70-75% of the minimum pachymetry at the insertion site. Some studies have reported good visual results using the mechanical method, but it can be associated with epithelial defects, shallow placement of the segments, stromal thinning, and edema (Pinero and Alio, 2010).

So, combining Intacs with CXL is suggested in moderate to severe KC with minimum corneal thickness of 450 mm. Also, irregular astigmatism is reduced, with improved visual acuity by 60% with decreased corneal curvature. To achieve maximal flattening, ICRS should be implanted before or simultaneously with UV-CXL. However, the opposite (UV-CXL, then later ICRS) limits the flattening effect of the segments because the cornea has been already fixed into a sub-optimal configuration. A significant advantage of ICRS is the procedure's reversibility as the rings may be re-inserted at a later time.

However, complications can occur during or after surgery. Intraoperative complications are rare, and are usually related to creating the corneal tunnel,

insufficient tunnel depth, asymmetry or decentration, or bowman's layer perforation (Theuring et al., 2015)

Penetrating keratoplasty (PK)

The major progress in Penetrating keratoplasty (PK) has been the introduction of the femtosecond laser to cut the recipient and donor tissues to theoretically provide better apposition and quicker curing. After PK for advanced KC, final uncorrected visual acuity (UCVA) ranges from 20/50 to 20/100, with just over 40% of patients reading 20/40. (Reeves et al., 2005) Spectacle correction gives better results with a mean acuity (best spectacle corrected visual acuity, BSCVA) of 20/30e20/40. These gains may move away over time owing to increasing irregular astigmatism in the graft that cannot be correct with spectacles. So, CLs may be required postoperatively for some patients. Because vision doesn't stabilize until at least 12 months after surgery, a primary restriction to PK is the delay in achieving visual results (Gordon et al., 2006).

Deep anterior lamellar keratoplasty (DALK)

There are two basic currently practiced strategies of deep anterior lamellar keratoplasty (DALK) techniques: the Anwar big bubble and the Melles manual dissection. The big bubble technique is ingrained in Anwar's 1998 discovery that an intrastromal injection of balanced salt solution (BSS) was often successful in performing a cleavage plane just above DM. In 2003, he developed the technique to apply air instead of BSS establishing the "big bubble" technique (Anwar and Teichmann, 2002). In contrast, Melles manual dissection is more particular. Initially, the anterior chamber is filled with air followed by using a series of curved spatulas to dissect away the anterior stroma from the underlying DM. The accurate depth of dissection can be determined by using the air endothelium interface: When the anterior chamber is filled with air, a reflected image of the tip of the dissecting spatula appears. The distance of reflection from the spatula represents the depth of the dissection, so that the deeper the dissection, the closer the reflection to the tip of the instrument. Therefore, a controlled dissection down to the level of DM is probable (Basu and Sangwan, 2011a, Basu and Sangwan, 2011b).

Bowman layer transplantation

Bowman layer (BL) transplantation is a novel surgical technique. Its idea is that an isolated BL inlay for eyes with advanced KC aiming to graft an isolated BL in the mid-stroma to improve corneal constancy and stop KC progression. The graft is prepared by manual peeling of the BL from the donor anterior stroma corneoscleral rim. The procedure begins by securing a corneoscleral button atop an artificial anterior chamber, debriding the epithelium by surgical spears, then dripping Trypan blue over the anterior corneal surface. After scoring a circular area, 9.0-11.0 mm in diameter with a 30-g needle, McPherson forceps are used to peel the BL away from the underlying stroma using small circular movements. Because the layer is acellular, it is physically tough and suitable to gentle handling despite being only 10-15 mm thick. Once detachment is complete, a Bowman roll forms suddenly, owing to the natural elastic features of the tissue itself. The graft is then flooded in 70% ethanol to remove any persistent epithelial cells, rinsed with BSS, and then preserved in tissue culture prior to transplantation (Sharma et al., 2018).

The early stages of the operation mimic Melles manual DALK. After creating a side port at either the 3- or 9-o'clock position, the anterior chamber is packed with air. A 5-mm frown-shaped scleral incision is designed at 12-o'clock, 1-2mm outside the limbus, and tunneled just inside the clear cornea. Afterwards, Lamellar dissection using the same set of curved spatulas used in the Melles manual DALK technique is performed. Again, the air-endothelium interface is used to determine stromal depth, except that for BL transplantation the intended depth is 50%, rather than the 99% aimed for with DALK. The reason for this divergence is that BL transplantation is commonly performed in particularly thin cornea and by aiming at a mid-stromal dissection, the chances of unintentional anterior or posterior corneal perforation may be minimized. In the majority of patients KC progression is under control, and functional vision is enhanced. Possible complications include DM perforation which is observed in about 6% of patients, and in such cases, PK or DALK may be used (van Dijk et al., 2015).

Epikeratoplasty

Epikeratoplasty restrictly gained approval as a mode of treatment for keratoconus with a clear visual axis in certain high-risk circumstances. For example, keratoconic patients with Down syndrome, because of its noninvasive nature and the decreased possibility for corneal graft rejection.

Conductive keratoplasty and new microwave procedure

Conductive keratoplasty (CK) is a tissue-saving non-invasive technique where no laser or incisions are involved. In its place, radio wave (350 HZ) energy is applied to the corneal stroma at 8-32 points. As a result of the generated heat, tissue temperature rises up to 65 ^{o}C which causes corneal remodeling through

everlasting collagen shrinkage, corneal steepening in flat regions, and correction of refractive errors. In this way, it may also be helpful for thin corneas since no tissue is removed,.167,168 This method was FDA approved in 2002 and can be used for the correction of low and moderate hyperopia (+0.75 to +3.00 D) and astigmatism less than 0.75 D. However, CK needs to be combined with other options, or the surgeon may need to apply more spots in flat areas to be effective for high astigmatism and keratoconus. Using topography-guided conductive keraoplasty (TGCK) in advanced keratoconus, Kato et al. observed visual improvement at 12 months after surgery in 70% of the eyes. Therefore, TGCK is recommended for non-progressive advanced keratoconus in patients refusing contact lenses (Kato et al., 2010).

Other surgeries

In cases of non progressive keratoconus, spherical and toric implantable collamer lenses (ICLs) have been used to reduce the spherical refractive error, leading to an improvement visual acuity. The use of ICLs is absolutely contraindicated in angle closure disease and diseased corneal endothelium (Hashemian et al., 2013). Eyes with high irregular astigmatism may be unsuitable for toric ICL implantation, due to difficult calculation of axis of placement and the induced higher order aberrations leading to unpredictable outcome (Izquierdo et al., 2011).

GENE THERAPY:

Genome studies discovered highly complex genetic factors associated with keratoconus. In gene therapy, the gene of interest is delivered into the target cell using a vector and genetic expression begins with protein synthesis. Gene therapy can be a very promising and successful way to change the pathway of KC upon identifying pathogenic genes and changing the structure of cell proteins.

DISCLOSURE:

The author reports no conflicts of interest in this work

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