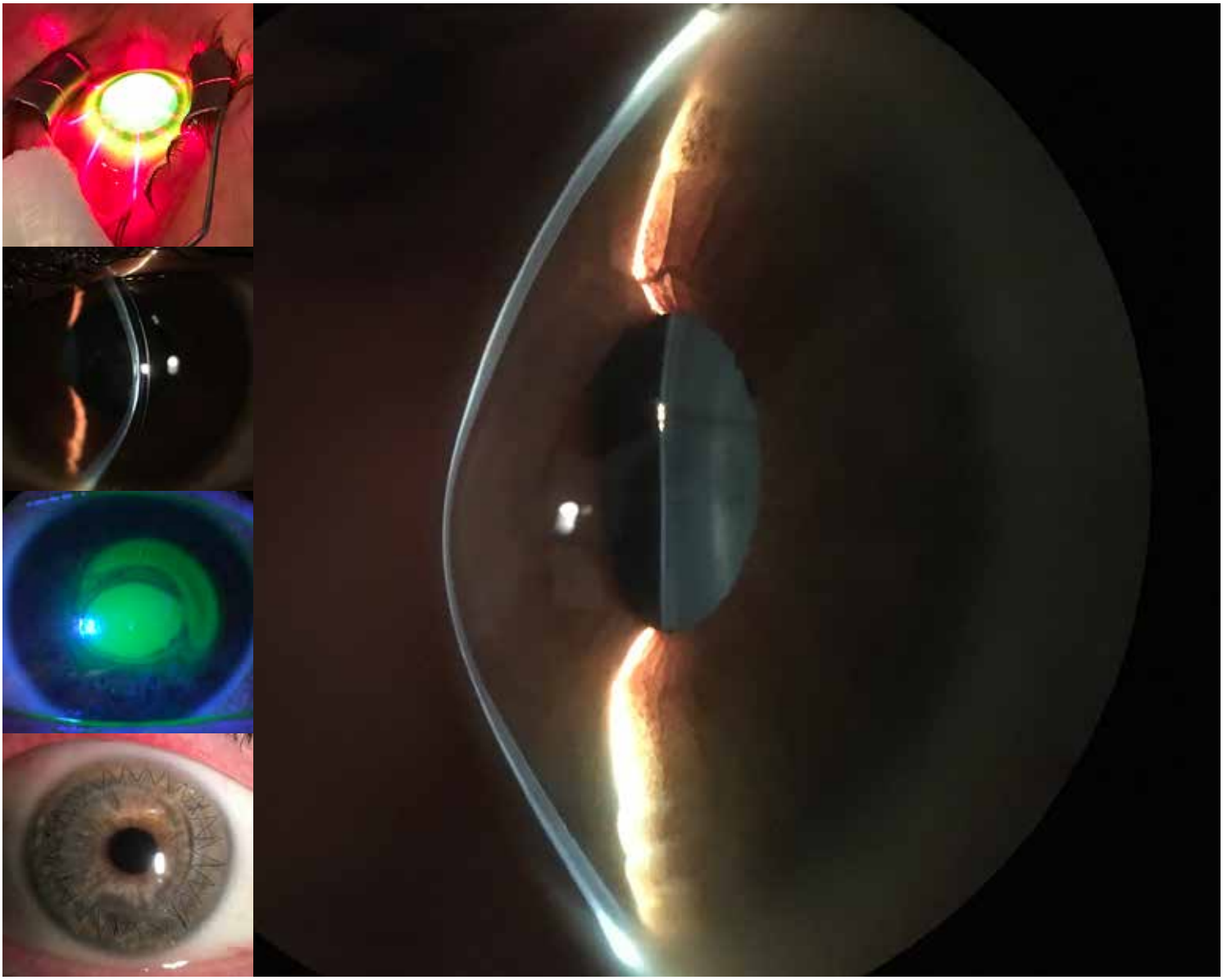
KERATOCONUS 2023

A COMPREHENSIVE GUIDE TO THE MODERN MANAGEMENT OF KERATOCONUS



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The Modern Management of Keratoconus

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John D. Gelles, OD, FAAO, FIAOMC, FCLSA, FSLS, FBCLA
Steven A. Greenstein, MD
Peter S. Hersh, MD

To our colleagues,

Following the success of the *Scleral Lens Education Initiative*, it was clear that focused supplemental guides are of value to practitioners. With this in mind, it is our distinct honor to create this comprehensive document on keratoconus (KC). We have assembled a group of internationally respected experts in the field of KC to discuss all aspects of the condition, from diagnosis to management. Although this publication has the greatest relevance for the United States, it will have applications to caring for patients affected by KC in any country.

The management of KC has changed drastically with the introduction of corneal crosslinking (CXL) as a treatment to slow or halt disease progression. Contemporary KC management has a new mantra that hinges on the ability to diagnose the disease as early as possible with advanced techniques. The comprehensive approach to KC is to halt disease progression with CXL, improve vision with medical contact lenses, and consider surgery to improve the corneal contour.

Additionally and most importantly, successful KC management is a collaborative effort among eye care providers. This is reflected in the selection of our authors, a collective of experts ranging from clinicians to researchers, and our two guest editors, Dr. Steven Greenstein and Dr. Peter Hersh.

Thank you for taking the time to read this comprehensive document. We hope you find it helpful in delivering the best care for individuals afflicted with KC.

Melissa, John, Steven, and Peter

DR. MELISSA BARNETT is a Principal Optometrist at the University of California, Davis Eye Center in Sacramento and Davis, California. She is an internationally recognized key opinion leader, specializing in dry eye disease, specialty contact lenses, keratoconus, and presbyopia. Dr. Barnett lectures globally and publishes extensively on topics including dry eye, anterior segment disease, contact lenses, presbyopia, and creating a healthy balance between work and home life for women in optometry. She is Immediate Past Chair of the American Optometric Association Contact Lens and Cornea Section, a Fellow of the American Academy of Optometry, a Diplomate of the American Board of Certification in Medical Optometry, a Fellow and Global Ambassador of the British Contact Lens Association, serves on the board of the Gas Permeable Lens Institute and the International Society of Contact Lens Specialists, and is the Past President of the Scleral Lens Education Society. Drs. Melissa Barnett and Lynette Johns authored and edited the book *Contemporary Scleral Lenses: Theory and Application* with the unique perspectives and contributions of international experts. Dr. Barnett most recently chaired the BCLA CLEAR report on scleral lenses. She is currently serving on the Tear Film & Ocular Surface Society (TFOS): A Lifestyle Epidemic Ocular Surface Disease Workshop. Dr. Barnett was awarded the inaugural Theia Award for Excellence for Mentoring by *Women in Optometry*. She was granted the Most Influential Women in Optical from *Vision Monday* in 2019. Dr. Barnett and Dr. Tom Arnold are co-hosts of the popular podcast GlobalEyes. In her spare time, she enjoys cooking, yoga, hiking, and spending time with family.

DR. JOHN D. GELLES is the Director of the Specialty Contact Lens Division of the Cornea and Laser Eye Institute and the CLEI Center for Keratoconus in Teaneck, New Jersey. He is an Assistant Clinical Professor at Rutgers New Jersey Medical School in the Department of Ophthalmology and Visual Sciences and an Adjunct Clinical Professor at the State University of New York College of Optometry, Illinois College of Optometry, and New England College of Optometry. He is a Fellow of the American Academy of Optometry, Scleral Lens Society, Contact Lens Society of America, British Contact Lens Association, the International Academy of Orthokeratology and Myopia Control, and a PROSE Clinical Fellow. In addition, he is a Board Member of the Contact Lens Society of America, an Executive Board Member and Education Chair of the International Keratoconus Academy, an Advisory Board Member for the Gas Permeable Lens Institute, the Education Chair of the Intrepid Eye Society, the Chair of Refractive Surgery Alliance's Collaborative Care Section, and serves on the American Academy of Optometry's Innovations Council. His clinical work is dedicated exclusively to specialty contact lenses for managing keratoconus, corneal disease, ocular surface disease, and post-surgical corneal conditions. Additionally, he is a clinical investigator for multiple keratoconus and specialty contact lens-related clinical trials at CLEI.

DR. STEVEN A. GREENSTEIN received his medical degree from the Albert Einstein College of Medicine. After completing a one-year pre-residency research fellowship, he graduated with a unique distinction in clinical research, concentrating on keratoconus and corneal crosslinking. In addition, he completed an Ophthalmology Residency at Rutgers New Jersey Medical School and a Cornea, Refractive, and External Disease Fellowship at Harvard Medical School. He is an Assistant Clinical Professor at Rutgers New Jersey Medical School and an Associate Team Ophthalmologist for the New York Jets. Dr. Greenstein specializes in keratoconus and corneal and refractive surgery. His research interests include surgical treatment for keratoconus and novel techniques for corneal surgery. He is also involved in several clinical research studies designed to evaluate the safety and efficacy of new therapies and methods for keratoconus and refractive procedures. He has published many articles in prestigious medical journals; many of these papers are considered landmark papers out of the U.S. on crosslinking. In addition to publications, he has presented at numerous scientific meetings on keratoconus-related research. He has co-authored several book chapters with Dr. Peter Hersh on corneal collagen crosslinking for keratoconus and corneal ectasia.

DR. PETER S. HERSH graduated from Princeton University and received his medical degree from Johns Hopkins Medical School. He completed his ophthalmology residency and subspecialty training in corneal surgery at Harvard Medical School. After serving on the full-time Harvard ophthalmology faculty for several years, Dr. Hersh founded The Cornea and Laser Eye Institute, dedicated to clinical care and research in cornea and refractive surgery. In 2002, he founded the CLEI Center for Keratoconus, a subspecialty center focused on keratoconus. Dr. Hersh is also a Clinical Professor of Ophthalmology and Chief of Cornea and Refractive Surgery at Rutgers Medical School and a Visiting Researcher at Princeton University. Dr. Hersh has written 100 peer-reviewed research publications and four textbooks. Notably, he was lead author of the clinical study that led to the first FDA approval of laser vision correction in the United States in 1995. More recently, Dr. Hersh served as medical monitor and was lead author of the studies leading to FDA approval of corneal collagen crosslinking for keratoconus. Dr. Hersh has been selected for Best Doctors in America for over 20 years running and is the Team Ophthalmologist for the New York Jets.

Keratoconus Prevalence

By Emilio A. Torres-Netto, MD, PhD,[*†‡] Andrew Morgenstern, OD, FAAO, FNAP, [‖,**] Mark Hillen, PhD,[†] Nikki Hafezi, MAS, IP, ETHZ,[†] and Farhad Hafezi, MD, PhD, FARVO[*†‡,§,¶]

Historically, keratoconus (KC) was treated with rigid contact lenses and keratoplasty, but since the introduction of corneal crosslinking (CXL), in combination with post-treatment medical contact lenses over 20 years ago, KC has a relatively straightforward and effective treatment that can slow, or in most cases halt, disease progression and preserve high-quality vision. However, as CXL simply halts the disease at the stage it was at the time of intervention, this means that loss of vision before that point normally remains lost.[1] Accordingly, early screening, identification, and treatment are essential in order for people to retain as much vision as possible. Understanding the true prevalence of KC in the population can help practitioners be more aware of the potential for their patients to present with the disease and enable them to be treated as soon as possible.

Historic Keratoconus Prevalence Studies

The true prevalence of KC has historically been poorly characterized. Part of the reason for this is a study published in 1986 by Kennedy et al.,[2] which found a KC prevalence of 0.054% in the population of Rochester County, Minnesota.

Contemporary studies also found relatively low KC prevalence in Finland[3] and the Ural mountain region of Russia.[4] However, the issue at the time was the quality of technology available to screen for KC. Ophthalmic clinics today often have access to corneal topographers/tomographers (particularly in clinics that perform refractive or cataract surgery), which can detect the presence of the disease at earlier, preclinical stages, but the technology used in the 1980s studies was far less sensitive. For example, the Kennedy et al.[2] paper (which involved patients with a KC diagnosis made between the years 1935 and 1982) simply used scissor movement in retinoscopy or manual keratoscopy; later, they used keratometry as the method of diagnosing KC.[2] It should be no surprise that more recent publications that employed Scheimpflug technology/corneal tomography have found higher prevalences of KC.[5]

FIGURE 1. Published general population keratoconus prevalence values

Current Understanding of Keratoconus Prevalence

The prevalence of KC varies by geographical location (Figure 1) and also by race. KC prevalence has been found to be relatively low in Northern Europe, North America, Western Russia, and Japan,[2-4,6-9] whereas its prevalence is considerably higher in Australia,[10] India,[11] China,[12] and the Middle East.[13-17]

In 2018, Torres-Netto et al. published the first results from Saudi Arabia of the K-MAP Study, which used Scheimpflug corneal tomography to determine the prevalence of KC in people aged 6-21 years.[18] The study found a prevalence of 4.79% or 1:21, which is the highest KC prevalence reported to date.[18] A recent meta-analysis that included more than 50 million individuals from 15

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countries estimated that the prevalence of KC was 138/100,000.[19] Currently, with a multicenter effort from countries on all continents, the above mentioned study group is collecting and evaluating thousands of corneal tomography data as part of the K-MAP Study effort to define the global prevalence of KC.

A potential reason for regional differences in prevalence may be climate. It has been hypothesized that the corneas of those living in hotter and drier regions of the world are exposed to greater amounts of ultraviolet light, and this, combined with nutritional and ethnic differences in these regions, may drive the increased KC prevalence found there. Despite this, there has been no concrete evidence of such to date. In terms of ethnic background, the Dundee University for Scottish KC Study (DUSK) found that in Scotland, the KC prevalence was 5% in those with a Caucasian origin, but it was 25% for the subgroup of participants with Asian heritage.[20]

Other Factors that Predispose for Keratoconus

KC has been associated with atopy and eye rubbing, although whether eye rubbing alone is sufficient to cause KC, or if it simply reveals or exacerbates KC in an already weakened cornea, is still a matter of debate.[21-24] Several systemic disorders have been associated with KC, including Down syndrome, Leber congenital amaurosis, and several connective tissue disorders.[25] Systemic estrogen levels may alter corneal biomechanical properties and predispose people to developing KC, as the high estrogen levels during pregnancy can degrade corneal biomechanical strength and reduce the thickness of the cornea.[26,27] Selective tissue estrogen regulator (STEAR) therapy has been associated with the rapid progression of KC in a 49-year-old woman receiving the therapy for endometriosis.[28,29] Finally, thyroid hormone imbalance has also been associated with the development of KC.[30]

Many cases of KC are sporadic, but there is also evidence that KC is heritable in an autosomal dominant manner.[31] The prevalence of KC in relatives of people with KC is 3.34% – 15 to 67 times greater than in the general population.[32,33] The United States-based Collaborative Longitudinal Assessment of KC (CLEK) Study found that 13.5% of patients with KC had a positive family history of the disease. A study performed in France examined 94 (unrelated) patients with KC and found that 9% had clinically manifest KC, and a further 15.4% had subclinical KC, equating to estimated prevalences of 0.14, 0.03, and 0.10 among parents, offspring, and children, respectively.[34] The familial correlation of KC among probands' first-degree relatives was estimated at 0.29, 0.49, and 0.55 among parents, offspring, and siblings.[34] Consanguinity is also a large risk factor for KC; one study performed in an Arab community known to have a high degree of consanguinity found that consanguinity was associated with an odds ratio of 3.96 (p=0.001) for the presence of KC. Genetic studies have identified at least 16 loci for KC.[33,35,36] Several biochemical pathways have been implicated, including those that involve matrix metalloproteinase dysregulation, oxidative stress, and apoptosis.[37]

Conclusion

Improvements in corneal imaging and mapping technology have dramatically improved eye care professionals' ability to detect KC, particularly in the early stages of the disease. This is an important development, as the non-keratoplasty treatment for KC, CXL, typically only arrests disease progression, meaning that loss of vision before the intervention tends to remain lost, underscoring the importance of early screening and treatment. As KC prevalence in some populations can be as high as 5%, the importance of identifying and treating this disease early is clear.

DR. EMILIO A. TORRES-NETTO is a cornea, cataract, and refractive surgeon trained in Brazil, the U.S., France, and Switzerland. He is engaged in the development of innovative approaches for keratoconus, crosslinking, and refractive surgeries at the ELZA Institute and the University of Zurich. He has received multiple international awards from the largest societies in ophthalmology and was named among the 50 global key opinion leaders in ophthalmology by Media Mice in 2021. In 2018, Dr. Torres-Netto was chosen as the inaugural World Winner of the International Council of Ophthalmology Award, and in 2022 he had the honor of being awarded with the José Ignácio Barraquer Medal by BRASCRS for his work and contribution to the cornea and refractive surgery field. He is a reviewer of multiple international peer-reviewed journals and serves on the Editorial Board of the *Journal of Refractive Surgery Case Reports, Oftalmologia em Foco* (Brazil), and *Ophta* (Switzerland). Dr. Torres-Netto has been appointed as an International Member of the International Society of Refractive Surgery, an affiliate to the American Academy of Ophthalmology (USA).

DR. ANDREW MORGENSTERN is a graduate of Boston University (BS) and Nova Southeastern University College of Optometry (OD, Clinical Honors), and he completed his training at the Bascom Palmer Eye Institute (BPEI) at the University of Miami School of Medicine, Department of Ophthalmology. He is a clinician at the Walter Reed National Military Medical Center in Bethesda, Maryland, with additional contract duties researching acute eye injury, blast eye injury, and vision dysfunction associated with Traumatic Brain Injury (TBI). Dr. Morgenstern is also the Director of the American Optometric Association (AOA) Clinical Resources Group that develops the AOA Evidence Based Clinical Practice Guidelines. Additionally, he has the faculty rank of Assistant Professor in the Department of Surgery at the Uniformed Services University. Dr. Morgenstern is the Co-Founder and President of the International Keratoconus Academy of Eye Care Professionals (IKA), Past President of the Optometric Cornea, Cataract and Refractive Society (OCCRS), Past President of the Maryland Optometric Association, and Chief Medical Editor Emeritus of *Advanced Ocular Care and Collaborative Eye*. Dr. Morgenstern has been an invited lecturer at the United States National Academy of Sciences Engineering and Medicine (NASEM). He is board certified by the American Board of Optometry, a Fellow of the American Academy of Optometry, and a Distinguished Practitioner and Fellow of the National Academies of Practice. He is the recipient of the 2019 Orion Award from the Armed Forces Optometric Society, as well as the 2015 Distinguished Alumni Award from Nova Southeastern University College of Optometry and the 2012 Distinguished Alumni Award from Boston University. Dr. Morgenstern is published and has lectured extensively both nationally and internationally on a variety of topics related to vision and eye care.

DR. MARK HILLEN is a senior team member of the ELZA Institute in Zurich, Switzerland, and he has an extensive academic research and publishing background. Holding a PhD in Developmental Neurobiology, Dr. Hillen has held senior positions in academia, publishing, and industry. He has worked in the field of ophthalmology for the past decade, and he has published 20 peer-reviewed academic publications and co-written four book chapters since joining the ELZA Institute.

DR. FARHAD HAFEZI is a pioneer and key opinion leader of corneal crosslinking, a professor of ophthalmology, an anterior segment surgeon, and an ocular cell biologist. Dr. Hafezi became Chairman of Ophthalmology at the University of Geneva and Director of the Geneva University Hospital Eye Clinic. In 2014, Dr. Hafezi founded ELZA Institute AG (Zurich, Switzerland), where he now works clinically. Academically, Dr. Hafezi remains a professor of ophthalmology at the University of Geneva, the University of Southern California, and Wenzhou Medical University in China, and he is the group leader of the Ocular Cell Biology Laboratory at the University of Zurich. In 2014, 2016, 2018, and 2020, he was voted by his peers onto the biennial PowerList100, a list of the 100 most influential people in ophthalmology. His work spans patient care, research and development, and teaching. Dr. Hafezi undertakes humanitarian work to help children with keratoconus by serving as an active Board Member of the Light for Sight Foundation. Dr. Hafezi also serves on several industrial advisory boards, including EMAGine AG (Zug, Switzerland), which is dedicated to bringing access to CXL technology to all.

MRS. NIKKI HAFEZI is CEO of EMAGine AG and the ELZA Institute, a partner at GroupAdvance Consulting GmbH, and Chief Strategy Officer at the Tashkent International Clinic. Her principal pursuits include business development, strategic management consulting, intellectual property and patents, strategic planning, and fundraising. Hafezi is also undertaking a PhD in corneal biology with a special focus on corneal crosslinking at the University of Antwerp, Belgium. In 2012, she co-founded Light for Sight, an international initiative that aims to recognize keratoconus early and treat the condition in children and adolescents.

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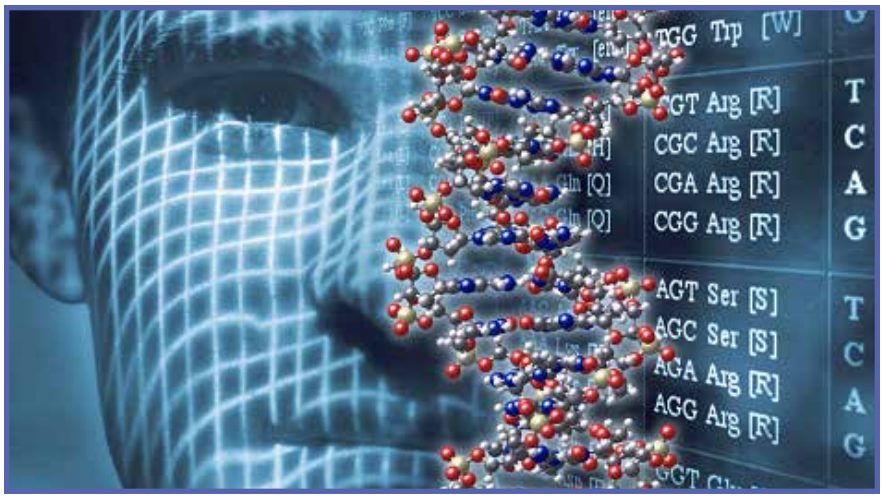
Etiology, Pathophysiology, Genetics, and Associated Disease

By Austin Yu, BA[*], Becky Su, OD[*], and Loretta Szczotka-Flynn, OD, PhD, FAAO, Dip CCLRT[†]

Keratoconus (KC) is considered to be a complex, polygenic disease with multifactorial associations that interact with the environment via inflammation, eye rubbing, allergies, or contact lens wearing among other factors. While the majority of KC patients are non-syndromic and do not exhibit other symptoms or phenotypes of other genetic disorders, certain conditions such as Down syndrome have been associated with an increased risk of KC development.[1] KC is most commonly reported to be sporadic via isolated polygenic changes, but familial linkage, twin, and consanguinity studies have also pointed toward a familial association with genetic inheritance.



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Familial Keratoconus

Studies of KC patients have shown between 5% to 27.9% of patients have a family history of KC, evidencing a need for early diagnosis and screening.[2–5] Some studies have reported KC prevalence in first-degree relatives at 3.34%, 15-67 times greater than the general population (0.05-0.23%).[6] Familial KC is most commonly seen in autosomal dominant fashion,[2,7] but autosomal recessive patterns have been reported, particularly in populations with high consanguinity.[6,8,9] Inheritance is not always represented in a classic Mendelian manner, with cases of subclinical (fruste-type), incomplete penetrance, or variant expression.[10,11] Twin studies have also substantiated the genetic basis of KC, showing that monozygotic twins have a higher concordance than dizygotic twins, with greater correlation in phenotypic presentation.[12] One study sequencing rare variants in twins found that some came from the father and some from the mother, reaffirming a familial basis of transmission.[13] Studies of regions with high degrees of consanguinity have also corroborated the genetic connection of KC. One study found that children of consanguineous parents had four times the risk of KC development compared to unrelated parents, with increased risk in parents married to first cousins compared to second cousins.[14]

Associated Disease

Despite being largely non-syndromic, KC has been commonly associated with various genetic syndromes, including Down syndrome, Marfan syndrome, osteogenesis imperfecta, Apert syndrome, Ehlers-Danlos syndrome, and Leber congenital amaurosis.[6] Down syndrome has reported one of the highest associations with KC, with incidence ranging from 0.5-15% (10-300 times greater than the general population).[15] Although the pathophysiology of Down syndrome-related KC remains unclear, some have hypothesized about collagen-related abnormalities[16]; others hypothesized about increased frequency of eye rubbing leading to the mechanical wear involved with KC.[17]

Recent literature has also explored the association between elevated glucose in patients with diabetes mellitus (DM), which can cause increased glycosylation and subsequent corneal crosslinking (CXL) of corneal fibers, potentially reducing the risk of KC and ectasia.[18–21] This theory was supported by a large

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retrospective cohort study, where KC patients were matched with controls to determine the significance certain sociodemographic factors and systemic diseases had on the odds of KC.[20] Patients with both uncomplicated and complicated DM were found to have lower odds of KC.[20] However, persons with collagen vascular disease were also found to have lower odds of KC, contrasting with other studies establishing a relationship between collagen-related pathways and the pathophysiology of KC.[18]

Other diseases found to have increased odds of KC include asthma, sleep apnea, and atopic dermatitis. Among systemic diseases, there was a 13% and 31% increased chance of KC in those with sleep apnea and asthma, respectively. Sleep apnea and asthma have also been associated with increased odds of developing severe KC, with studies reporting a 21% chance of developing severe KC in those with asthma.[21,22]

Research has also reported a hazard ratio for KC to be 3.06 in those with mild atopic dermatitis and 10.01 with severe atopic dermatitis,[23] emphasizing the strong association of atopic dermatitis and KC. One theory hypothesizes an association between KC and atopy, stemming from the inherent pruritus and subsequent increased eye rubbing, leading to a mechanical depreciation of the cornea. Studies have also explored the possibility of KC and allergic conditions being activated by the same human leukocyte antigens.[24,25]

KC affects people of all nationalities and ethnicities. However, adjustment for confounders found that Black and Latino persons had higher odds of being diagnosed with KC compared to Whites, while Asians had reduced odds compared to Whites.[21] Additionally, another study in Denmark found non-Europeans to have more than threefold higher odds of KC compared to Europeans.[26] The etiology of KC remains multifaceted with a wide array of genetic, environmental, and socioeconomic components.

Genetic Studies

As a result of the complicated genetic heterogeneity of KC, identification of specific causative genes implicated in its pathogenesis has been difficult. To date, no direct causative gene mutations have been definitively identified. However, genomic advancements over the past decade have rapidly advanced our understanding of the genetics of KC.

One early strategy implemented was the use of genome-wide linkage analyses to compare family pedigrees across multiple generations. Chromosomal regions of unaffected and affected family members are compared for differential distribution of isolated regions (loci) and corresponding genes at those locations, which are subsequently mapped via genotyping or sequencing.[27-31] These genes are labeled as candidate genes, with the goal to identify potential mutations or polymorphisms that may play a role in disease pathogenesis. The development of Next-Generation Sequencing exponentially decreased the time and cost of gene analysis, allowing for identification of rare DNA variations previously unfeasible to detect. However, the inherent genetic heterogeneity of KC limits the reliability of linkage studies. Some individuals may be phenocopies, presenting with the disease phenotype, but without the underlying genetic changes. Variability in penetration can also cloud diagnosis, as patients may have a positive genotype but not show presenting clinical symptoms. Furthermore, linkage studies map large chromosome intervals with multiple potential candidate genes to be evaluated, which requires substantial time and effort to analyze.[28]

Another approach that has expanded in recent years is the application of genome-wide association studies (GWAS), which utilize case-control cohorts with thousands of patients to analyze massive volumes of single nucleotide polymorphisms, single base-pair changes in a DNA sequence, to identify common risk variants associated with the disease/phenotype of interest. Lower central corneal thickness (CCT) has long-been established as a key risk factor for KC. Thus, initial early GWAS studies analyzed known CCT-associated loci for a relationship with KC. However, with growing databases of KC patients, starting in 2011 by Burdon et al.,[32] more GWAS studies of individual or pooled KC patients have arisen. In 2021, Hardcastle et al. published a pivotal study presenting the largest GWAS for KC to date with 4,669 cases and 116,547 controls.[19] Final meta-analysis of this study found 36 loci with significant association with KC, 31 of which were discovered for the first time by GWAS. Key genes identified in this study established a connection between genes implicated in extracellular matrix (ECM) or cell differentiation pathways and KC development. Collagen and ECM pathways are preferentially regulated by CCT-associated loci, and thus have been predicted to be involved in the population variation of CCT.

Clinical Implications

In June 2021, Avellino launched the AvaGen genetic test, releasing the first genetic screening test widely available to help determine the risk for KC and corneal dystrophies. This screen tests 70 TGFB gene variants associated with corneal dystrophies and 2,000 variants of 75 genes related to KC. Currently, no studies have yet reported long-term utility or detailed clinical applications of this novel advancement.

There are two suggested screening applications for this genetic test: screening KC suspects before refractive surgery and familial KC screening. To date, current knowledge regarding predictive modeling for post-refractive surgery ectasia is limited and lacks definitive risk assessment methods. Application of the genetic test in patients with suspect topography (i.e. high or irregular astigmatism, steep corneal curvature) or pachymetry (i.e. thin or irregular corneal thickness measurements)

may provide an additional reference point to aid in the determination of predisposition for corneal ectasia or dystrophy. Current practices have already begun implementing the AvaGen test into the decision-making algorithm,[33] utilizing genetic risk scores to stratify between stepping up/down in treatment modalities (i.e. deciding between LASIK, PRK, ICL, or withholding surgery altogether). Several studies are active to assess the genetic risk profile in the development of ectasia post-corneal refractive surgery using the AvaGen test.

The second proposed utility of this genetic test is for early familial KC screening. Families of patients diagnosed with KC may benefit from preliminary genetic screening to provide risk stratification for siblings and children of the affected KC patients. Understanding the genetic risk profile is also gaining importance in early diagnosis, which is essential for determining the urgency or need for CXL. Integrating early topographical screening with genetic screening may be pivotal in universally improving KC outcomes via early diagnosis and stabilization with CXL.

Conclusion/Future Directions

Through novel genomic testing, more positive associations between various risk factors and genes will be connected to KC. Subsequently, our understanding of associated pathways (i.e. ECM/collagen/cell differentiation) and syndromes (i.e. Down syndrome) will continue to grow and can be utilized to expand future polygenic screening to include more genes/variants as well. As our foundation of KC genetics expands, key clinical applications such as genetic risk tests may be effectively integrated into clinical practice to assist in risk stratification prior to refractive surgery, or for an adjunct to clinical decision making when considering CXL. The potential for developing predictive models for risk percentage thresholds toward guidelines for use in clinical practice leaves room for enormous growth in intertwining genomic advancements with KC management.

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Corneal Biomechanics and Its Relationship to Keratoconus

By Sabine Kling, PhD, MSc, Dipl-Ing (FH)*

The refractive performance of the eye is determined to a large extent by the corneal shape, which is governed by its mechanical properties and tissue microstructure. Structural analyses of the corneal extracellular matrix have shown that in keratoconic corneas, the originally orthogonal[1] collagen lamellae orientation is lost[2] and the collagen fibrillar mass is unevenly distributed.[2] Macroscopically, this has been associated with tissue thinning, a general deformation of the cornea into a conical shape, the rupturing of Bowman's layer,[3] and a spatially limited material weakening.[4] Bowman's layer is speculated to play a critical role in corneal stability, even though mechanical material characterization could not confirm an increased stiffness.[5] Nonetheless, corneal buttons with an intact Bowman's layer maintained a more stable curvature upon inflation than corneas with the layer removed.[6]

The origin of these structural and functional alterations in keratoconus (KC) is still controversial but most likely contains a genetic and environmental component.[7] While in diseases such as Trisomy 21, Leber's congenital amaurosis, Ehler-Danlos syndrome, and osteogenesis imperfecta, an increased susceptibility to contract KC has been reported,[8] there is no clear pattern of inheritance for KC. Still, a predisposition to an abnormal collagen metabolism seems to favor mechanical destabilization and thus the incidence of the disease. At the same time, eye rubbing is an acknowledged risk factor for KC. It appears to not directly mechanically weaken the tissue[9] but rather to trigger an inflammatory reaction stimulating an excessive degradation of the extracellular matrix.[10] In agreement with recent biochemical analyses in tear film,[11] inflammation is considered the driver of collagen loss and geometrical degradation in KC.

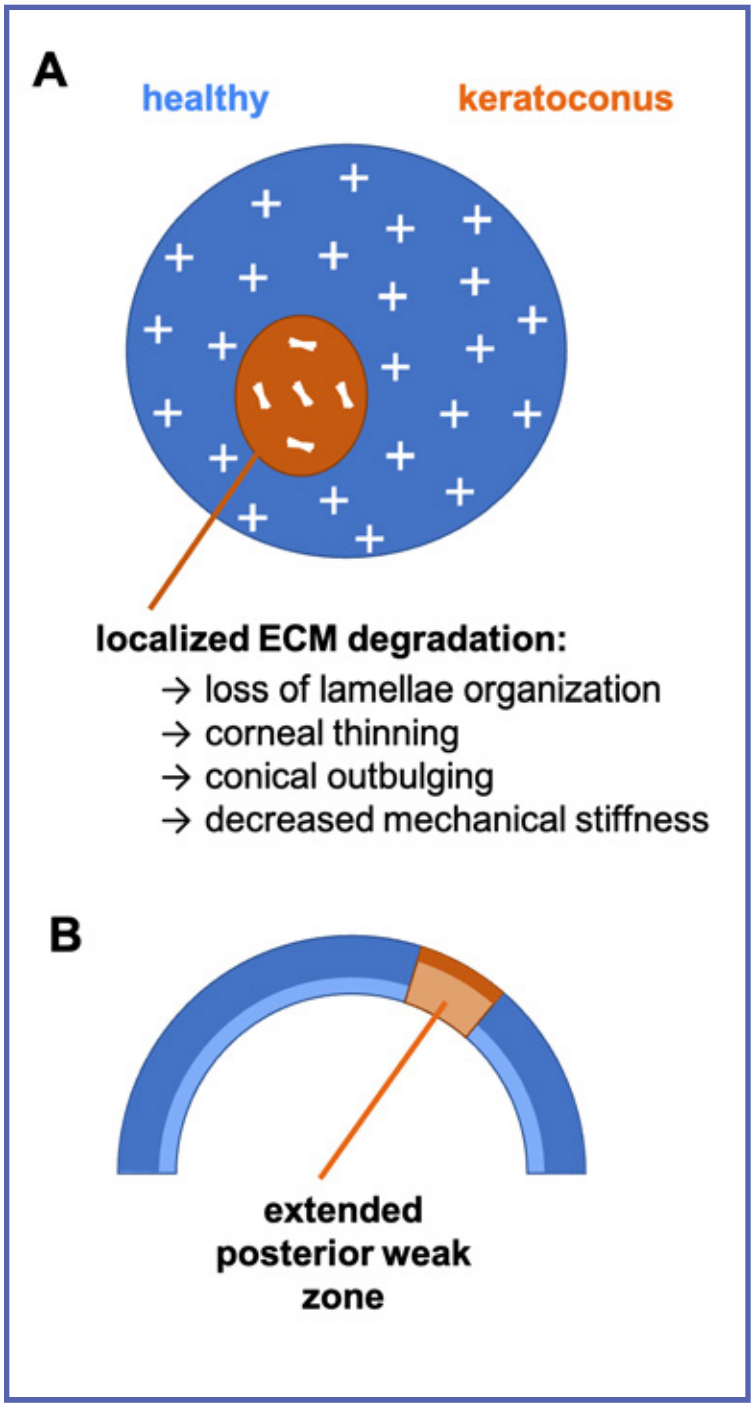

FIGURE 1. (A) Enface and (B) cross-sectional view of biomechanical alterations observed with keratoconus.

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Differences in Biomechanics Between Normal and Keratoconic Corneas

When inspecting the location most severely affected by KC, the thinnest point of the cornea showed a reduced Brillouin modulus when compared to its supposedly unaffected periphery,[12] which was more pronounced at more severe stages of the disease (5.677 vs 5.728 GHz at stage III-IV). In healthy subjects, there was no significant difference between the thinnest point and its periphery. The spatially concentrated biomechanical weakening is also in agreement with changes in the stress-strain index map reported in progressive KC.[13] When looking at the depth distribution of Brillouin modulus, a marked decrease in the posterior stroma is observed, which in healthy corneas and in the periphery of the cone, is limited to approximately one-quarter of the most posterior stroma. In contrast, within the cone region, the weaker region was substantially larger, spanning over approximately two-thirds of the posterior KC cornea.[14] Applanation-based optical coherence elastography found differences in the depth deformation profile and showed that healthy corneas more often presented a band of reduced deformation (with a supposedly higher stiffness) in the anterior stroma than KC corneas.[15]

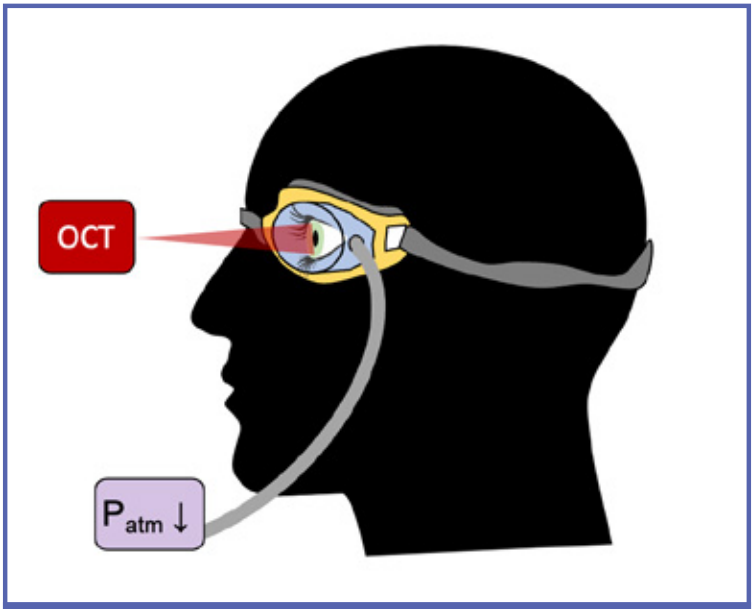

FIGURE 2. Measurement principle of ambient pressure modulation OCE.

Methods of Measuring Biomechanics

Gold-standard methods of material characterization rely on tissue excision and typically involve material destruction during testing. The advantage of such approaches is that either the test force or the degree of extension can be externally controlled, permitting distinct testing approaches, including stress-strain analysis, creep, and relaxation tests, as well as dynamic material characterization. Up-to-date literature on the ex vivo material characterization of KC corneas is sparse. Uniaxial strip extensometry demonstrated a weaker behavior of the KC cornea, which resulted in a lower load needed to reach a certain tissue strain,[16] or in an altered non-linearity of the stress-strain curve, which was particularly pronounced at loading forces exceeding the physiological range.[17]

The only commercially available devices to estimate corneal biomechanical properties non-invasively are based on air-puff stimulation. By quantifying the temporal and spatial corneal deformation pattern resulting from an air-puff directed onto the central cornea, not only the intraocular pressure, but also differences in tissue stiffness can be derived. In a sex-, age-, and corneal-thickness-matched study, the ocular response analyzer measured a significantly lower *"corneal hysteresis"* and *"corneal resistance factor"*[18] in KC than in healthy corneas. Nevertheless, both parameters had low sensitivity and specificity and thus seemed unsuitable as a diagnostic criterion. In Corvis ST, the parameters *"first applanation time"* and *"highest concavity radius"* demonstrated the highest diagnostic potential with an area under the curve of 0.955 and 0.936, respectively.

Another type of in vivo biomechanical assessment is based on Brillouin microscopy, which is still under development but is available to a limited extent for application in ophthalmic patients. The analysis relies on a non-linear optical effect, which results from an interaction of light with material waves inducing an optical *"frequency shift"* in the scattered light, which is related to the stiffness of the sample, its density, and refractive index. A study in healthy and KC patients found a significantly lower frequency shift at the thinnest location[4] of the diseased eyes corresponding to a weaker material. Interestingly, the frequency shift at the maximum posterior elevation did correlate best with geometry-derived KC indices.[4] The frequency shift measured at the cone had an area under the curve of 0.92 and thus performed better as a diagnostic criterion than corneal thickness or maximal curvature.[12]

Elastography based on optical coherence tomography (OCT) has most recently been proposed for corneal biomechanical assessment. This technique relies on the combination of a mechanical stimulus with structural OCT in order to enable functional mechanical imaging. Different groups have

investigated distinct types of mechanical stimuli, however, only few of them have been investigated in KC. One approach used a gonioscopy lens to compress the anterior cornea and to quantify the induced displacement map.[15] It demonstrated that KC corneas had a lower *biomechanical property ratio* and seemed to more often present an altered deformation pattern in the anterior stroma. Another approach used swimming goggles to stimulate eye globe expansion.[19] This study observed a significantly different relative displacement pattern in the anterior and posterior cornea in KC patients than in healthy participants, suggesting a stronger compression in the former. Another type of OCT elastography exploits the endogenous random motion of biological tissues, which can be measured via a phase decorrelation analysis of the complex-valued OCT signal.[20] This technique has been demonstrated successfully in the detection of corneal weakening in an ectasia model based on enzymatic digestion.[21]

A convincing advantage of non-contact biomechanical assessment is its comfortability for the patient and easy clinical integration. Yet these approaches come with the challenge of a more complex data interpretation and several confounders that can bias the measurement.

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Optics of Keratoconus and Correcting Aberrations with Wavefront-Guided Lenses

By Jason Marsack, PhD*, Geunyoung Yoon, PhD*

Those with keratoconus (KC) can often be thought of as "challenging" or "demanding" when compared to typical refractive error patients.[1] But why do these perceptions exist? Why might the KC group, as a whole, be perceived as more challenging than the typical refractive error group by their practitioners? In addition, why might they tend to be less satisfied with the level of optical correction provided to them? One reason is that nearly all of today's refractive corrections are not designed to specifically target the full spectrum of optical imperfections that are present in KC eyes.

In this section, we will describe the differences in optical characteristics between those with KC and typical refractive errors, the reason that traditional corrections can fall short of correcting the full spectrum of optical imperfections present in KC, the emerging novel methods that customize a correction to the optical needs of the individual eye, and the challenges that keep these custom methods from being widely available.

Keratoconus vs. Typical Refractive Error

With the advent of ocular wavefront-sensing technology (or aberrometry), the ability to characterize the optical characteristics of the eye has become objective, accurate, and fast. It has been established that the majority of the aberration in the typical eye is sphero-cylindrical. However, higher-order aberrations are present in typical eyes, and their magnitude increases as pupil diameter increases.[2,3] Fortunately, typical myopic and hyperopic patients are able to reach satisfactory levels of visual performance without considering the higher-order aberrations that are present (which tend to be, relatively speaking, low). In the case of the KC eye, the amount of higher-order aberration is elevated compared to the

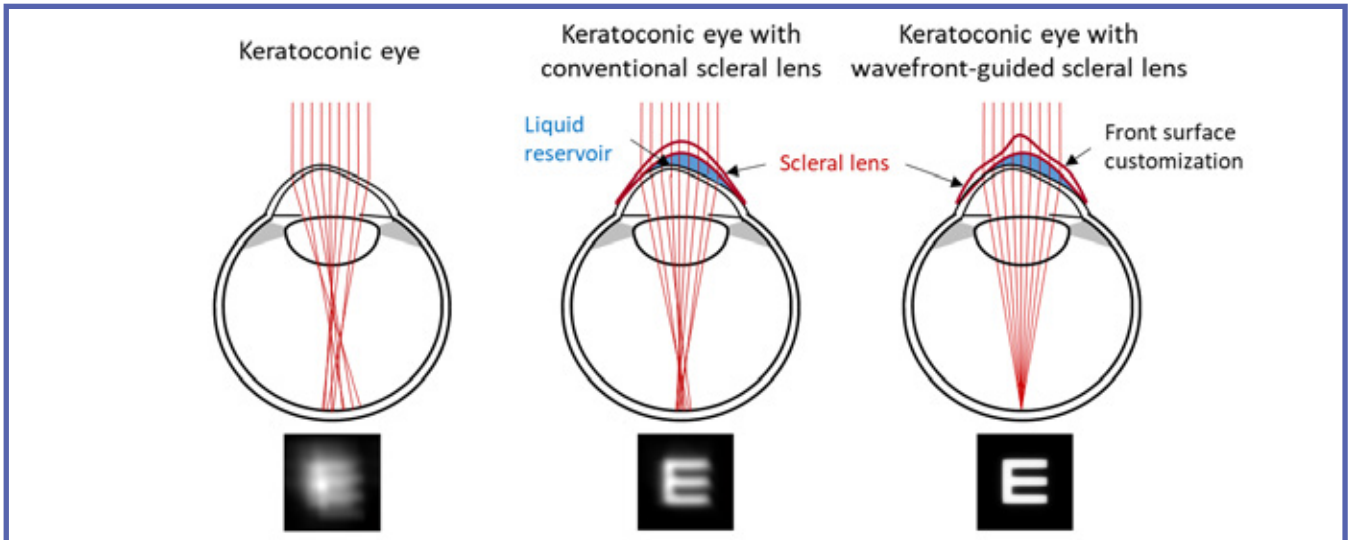

FIGURE 1. Schematic diagram illustrates how the aberration of a keratoconic (left) eye is corrected with a conventional and a wavefront-guided scleral lens. The liquid reservoir between the scleral lens and the cornea reduces aberrations induced by the anterior corneal surface (middle). However, aberrations from the posterior corneal surface and the scleral lens remain uncorrected and can be corrected by customizing the front surface of the lens (right).

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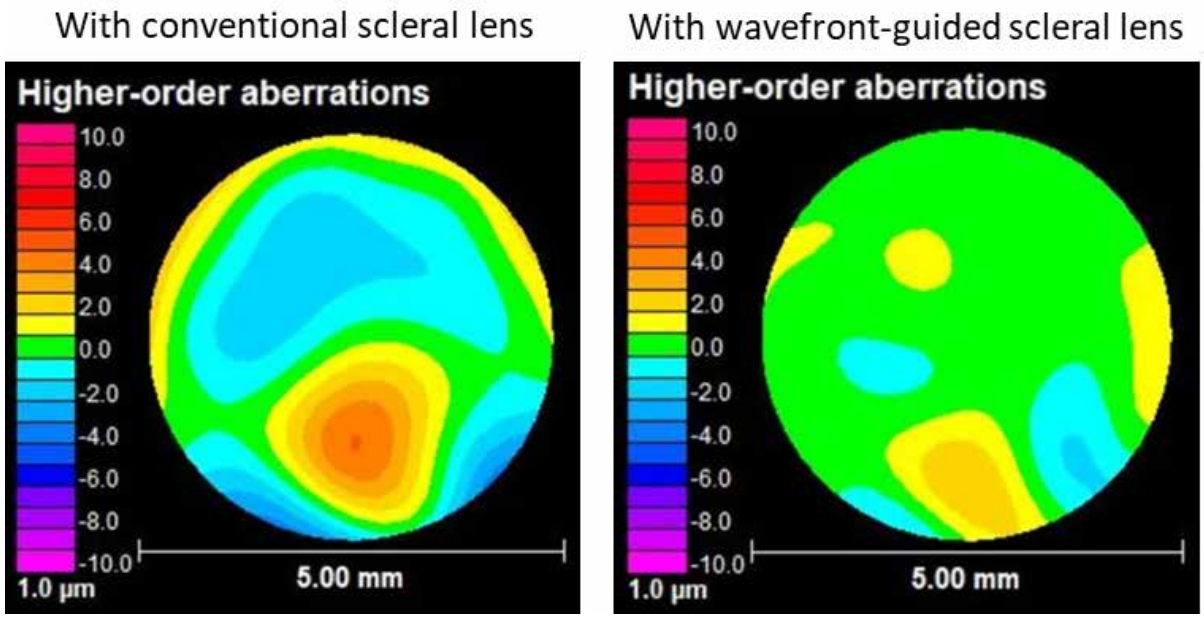


FIGURE 2. Wavefront aberration maps represent the residual, uncorrected higher-order aberrations for an individual with severe keratoconus in the left eye while wearing a conventional scleral lens (left) and a wavefront-guided scleral lens (right). Note the dominant, vertically oriented blue/red pattern in this figure, representing uncorrected positive vertical coma. The elevated level of higher-order aberration present here manifests as complaints by an individual who is able to read the letter chart but reports that it is still not crisp. With the wavefront-guided scleral lens, note the reduction in red/blue pattern, which has been replaced to a large degree by green (indicating the reduction in higher-order aberrations). This resulted in a reduction of the visual complaints that were reported during conventional scleral lens wear.

typical eye.[4] Depending on the level and type/distribution of these higher-order aberrations, conventional glasses and soft contact lenses may provide adequate vision, but more than likely, as the disease progresses, they may not. At that point, what are the options available for improving vision?

Why Traditional Corrections Fall Short of Correcting Keratoconus

Most commonly, when conventional spectacles and soft contact lenses do not provide adequate vision, patients turn to rigid forms of contact lens correction (historically rigid corneal lenses, hybrid lenses, and scleral lenses). The benefits of a rigid form of correction are that 1) the rigid nature of the lens provides a more regular (spherical or aspherical) first refracting surface as light enters the eye and 2) the filling of tears between the rigid lens and cornea masks (reduces) higher-order aberrations. However, this masking method does not "target" the exact amount of aberration that is present in an individual eye, and it can leave behind elevated levels of higher-order aberration. In fact, many individuals with KC continue to exhibit levels of higher-order aberration higher than typical, even while wearing rigid corrections.[5] This would explain why patients continue to vocalize complaints about the quality of their vision and why practitioners may view these complaints as originating from a "challenging" or "demanding" patient. This problem is exacerbated by the fact that the level of higher-order aberration present in the eye/lens system is not routinely measured (with a wavefront sensor) in clinic, so many practitioners do not have a sense of the magnitude of uncorrected aberration that patients continue to experience during rigid lens wear.

Previous studies reported two main sources of the residual aberrations: the posterior corneal surface and the spherical rigid lens decentered with respect to the pupil. The irregularity of the posterior corneal surface is more severe than the anterior surface, but the masking effect is only applied to the anterior surface, leaving the aberrations induced by the posterior surface uncorrected.[6] From an ophthalmic optics perspective, a spherical lens surface decentered from the line of sight induces horizontal and/or vertical coma depending on the direction of the decentration.

Emerging Novel Methods Customize a Correction for the Individual Eye

Practical forms of an emerging method, known as "wavefront-guided" corrections, that directly target higher-order aberrations in KC eyes, have been demonstrated.[5,7] The

principle of the correction is to design a lens that mimics a diagnostic lens in every way, except that it also targets the residual aberrations measured while the eye is wearing the diagnostic lens. Such a method would compensate for the aberrations originating from all elements in the optical path, including the posterior cornea and decentered lens. The method is well suited to rigid forms of correction. When done successfully, levels of higher-order aberration are reduced to typical levels (in some cases, better than typical levels), which leads to improved visual outcomes.[5,7]

Challenges That Keep These Custom Methods From Being Widely Available

While higher-order aberration correction has been demonstrated, it is by no means widespread. The reason for this is partly due to the complexity of the process required to fit, design, and construct a wavefront-guided lens. The process is different from manufacturing a spherical or sphero-cylindrical lens. In essence, the manufacture of a wavefront-guided lens completely customizes the optical correction (as well as the fit) of the lens to meet the needs of a single eye. This requires specialized measurements in the clinic, including measurement of the residual lower and higher-order aberrations with a wavefront sensor, as well as the offset of the lens optics from the geometric center of the lens. Also, these lenses tend to be expensive compared to other forms of correction, which is a significant consideration for many patients. Developing a system that allows lens fit, aberrometry measurement, lens design, and lens ordering in a streamlined and seamless manner would simplify the process and potentially provide a larger segment of the KC population with significant visual benefit in their daily life.

Customization of corrections for the population of individuals with KC is emerging, but much work is left to do before these lenses are commonplace. Additional scientific understanding of how the human visual system perceives the improved visual quality, and engineering developments to stabilize the lenses on-eye without affecting ocular health, are needed. These endeavors will perhaps motivate all of us to move toward a more complete form of correction for this segment of the population, with the result that the KC group is seen as not so "challenging" or "demanding" after all. Truth be told, what the KC population is really asking for as a whole is simply to have a level of corrected visual performance that the typical myope and hyperope might currently take for granted.

Application and Availability of Wavefront-Guided Scleral Lenses in Clinical Practice

Afterward by John D. Gelles, OD, FAAO, FIAOMC, FCSLA, FSLS, FBCLA

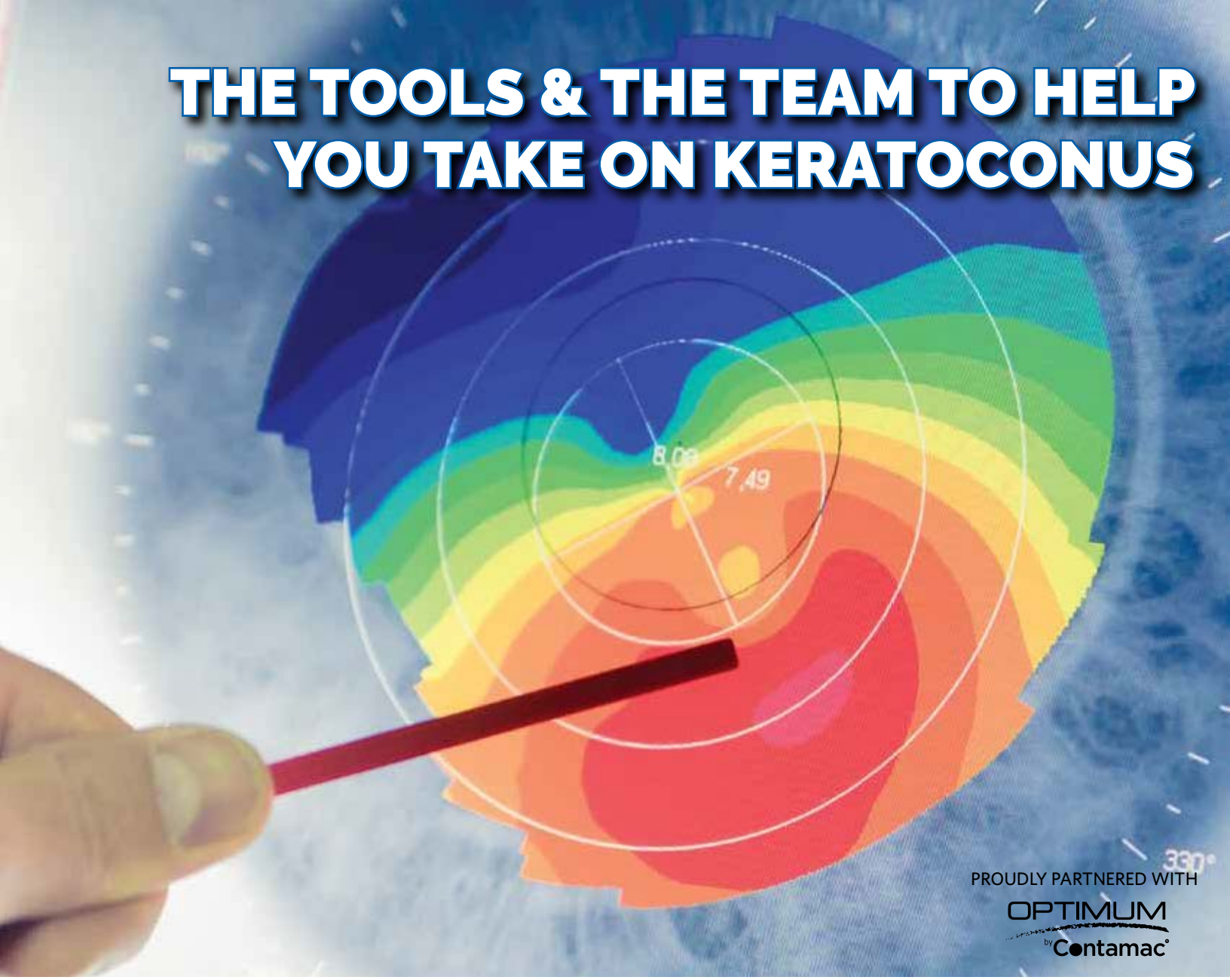
The quality of vision in patients afflicted with KC, even when corrected with rigid contact lenses, is oftentimes subpar compared to individuals with normal corneas, especially in advanced KC. This degraded visual quality is primarily due to residual aberrations. Though patients may be able to "blur interpret" or reason their way through reading a Snellen chart, in the real world this can impact activities of daily living.

Until recently, lens optics modifications such as front surface torics, optical zone size, or asphericity were the only options that might enhance visual quality. Patients and their care providers were forced to accept "good enough" or "the best we can do."

Dr. Marsack and Dr. Yoon's contributions to the understanding of physiologic optics, optics of keratoconus, and the development of methods to improve visual quality with customized wavefront-guided optics have led to the availability of these as options on scleral lenses in clinical practice. Early manuscripts [7,9] reported that customized wavefront-guided optics on scleral lenses produced significantly improved vision and reduced higher-order aberrations in patients with KC. However, the availablity of this innovation was limited to their respective research centers.

Finally, a commercially available system has enabled wavefront-guided scleral lenses to be available in clinical practice. The system has proven successful in reducing aberrations and improving visual acuity.[8] Several labs are currently offering this option on their scleral lens designs, with more adopting this technology. Additional companies are working on similar systems to provide these optics.

Over 20 years after the original patent by Magnate,[10] and nearly 10 years after the original manuscripts on wavefront-guided optics on scleral lenses, we can finally offer customized optics to better address the visual needs of patients with keratoconus.



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DR. JASON MARSACK is a scientist/engineer with a passion for teaching and a strong interest in applied and translational research. His laboratory at the University of Houston College of Optometry focuses on developing and translating optical correction strategies for eyes with poor visual quality to the clinical environment and investigating the relationship between optical quality and visual performance. Dr. Marsack teaches geometric optics to students in the Optometry Professional Program, advanced optical topics to students in the Physiological Optics Program, and mentors students seeking MS and/or PhD degrees.

DR. GEUNYOUNG YOON is currently appointed as the Irvin M. Borish Chair Professor at the University of Houston College of Optometry. He previously served on the faculty at the University of Rochester. His laboratory's overarching research goal is to enhance our understanding of optical and neural mechanisms underlying vision and eye problems by conducting human-based translational research. To achieve this goal, his laboratory has been developing various state-of-the-art technologies including advanced ocular aberrometers, wavefront-guided vision correction methods, binocular adaptive optics visual simulator, and in-vivo cornea/anterior segment imaging modalities. These capabilities have been used for studying mechanistic interactions between the optics of the eye and the neural system, vision improvement for patients with corneal pathologies, diagnosis and treatment of corneal diseases, presbyopia correction, and myopia development/control. Dr. Yoon's laboratory is funded by NIH, other non-profit funding agencies, and the industry. He is a recipient of the Research to Prevent Blindness Dolly Green Special Scholars Award and the David E. Bryant Trust Research Award. He is a panel member for the FDA's Center for Devices and Radiological Health and serves as a member of editorial boards for *Frontiers in Ophthalmology, Annals of Optometry and Contact Lenses,* and *Journal of the Korean Ophthalmological Society.*

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Diagnostics and Monitoring

By Louise Pellegrino Gomes Esporcatte, MD, MsC,[*,†,‡] Renato Ambrosio, MD, PhD,[*,‡,§] Brooke Messer, OD, FAAO, FSLS,[¶] Katie Greiner, OD MS MBA FAAO,[||] and S. Barry Eiden, OD, FAAO, FSLS[**]

The most critical element to the modern management of keratoconus (KC) is the ability to diagnose the disease early. In addition, this is important to stage the disease severity and to objectively follow the patient over time. The earlier disease progression is confirmed, the earlier that patient can be treated with corneal crosslinking (CXL) to prevent visual degradation and preserve quality of life. Progression of KC can be rapid, and delays in treatment, even of just three months, can result in worsening of disease.[1] The ability to identify the need for further testing can be challenging, as the earliest signs of disease are subclinical; thus, remembering certain red flags and the use of sophisticated diagnostic devices is critical to diagnosis as well as to disease monitoring.

Red Flags in Primary Care Examinations

The ability to diagnose and monitor KC has improved with technological advancements such as global corneal pachymetry and tomographic elevation of the posterior cornea, but many of these instruments are in the practices of a corneal specialist and may not be available in a primary eye care setting. However, there are well-established clinical signs and patient symptoms that should alert a practitioner to recommend screening for KC.

Beginning with patient history, patients may complain of seeing multiple images out of each eye, in addition to other complaints such as significant glare when driving at night. Their health history may include connective tissue-related conditions such as floppy eyelid syndrome, sleep apnea, Down syndrome, Marfan syndrome, or Ehlers-Danlos syndrome. They may also report atopic or

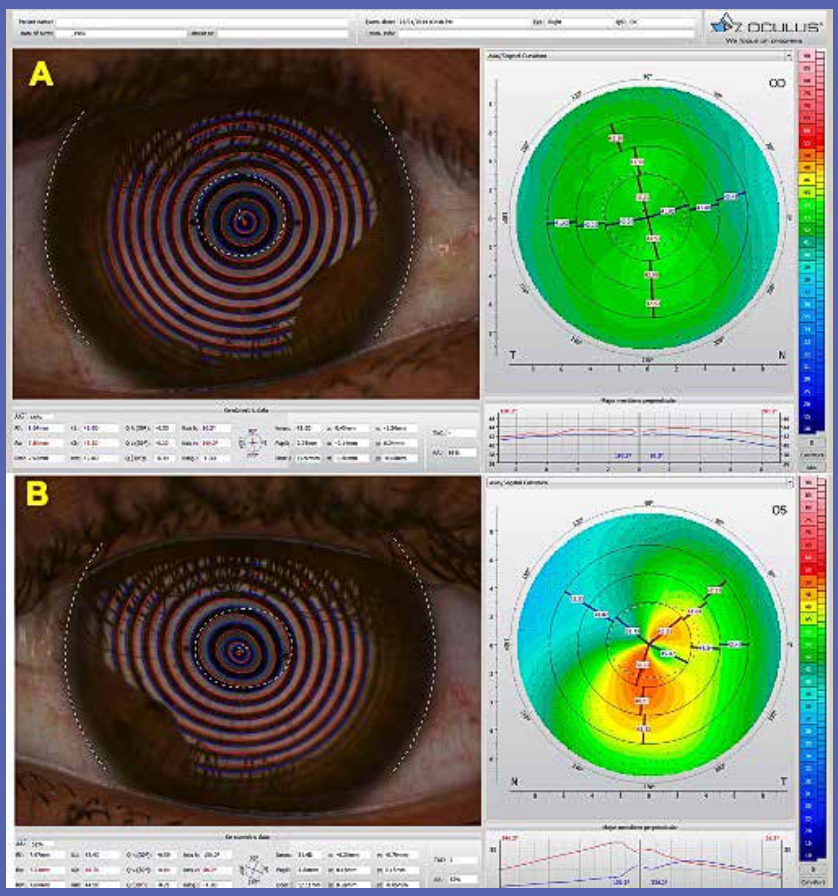

FIGURE 1. Normal topography in OD (A) and a moderate KC diagnostic pattern in OS (B).

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allergic findings such as eczema, dermatitis, and asthma. Patients will often have a habit of vigorous eye rubbing and may also report needing to frequently change the prescription of their glasses and/or contact lenses.

There are numerous clinical signs that assist in the diagnosis of KC. Automated testing, such as autorefraction and autokeratometry, may show high astigmatism and steep keratometry readings at oblique or against-the-rule axes, or possibly erroneous findings due to the corneal irregularity. Retinoscopy can show a scissoring reflex as well as a "tear-drop" shape highlighting the apex of the cornea on retroillumination. Manifest refraction is often frustrating for patients with KC, and best-corrected spectacle acuity can be reduced. Slit lamp examination may appear clear, but moderate to advanced cases of KC can present with Vogt's striae, a Fleisher ring, and apical scarring. Advanced cases will demonstrate Munson's sign, which is a protrusion of the lower eyelid in downgaze due to the deep cone shape of the cornea.

When one or more clinical findings are present, especially when paired with a suspicious finding or red flag from medical history, diagnostic testing and instrumentation can be very helpful in confirming the diagnosis.

Value of A Contact Lens Over-Refraction

When a patient with otherwise normal ocular health is not correctable to a crisp 20/20 and there is not quick access to a corneal topographer, reach for a corneal gas permeable lens from a diagnostic fitting set, fit off mean auto-Ks, then perform an over-refraction. This is a simple way to tell if there is irregularity to the cornea as the lens will negate the irregularity, producing a more regular corneal shape. When vision corrects better than with spectacles and/or the patient states there is an improvement in the quality of vision, then the answer becomes more clear that there is a corneal problem. It is important to remember that an improvement in vision by this means does not necessarily mean restoration of 20/20 vision, but it can certainly aid in quality and quantity of vision with the initiation of specialty lens fitting. A corneal lens can be used as a form of topography. If there is even a mild cone, placing a spherical corneal lens on the eye will show an apical bearing pattern that is highly indicative of KC. From here, a specialized KC or scleral lens is indicated for best-corrected visual acuity. This simple test can provide important information about your KC patient and set them on a path toward improved vision and daily functions.

Basic Testing Limitations

KC detection depends on the sensitivity of the diagnostic methods utilized. Basic testing that depends on perceived visual symptoms, refractive change anomalies, keratometric/retinoscopic abnormalities, and biomicroscopic findings that are typically classic for the disease all suffer from the fact that they are detectable in more advanced phases of KC. In most of these cases, vision has already been compromised. In light of the development of advanced diagnostic technologies that can detect KC with high sensitivity and specificity before vision loss, along with our ability to control the progression of disease with CXL, we can now preserve vision.

Advanced Technology to Diagnose and Monitor

Corneal Topography

Placido disk-based corneal topography, or reflection topography, projects a series of concentric rings onto the anterior corneal surface and uses quantitative data to generate color-coded maps.[2,3] Different indices for KC detection have been proposed and widely used, such as Rabinowitz and McDonnell's inferior-superior asymmetry.[4] Corneal topography represented a true revolution in corneal imaging and has proven to be sensitive to detect ectatic disease, even before any loss of best-corrected visual acuity and any remarkable slit-lamp exam findings develop.[5,6]

KC is classically identified with the typical topographic pattern of inferior steepening, but other different patterns are also identifiable.[7,8] Generally, higher corneal curvature values over 47.2D are suspected cases of KC.[7-9] Additionally, the asymmetry between the values in the 3 mm radius in the upper and lower regions (or between the nasal and temporal areas) are suspected cases of KC when greater than 1.4D.

In addition to front surface curvature characterization, Placido-disk reflection enables the assessment of the tear film break-up time non-invasively, which can be combined with other digital imaging resources to further enhance the evaluation of the ocular surface. An irregular and unstable tear film will impact the measurements of the topography.

Corneal Tomography

Corneal topography evolved into 3D corneal tomography by adding measurements of the posterior surface and a full pachymetric map to the anterior surface evaluation.[10]

Slit scanning, rotating Scheimpflug, high-frequency ultrasound, and optical coherence tomography are among the technologies that enable such study. The Galilei Dual-Scheimpflug analyzer (Ziemer; Port, Switzerland) combines Scheimpflug imaging with Placido disk-based topography, and the first rotating Scheimpflug system was the Pentacam (Oculus, Wetzlar, Germany).

Diagnostics Quick Reference Guide

Test	Values	Simplified Appearance	Quality checks	Limitations	Advantages
Topography	>47D Axis skew >20 degrees IS >1.4D	Asymmetric Skewed astigmatism	Tear film quality Alignment	Anterior surface analysis only	Instantaneous capture
Tomography	Same as above plus Anterior elevation > 15 um Posterior elevation > 15 um Thinnest point < 500um Epithealial thinning	Same as above plus Posterior bowing, 'hot spot,' Epithelial donut pattern	Alignment, Patient fixation, Corneal epithelial quality	Patient must remain still with good fixation	Earlier detection of cornea changes, can measure pachymetry of large area and locate thinnest point Features ectasia detection and progression indices such as Belin ABCD, Belin-Ambrosio Enhanced Ectasia Display (BAD).
Aberrometry	Increased (-) vertical coma, increased RMS, increased trefoil	Increased (-) vertical coma, increased RMS, increased trefoil	Tear film and fixation Specify corneal findings and not entire optical system	Tear film and fixation	Validates patient vision complaints Assist in identifying mild cases
Genetic Testing	Classified as low, medium, and high risk for KC. Also identifies genes that are more pathologic	Identifies patients with genetically higher disposition to KC development	Determined by laboratory, follow instructions to ensure sufficient collection from cheek	Does not diagnose KC, only gives genetic risk	Non-invasive, can be completed by support team Genetic counselor provided by the company
Biomechanics	Normal corneas CH and CRF ~ 10.7, KC eyes are lower, ~8.9 or less	Corneas with KC are weaker than normal eyes	Fixation	Lid involvement Patient positioning can be a challenge	Quick test Good quality results most of the time

Segmental or Layered Corneal Tomography

Further evolution in corneal tomography allowed the characterization of the individual corneal layers, such as the epithelium, Bowman's layer, and Descemet's membrane. Segmental or layered tomography first started with corneal epithelial thickness measurements with very high-frequency ultrasound (VHF-US).[11] The role of corneal epithelial measurements has been highlighted in different ophthalmological conditions, especially in the refractive surgery field and ectatic disease investigation.[12] Reinstein introduced corneal epithelial indices derived from VHF-US, and he described this approach as a valuable tool to identify KC, even in milder forms of the disease.[13,14] Alternatively, Huang and collaborators used optical coherence tomography (OCT) technology to develop an extended epithelial thickness map, which along with epithelial indices, could detect KC in milder stages.[15,16]

In normal corneas, the average central epithelial thickness is 54 mm, with an SD of 4–5 mm. A non-uniform pattern of epithelial thickness is thinner in the superior area and thicker in the inferior region. Thickness asymmetry was also documented by comparing nasal and temporal areas with nasal thickening and temporal thinning.[13]

Studies suggest that within the cone area, there is a localized zone of epithelial thinning over the steep area, surrounded by an annulus of thickened epithelium, which is classically referred to as an "epithelial doughnut pattern."[13] Moreover, a new Bowman's roughness index derived from OCT technology was recently proposed by Sinha-Roy and colleagues. In this study, the authors compared the level of the irregularity of the Bowman's layer in healthy and ectatic eyes. They found that the index had a good performance in detecting KC.[17]

Aberrometry

Ocular aberrometry is a diagnostic tool

that offers valuable information about the eye's refractive status. Although commonly used to look into lower- and higher-order aberrations and to plan wavefront-guided refractive surgery, studying higher-order aberrations has raised considerable interest in corneal diseases, including KC.[18] Irregular astigmatism resulting from corneal distortion is associated with a decrease in the optical quality of the cornea and a substantial increase in higher-order aberrations.[19]

There are some discrepancies in the performance to discriminate KC compared to normals. Gobbe and coworkers showed that the best detector to differentiate between suspected KC and normal corneas was a vertical coma, with a specificity of 71.9% and sensitivity of 89.3%.[20] Alio and Shabayek also proposed a modified Amsler-Krumeich classification for KC, which integrates corneal aberrometry, mainly from the magnitude of coma-like aberrations.[21]

The total ocular wavefront was also analyzed in KC eyes. In a prospective observational case-control study, Maeda and coworkers reported the corneal and ocular wavefront aberrations of normal and KC eyes using a Hartmann-Shack sensor combined with a Placido disk-based topographer (KR-9000 PWc, Topcon, Tokyo, Japan). There were significantly more total ocular higher-order aberrations, such as coma, which were 2.32 times higher than spherical-like aberrations in KC eyes.[22]

This technology can assist refraction in KC patients. This approach also can improve best-corrected distance visual acuity in cases with advanced KC.[23]

Biomechanics

Ocular Response Analyzer

The first *in vivo* corneal biomechanical response measurements became available with the Ocular Response Analyzer (ORA, Reichert Ophthalmic Instruments, Buffalo, NY, USA) in 2005 by David Luce.[24,25] The ORA is a non-contact tonometer with a collimated air puff that indents a central 3-6 mm apical corneal area that can monitor the bidirectional movement of the cornea by an advanced electro-optical system.[25-27] It was designed to provide intraocular pressure measurements after understanding and compensating biomechanical properties.[25]

The ORA applies an air jet to the eye, and the pressure is measured and registered at two corneal applanation times. The corneal deformation is monitored by an electro-optical system involving a collimated beam of IR light and a photodetector. The ORA generates two main pressure-derived parameters: corneal hysteresis (CH) and a corneal resistance factor (CRF). Despite having a significantly different distribution among healthy and ectatic eyes (studies have reported CH and CRF to be lower in KC),[28] CH and CRF revealed a limited role in KC diagnosis, so that sensitivity and specificity for reasonable diagnostic accuracy can be considered somewhat poor.[29,30]

Corvis ST Dynamic Scheimpflug Analyzer

The Corvis ST (Oculus, Wetzlar, Germany) is a non-contact tonometer system that uses an ultra-high-speed Scheimpflug camera that acquires 4,300 frames per second, allowing for dynamic observation of the corneal deformation response over a 5-6 mm area during a consistent air pulse application. Once the measurement is complete, the device provides corneal deformation parameters based on the dynamic inspection of the corneal response.[31,32] Using an ultra-high-speed Scheimpflug camera, this approach allows a more detailed evaluation of the deformation process than the ORA, and it yields a fixed maximal peak pressure for the air puff in every examination, unlike the ORA.[31]

Corvis ST analyzes corneal defor-

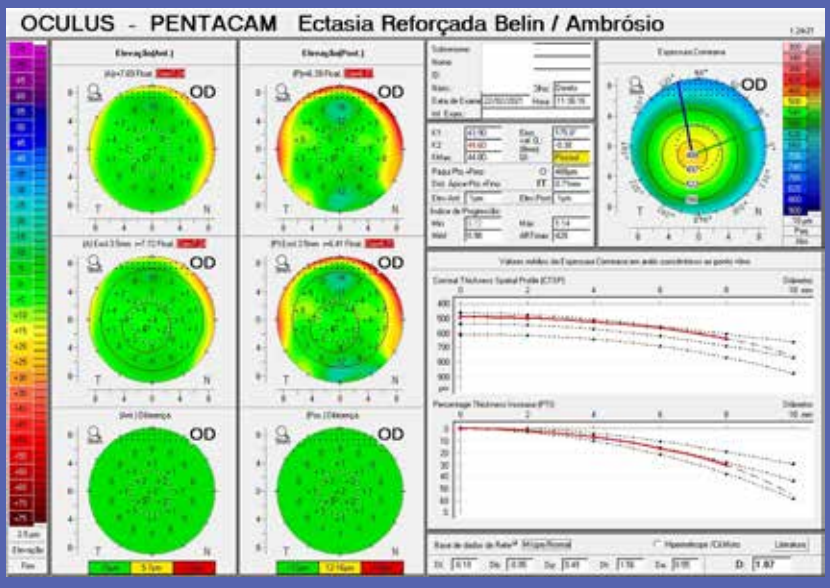

FIGURE 2. The Pentacam Belin/Ambrósio Enhanced Ectasia shows a BAD-D of 1.07 in OD.

mation parameters based on the dynamic examination of the corneal response. The deformation data allows for more precise intraocular pressure measurements, influencing the deformation response. Several parameters derived from this instrument have been introduced, such as the deformation amplitude, the radius of curvature at the highest concavity, the applanation lengths, and the corneal velocities.[31] A greater concave radius is associated with greater resistance to deformation or a stiffer cornea. So, the higher the integrated inverse radius and maximum inverse radius, the less resistance to deformation and lower corneal stiffness.[32,33]

Once again, artificial intelligence (AI) algorithms demonstrated that the combination of deformation parameters enhanced the accuracy of distinguishing healthy and KC eyes, even in mild stages.[32] Additionally, waveform analysis of the deformation amplitude and deflection amplitude signals from the Corvis ST presented excellent performance in differentiating normal, suspect, and KC eyes.[34] These include calculating accurate measurements of intraocular pressure (IOP),[35,36] the investigation of CXL results,[37] and screening refractive surgery candidates.[38]

Genetics and Molecular Biology

There is general agreement that inheritance and environmental factors play a mutual role in the pathogenesis of KC and corneal ectasias. More than 700 genetic mutations cause KC, with 8% of cases resulting from genetic mutations and 92% environmental factors.[39,40]

It has been suggested that 73% of loci of human autosomal chromosomes are involved in KC, and 59% show statistically significant associations.[41]

At the time of publication, a single KC locus (5q21.2) has been replicated across multiple linkage studies,[42,43] suggesting a polygenic disease (two or more affected genes are required for the development of KC).

Genetic screening for the disease is a very complex task as several different genes have been implicated in the development of the disease, including VSX 1, miR-184, DOCK9, SOD1, RAB3GAP1, and HGF. Familial cases of KC have been reported, and it has been suggested that relatives of patients with KC are at increased risk of developing the disease[44] and that autosomal dominant and recessive patterns may be implicated.[45] At least 17 genomic loci have been identified in studies involving patients with KC, demonstrating significant genetic heterogeneity.[46]

In light of the development of advanced diagnostic technologies that can detect KC with high sensitivity and specificity before vision loss, along with our ability to control the progression of disease with CXL, we can now preserve vision.

Shortly, molecular biology might play a significant part in diagnosing and classifying KC. Histopathologic studies described molecular and cellular changes related to the pathogenesis of KC, including extracellular matrix degeneration. This suggests an up-regulation of degradative enzymes, oxidative stress, and inflammation,[47,48] which can eventually change the definition of the disease.

Adding the genetic and molecular biology study to evaluate KC is important, since studies detect that mothers of children with Down syndrome are more likely to have KC and thinner, steeper, and softer corneas than mothers with children who do not have Down syndrome.[49] Another study reviews the association between KC and Down syndrome, showing increasing evidence that supports the elevated risk (>100 times) of KC in patients with Down syndrome. The genetic association of sequence variants within or near the COL6A1 and COL6A2 genes on Chr21 with KC provides an additional functional link between KC and Down syndrome.[50]

A recent study shows that Lactoferrin (LTF) and Toll-like Receptors 2 (TLR2) are clinically and molecularly interrelated, increasing knowledge about KC pathophysiology and opening the door to future therapies. The dysregulation of LTF and TLR2 in the ocular surface of KC patients contributes to KC severity by maintaining a detrimental chronic immune-inflammatory state. The regulation of these immunomodulatory properties may be a potential therapeutic approach for KC. [51]

Algorithms and AI

Topography-based

The KISA index, described by Rabinowitz and Rasheed, was proposed by the integration of the calculation of the asymmetry between the values in the 3 mm radius in the upper and lower regions.[52]

Randleman and coworkers combined corneal topography, pachymetric measurements, and clinical variables to develop the Ectasia Risk Scoring System.[53,54] Nevertheless, limitations of this superficial analysis have been recognized after literature showed patients with identified

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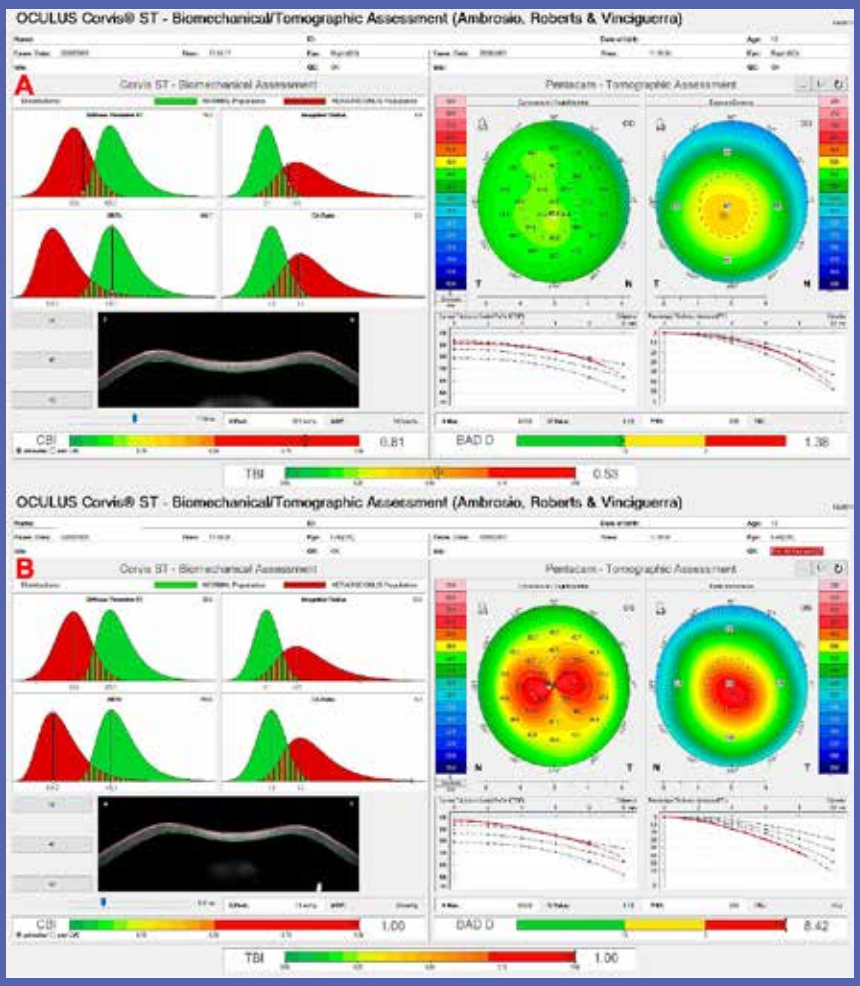

FIGURE 3. Mild (fruste) KC with a TBI of 1.0 confirmed OD; low biomechanical parameters indicate a high risk for progression OS.

risk factors and abnormal topographic maps who remain stable years after laser vision correction,[55] and patients who developed post-LVC ectasia, despite normal preoperative anterior surface maps.[56-58]

Tomography-based

Pentacam Belin-Ambrósio Enhanced Ectasia Display

The Pentacam Belin-Ambrósio Enhanced Ectasia Display (BAD) is a clinical tool designed to combine elevation and pachymetric data to facilitate the diagnosis of KC. Tomographic parameters, including data from front and back elevation, thinnest value and its vertical location, pachymetric distribution, Kmax, and Ambrósio's relational thickness (ART), are displayed as standard deviation from normality (d values). Linear regression analysis weights each parameter differently and calculates a final D value.[59,60] Each parameter is indicated in yellow (suspicious) when it is ≥ 1.6 SD from the mean and turns red (abnormal) at ≥ 2.6 SD from the mean. Values below 1.6 SD are reported in white and are viewed as within the normal range.

High sensitivity and specificity were found using this approach in comparative studies involving normal and KC eyes.[61] Additional studies have been conducted involving highly asymmetric cases, and the excellent ability of this method to detect abnormalities in these cases has also been evidenced.[61] Finally, eyes that developed ectasia after LASIK were retrospectively investigated, and researchers found higher accuracy of this method to identify susceptible cases, which have previously been considered good candidates, based on the corneal topographic evaluation.[57,62]

Pentacam parameters have also been combined and tested using machine-learning techniques and AI methods. Lopes and coworkers developed the Pentacam Random Forest Index. This index presented a high performance in discriminating between healthy eyes (preoperative status of stable post-LASIK cases), clinical KC, normal topographic eyes with very asymmetric ectasia, and ectasia susceptibility eyes (preoperative data of post-LASIK ectasia).[63] Additionally, Ambrósio and collaborators applied logistic regression analysis to compare preoperative data from stable LASIK eyes and eyes that developed iatrogenic ectasia after LASIK. The authors reported that clinical and tomographical data integration demonstrated higher sensitivity and specificity than individual parameters to identify ectasia susceptibility.[64]

ABCD – Tomographic Progression

AI can be developed to improve prognosis and clinical follow-up, as described by integrating biomechanical parameters into Belin's tomographic ABCD system.[65-66]

Data are from the corneal thickness at the thinnest point and the radial curvature of the anterior and posterior surfaces of the 3.0 mm zone centered at the thinnest point. The 3.0 mm zone was chosen because it is the zone excluded in the calculation of the BAD parameter for corneas with KC.

The ABCD grading system evaluated four parameters: (A) the radius of the ante-

rior corneal curvature, (B) the radius of the posterior corneal curvature, (C) corneal pachymetry at the thinnest point, and (D) visual acuity with the best correction. The sign of (-) is added for the absence of a scar, (+) for the presence of a scar that allows the visualization of the iris details, and (++) for the one that does not allow the visualization of the iris details.

The four parameters are displayed graphically with radial curvature and pachymetry values and with a five-stage rating ranging from zero to five.

The examiner needs to add visual acuity and the presence or absence of corneal scarring, and the program automatically classifies the cornea according to ABCD criteria.

Belin's ABCD progression system monitors ectasia and the ability to diagnose its progression earlier than possible with systems limited to the anterior corneal surface. This allows earlier interventions to prevent visual loss, not just determining it after it has happened.

Tomography + Biomechanics

Stress-Strain Index

The Stress-Strain Index (SSI) was the first standard mechanical metric that could be derived *in vivo* to build the whole stress-strain curve of corneal tissue. Obtaining the cornea's stress-strain curve is relevant due to its non-linear behavior under loads or stresses, making the tissue's material stiffness (tangent modulus, Et) not constant. So, a single measurement of the Et is insufficient to describe the corneal stiffness, as its value would change under different IOP levels. With the SSI providing the whole stress-strain curve, it can estimate the Et at any IOP.[68] The SSI behavior is under study in progressive KC cases and after CXL to evaluate the expected changes in the overall material stiffness that arises from these conditions.

The Corneal Biomechanical Index

The Corneal Biomechanical Index (CBI) was created by the best combination determined by logistic linear regression analysis to combine Ambrósio's Relational Thickness over the horizontal meridian (ARTh) with corneal deformation parameters.[69,70]

Vinciguerra and coworkers demonstrated in the training dataset that with a cut-off value of 0.5, CBI correctly identified 98.2% of KC cases among normal with 100% specificity and 94.1% sensitivity area under the ROC curve (AUC) of 0.983. Subsequently, the same cut-off value in the validation dataset accurately classified 98.8% of cases, with 98.4% specificity and 100% sensitivity, and an AUC of 0.999.[69]

In a recent study, the individual parameters included in the CBI (ARTh, SPA1, DA ratio 2 mm, A1 velocity, and integrated radius) proved to be highly reliable; however, they differ in the KC stage dependently.[71]

The Tomographic Biomechanical Index

The Tomographic Biomechanical Index (TBI) was built with a random forest model using data from the corneal deformation response and the corneal shape (tomography) to optimize our ability to split normal and altered eyes. The cut-off of 0.79 provided 100% sensitivity and specificity to detect clinical ectasia formed by KC and very asymmetric ectasia (VAE-E) cases. For the eyes with a normal topographic standard, an optimized cut-off of 0.29 offered 90.4% sensitivity and a specificity of 96%, with an area under the ROC curve of 0.985. The AUC of the TBI was statistically higher than all other analyzed parameters, including the CBI.[72,73]

Posterior external validation studies demonstrated that the TBI could detect

Red Flags Suggesting the Need for Further Testing

Test	Findings
Retinoscopy	Irregular Reflex aka Scissor Reflex
Refraction	Against the Rule or Oblique Axis, Monocular diplopia, Increase in astigmatism or myopic shift over time
Autorefraction	Against the Rule or Oblique Axis, Cylinder > 2.0D, error messages
Autokeratometry	Error messages, Max K > 47.0D, Distorted mires Difference > 2.0D between K1 and K2
Manual Keratometry	Distorted mires, Max K > 47.0 D Difference > 2.0D between K1 and K2
Retroillumination	Irregular 'oil droplet' reflex, known as Charleaux sign
Slit lamp	Apical thinning, Fleisher ring

mild forms of ectasia in very asymmetric ectasia with normal topography (VAE-NT) cases.[74-78] Although some of these studies have found a comparatively lower sensitivity for the VAE-NT eyes (some with normal topography and tomography [NTT]), it is relevant to observe that several of these cases can be genuinely unilateral ectasia due to mechanical trauma.[79,80] A recent study concluded that the TBI was the most sensitive index to verify a mild ectasia; 12 VAE-NTT fellow eyes of 14 KC eyes have abnormal TBI values.[81] Nevertheless, the TBI epitomizes the intrinsic ectasia susceptibility for ectasia progression, which can improve through reinforced learning using more data.

Recently, a novel optimized version of the TBI (TBIv2) has been developed with significantly higher accuracy (0.945) for detecting VAE-NT (84.4% sensitivity and 90.1% specificity; cutoff 0.43) and similar AUC for clinical ectasia (0.999; 98.7% sensitivity; 99.2% specificity; cutoff 0.8). Considering all cases, the TBIv2 had a higher AUC (0.985) than TBIv1 (0.974) [Ambrósio et al., data in press 2022].

Corvis-Derived Parameter 'E'

A recent study evaluates the potential of a novel biomechanical KC staging parameter "E,"[67] as an addition to the tomographic ABCD ectasia/KC staging.[82,83] This parameter is based on the Corvis Biomechanical Factor (CBiF), a modification of the linear CBI beta that provided a measure for different stages of the biomechanical destabilization of the cornea.[84] The CBiF is separated into five stages (E0 to E4).

The ABCDE staging aims not to diagnose KC based on these parameters biomechanically but to improve the severity classification. Combining tomographic and biomechanical parameters may offer clinical advantages over using either alone. Additional clinical application of the augmented staging system is required to determine its clinical applicability.[81]

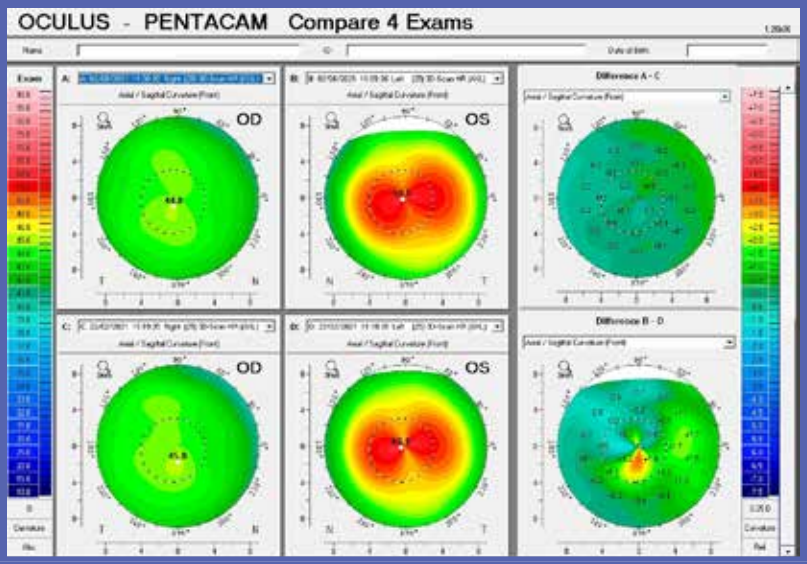

FIGURE 4. After six months of follow-up, the Pentacam differential maps revealed stability in OD and progression in OS.

Stiffness Parameter at First Applanation

The Stiffness Parameter at First Applanation (SP-A1) can help us regarding the prognosis of the disease. It is the result of dividing air pressure minus biomechanical IOP on the cornea by the movement of the corneal apex from the initial position until the first applanation instant, attends as a biomarker for corneal stiffness, and is reported to be lower in thin corneas (350 mm - 450 mm) than in normal thickness (500 mm - 600 mm) corneas.[69] Remarkably, SP-A1 negatively correlates with the corneal back-scattering (referred to as densitometry) values. This indicates that increased corneal densitometry values among patients with KC may indicate compromised corneal stiffness.[85,86]

Case Report

The example of a progressive ectasia in one eye and forme fruste of KC (FFKC) in the other demonstrates the role of tomography and corneal biomechanics to characterize better ectasia susceptibility or subclinical/milder forms of the ectatic disease.

In a 13-year-old male patient with distance-corrected visual acuity of 20/15 in the right eye (OD) and 20/60 in the left eye (OS), we noticed a normal topography in OD and a moderate KC pattern diagnostic in OS at the first visit (Figures 1A and 1B). The Pentacam Belin/Ambrósio Enhanced Ectasia shows a BAD-D of 1.07 in OD (Figure 2). The integrated biomechanical and tomographic display in OD confirmed mild (fruste) KC with a TBI of 1.0 (Figure 3). In OS, besides age, the low biomechanical parameters indicate a high risk for progression (Figure 3).

After six months of follow-up, the Pentacam differential maps revealed stability in OD and progression in OS (Figure 4). Note the sensitivity in diagnosing progression improvement in OS based on the axial subtraction map and Pentacam Belin ABCD display (Figure 5), despite the mild decrease in Kmax values from 60.6D to 59.5D.

Diagnostics Simplified

In general, diagnostics can be evaluated in a simplistic manner by recognizing patterns that are irregular. Normal corneas should be symmetric in nearly all aspects of topography and tomography. Elevation maps should have best fit spheres that generally align to the corneal surfaces without "islands" or "hotspots," pachymetric maps should be thick and uniform, aberrometry should have low levels of coma. Remember the following: asymmetric, elevated, thin, aberrated, and weak.

When diagnostic testing yields results that classify a patient as a "suspect" for KC, further testing can be completed to supplement the clinical findings. Genetic testing is available (Avagen, Avellino, Menlo Park, CA) in the form of a cheek swab to assess a patient's relative risk for developing KC. KC is considered to have a multifactorial etiology, meaning many genes and environmental factors can influence the manifestation of the condition. The more genes present, the higher the risk may be when in the presence of environmental conditions such as eye rubbing or corneal refractive surgery. Although results yielding a high genetic risk do not confirm nor deny the diagnosis of KC, they can assist in making clinical recommendations based on the genetic analysis.

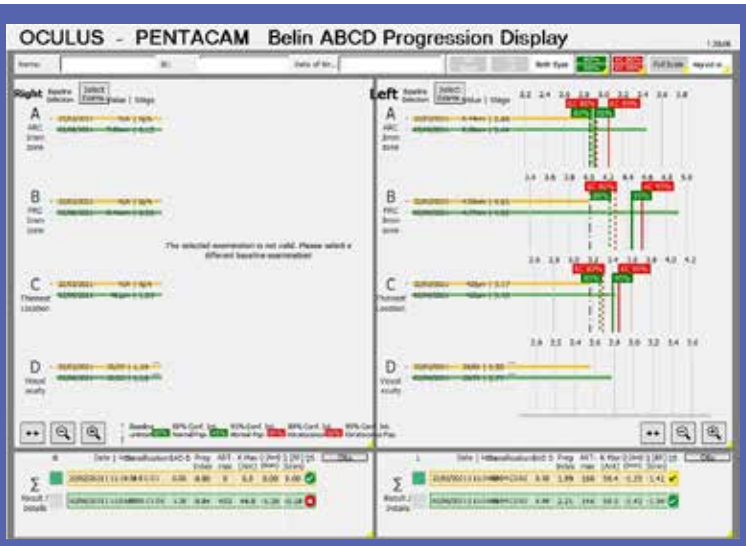

FIGURE 5. Note the sensitivity in diagnosing progression improvement in OS based on the axial subtraction map and Pentacam Belin ABCD display, despite the mild decrease in Kmax values from 60.6D to 59.5D.

Conclusion

KC is a progressive disease that can negatively impact a patient's visual function and overall quality of life. With the advent of highly sensitive and specific advanced diagnostic technologies, along with our ability to halt the progression of the disease with CXL, we now have the opportunity to preserve our patients' vision. Modern management relies on diagnosing KC as early as possible and monitoring for any evidence of progression. Should we detect progression or diagnose patients who are at high risk for progression, consideration of CXL must be made.

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Pediatrics and Keratoconus

By Ronald N. Gaster, MD, FACS,* Christina Twardowski, OD, FAAO,† and Melanie Frogozo, OD, FAAO, Diplomate CCLRT, FSLS‡

Keratoconus (KC) is a non-inflammatory, progressive, asymmetric, degenerative condition of the cornea resulting in biomechanical weakening, thinning, steepening, and increasing amounts of irregular astigmatism. KC typically starts showing corneal and refractive signs of KC during the second or third decade of life, but it often presents earlier. The condition has been reported in the pediatric population as early as age 4, with serious and rapid progression.[1]

Frequently, children with KC tend to be undiagnosed until they present with severe findings and substantial vision loss. This happens secondary to the early onset, rapid progression, and challenging eye examinations in this patient population. There is evidence to support that KC progresses at a much faster rate in pediatric patients compared to adults. In a study looking at the severity of KC upon diagnosis and its scalability over a two-year period, children were shown to be significantly more severe at diagnosis, with 27.8% being stage 4 vs 7.8% of adults.[2] This rapid progression of the cornea leads to a frequent shift in refractive findings, which can limit a child's vision if not found in a timely manner. It is important to remember these visual changes can occur during a child's vulnerable visual development period, leading to lifelong visual consequences.

KC in children usually progresses more rapidly than in adults with subsequent loss of visual acuity, worsening of myopia and irregular astigmatism, and poor vision with glasses and/or contact lenses.[3] Thus, early intervention in pediatric patients is of great importance.

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Pediatric Keratoconus Associations and Special Populations

The etiology of KC has been studied, but it remains poorly understood. It is related to both environmental and genetic factors, such as repeated eye rubbing, positive family history, and genetic syndromes. Inflammatory conditions in children, such as vernal keratoconjunctivitis, exacerbate the condition, causing frequent eye rubbing and progression. Other associated conditions with KC include atopy, Down syndrome, retinitis pigmentosa, and connective tissue disorders such as Marfan and Ehlers-Danlos syndromes. Genetic conditions such as Leber congenital amaurosis and mitral valve prolapse have also been linked to KC. Recent studies show the prevalence of KC is between 1-3% of the population.

Unfortunately, children who develop KC often present at a more advanced stage due to the difficulty of early diagnosis in this population, and most parents are unfamiliar with KC. Often, patients complain of visual loss, distortion of images, halos around lights, and starbursts. Increasing myopia and irregular astigmatism may occur rapidly. Younger patients are more likely to have corneal opacities, and if untreated, progress to keratoplasty faster than adults with KC.

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Some children progress to acute corneal hydrops with resultant pain, redness, corneal opacification, and edema, often necessitating a keratoplasty.

Clinical Examination of the Pediatric Keratoconus Patient

Pediatric patients in whom KC is suspected should have a complete eye examination, including manifest refraction, retinoscopy, slit lamp exam, ophthalmoscopy, and measurements of corneal curvature and thickness (including epithelial mapping, if available). During the slit lamp examination, there may be inferior steepening and thinning, development of corneal striae, haze, scarring, or opacities, which can all indicate clinical signs of KC. When performing retinoscopy, focusing on the reflex can provide excellent information regarding the architecture of the cornea, and it is quite accurate in determining the presence of KC.[4] In addition, remember that many times patients with early-stage KC do not have large amounts of cylinder, and asymmetric astigmatism is very common in KC patients[5] – especially children – with one eye advancing more quickly compared to the other. In the general KC population, manifest refraction against the rule and oblique axis of two diopters of astigmatism are common; this simple finding may warrant screening with corneal diagnostics such as topography.

Another important part of the examination is a detailed patient and parent history to determine if a positive family history of KC is present, and if the patient has a strong history of eye rubbing, which has been shown to be highly correlated with KC in this patient demographic. In addition, obtaining and reviewing previous ophthalmic and optometric records and prior glasses or contact lens prescriptions should be reviewed. These records can help determine if KC is present and progressing.

A decrease in visual acuity, increase in myopic astigmatism and topographic keratometry, decrease in corneal pachymetry, and/or development of corneal striae, haze, scarring, or opacities must be noted and compared to prior examinations. Close tracking of these changes should be carefully followed due to the rapid progression of KC in pediatric patients. These patients require follow-up as often as every one to three months. Typically, there is inferior steepening, thinning, and skewed radial axes on topography, and the worsening of these signs indicate disease progression. Genetic testing for a predisposition for KC is of interest. The test relies on an in-office cheek swab, which, once analyzed, provides a polygenic risk score of developing KC that highly correlates with the disease.[6]

Keratoconus progresses at a much faster rate in pediatric patients compared to adults. In a study, children were shown to be significantly more severe at diagnosis.

The differential diagnosis of KC includes congenital astigmatism, axial myopia, high myopia, pellucid marginal degeneration, and keratoglobus.

Treatment and Management Options for Pediatric Keratoconus

Treatment options for pediatric and adult KC include spectacles, contact lenses, corneal collagen crosslinking (CXL), intracorneal ring segments (very rarely used in pediatric patients), and keratoplasty, either penetrating or deep anterior lamellar keratoplasty (DALK). Although reports have been published, there is very little data on the use of intracorneal ring segments in this population. It is not standard of care and is very rarely used in the pediatric population. It is important to understand the impact each available option has for children and how this may differ from our adult patients. The preferred option depends on the stage/progression of the disease and the age of the patient. However, stopping progression with CXL is the single most important part of management of the pediatric KC patient, thus early diagnosis is imperative. In all cases, avoidance of eye rubbing and all traumas to the cornea and ocular surface is imperative. Ocular allergies must be well controlled, especially prior to any surgical procedure.

Corneal Collagen Crosslinking in Children

CXL is the only treatment for pediatric KC that has been proven to halt progression of the disease and prevent prolonged reduction in a child's visual acuity. For adult KC, the standard is to observe for progression of the disease prior to CXL. However, several authors recommend that for pediatric KC, demonstrated progression is not necessary and that CXL should be done soon after diagnosis so as not to lose visual function by possible rapid progression.

The standard epithelium-off Dresden protocol is the most common procedure in the U.S., and it is currently the only procedure approved by the FDA. Using riboflavin eye drops combined with UVA light, the goal is to increase the biomechanical stability and strength of the corneal stroma and thus halt

Figure 1. Fluorescein and a cobalt blue light can help determine appropriate sagittal depth of a scleral lens in children.

progression of the disease.[7] Approval currently is for patients as young as 14 years old. For those under the age of 14, the procedure can still be performed off-label. An ongoing FDA study down to age 10 is underway.

Alternative techniques for CXL may have benefits to the pediatric population, such as epithelium-on and accelerated. Hopefully, in the near future, epithelium-on CXL will be approved in the U.S.[8] It is proposed that there is faster postoperative recovery with less chance of infection, less chance of poor wound healing, and less pain with epithelium-on CXL. Accelerated CXL, where the UV fluence is tripled and the time of UV light exposure is reduced to one-third, thus keeping the total fluence the same, will be an improvement for children so that a shorter time for the procedure can occur. Overall, excellent post-CXL outcomes have been seen in children with stabilization or improvement in visual function, topographic keratometry, pachymetry, and cessation of progression.[9,10] It is important to note that reports have shown some late regression in pediatric patients. For those with continued progression, CXL can be repeated[11] once progression has been proven. Nevertheless, careful follow-up of these post-CXL pediatric patients is essential for many years.

Spectacles

Spectacles are limited to correcting regular astigmatism and do not optically address irregular astigmatism in KC. Children with uncorrected refractive error are at risk for amblyopia. Therefore, it is of utmost importance to provide full optical correction to young children with KC in order to avoid irreversible vision loss from amblyopia. In comparison to spectacles, medical contact lenses provide superior optical correction of high amounts of myopia and astigmatism found in KC.

Contact Lenses

Medical lens options for managing irregular astigmatism in pediatric KC include soft toric, corneal gas permeable (GP), hybrid, and scleral lenses. Mild disease may be corrected with soft contact lenses. Nevertheless, for children who have advanced KC, rigid GP optics will offer more stable and improved visual correction of irregular astigmatism over soft lenses.

Corneal GP lenses are more difficult to fit on children presenting with advanced disease signs such as corneal scarring and increased keratometry values. Problems such as lens decentration and patient intolerance in advanced KC lead to failure in corneal GP fitting.

Scleral lenses are a great option for fitting pediatric KC after CXL or corneal transplantation. Scleral lenses can be fitted as soon as two to three weeks after CXL because they vault completely over the cornea with no contact to the healing tissue.[12] Since CXL occasionally causes stromal hazing, visual acuity is initially reduced compared to baseline, but it improves during the next six to 12 months.[13]

The first consideration when choosing an appropriate scleral lens diameter is patients' horizontal visible iris diameter (HVID). Scleral lenses are designed to vault the cornea. Special testing is often difficult to perform on children, making diagnostic fitting crucial for determining the appro-

priate lens sagittal depth. In such cases, the initial sagittal depth of the lens can be based on patients' ocular sagittal depth. This can be estimated by looking at the side profile of the eye globe and determining whether the ocular sagittal depth is steep or flat. Learning to gauge sagittal depth using fluorescein and a cobalt blue light is especially useful to ensure adequate scleral lens corneal clearance in kids (Figure 1). Cooperative children are able to be examined with a slit lamp. Power of the lens for young and/or non-verbal children is determined by performing retinoscopy over the surface of the lens. In older children and adolescents, a subjective refraction can be performed over the diagnostic lens to determine the final lens power.

Corneal Transplantation

Corneal transplants for KC represent 15-20% of all corneal transplants in the pediatric population.[14] Transplantations come with a multitude of perioperative, intraoperative, and postoperative risks. In very advanced disease with central scarring and thinning, keratoplasty may be indicated.

Penetrating keratoplasty in pediatric patients requires special training and expertise, and it is associated with a poorer prognosis in pediatric patients than in adults. In addition, younger age at time of transplantation has been associated with a higher risk of rejection, leading to increased need for multiple transplants and a poorer visual prognosis.[15]

DALK is becoming more common than penetrating keratoplasty for KC due to reduced graft rejection and improved corneal stability. Unfortunately, pediatric patients often have low scleral rigidity, increased fibrin reaction, and require frequent follow-up examinations for suture evaluation and control of astigmatism postoperatively.

Although corneal transplants are a possibility and are sometimes the only option for an advanced stage of KC, it certainly presents high risks and does not guarantee a successful visual outcome. Additionally, considering age and the rate at which repeat corneal transplants are needed, it is likely that multiple keratoplasties would be necessary over the patient's lifetime.

Despite high success rates of corneal transplantation in adult KC, children have a poorer prognosis. There is an increased risk of graft failure, decreased graft survival rates, infectious keratitis, additional procedures, and increased rate of post-surgical cataract and glaucoma.[16,17] Both CXL and scleral lenses have been shown to decrease the rate of penetrating keratoplasty in KC.[18] Therefore, scleral lenses should be attempted to be fit on children with KC before referral for corneal transplantation.

Conclusion

In summary, early detection and treatment is paramount to avoid serious visual impairment. Corneal crosslinking offers a true treatment for KC, halting the corneal changes and avoiding the gamut of visual rehabilitation options. Pediatric patients with KC require early diagnosis, careful examination, and early intervention by CXL to ensure a positive visual prognosis and to avert vision loss.

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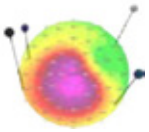

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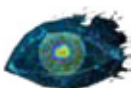

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Corneal Crosslinking for Keratoconus and Corneal Ectasia

By Peter S. Hersh, MD, FACS*,† and Steven A. Greenstein, MD*,†

Corneal crosslinking (CXL) is a treatment designed to decrease the progression of keratoconus (KC)[1] and other corneal thinning processes, such as post-LASIK or PRK ectasia. Studies have suggested that CXL can also have beneficial visual and optical effects, such as an improvement in corneal steepness, visual acuity, topography/tomography irregularity indices, higher order aberrations, and sometimes subjective visual function.[2-7]

Mechanism

In the CXL procedure, riboflavin (Vitamin B2), a photosensitizer, is administered in conjunction with ultraviolet A (UVA – 370 nm) irradiation. The reactive oxygen species (singlet oxygen) produced by this interaction, as well as UVA-excited molecules of riboflavin, result in the crosslinking effect and causes biomechanical stiffening of the cornea.[8] Most of this "crosslinking" occurs within the collagen molecules themselves and the corneal proteoglycan matrix.[9] It is unlikely that there are actual new covalent bonds between collagen fibers given the distances between the actual fibers.

Clinical Procedure

The procedure for the U.S. multicenter CXL trial was based on the technique described by Seiler and colleagues.[1] First, a topical anesthetic is administered and the central 9 mm epithelium is removed by mechanical debridement. Riboflavin is then administered topically every two minutes for a total of 30 minutes. Following riboflavin administration, riboflavin absorption is confirmed on slit lamp examination (Figure 1). Pachymetry measurements are performed, and if the cornea is <400 µm, hypotonic riboflavin is administered, one drop every 10 seconds for two-minute sessions, until the stroma has swelled to ≥400 µm; the goal is to provide adequate corneal thickness to protect the endothelium from damage by the UV-riboflavin interaction. The cornea is then exposed to UVA 365 nm light for 30 minutes at an irradiance of 3.0 mW/cm^2 (Figure 2).

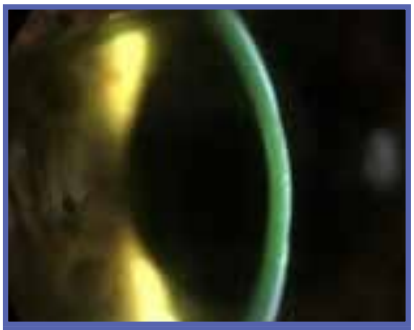

FIGURE 1. Riboflavin absorption confirmed.

FIGURE 2. Cornea exposed to UVA.

Postoperatively, antibiotic and corticosteroid drops are administered and a therapeutic contact lens is placed. The contact lens is then removed after the epithelial defect is closed.

Outcomes

Visual Acuity

Generally, CXL appears to stabilize visual acuity, and in some cases offer a modest improvement. In the U.S. multicenter trial, uncorrected and corrected distance visual acuity improved by an average of 4.4 logMAR letters and 5.7 letters, respectively.[10,11] Individually, best corrected visual acuity improved by 10 letters or more in 28% of eyes treated, 5% of eyes worsened by 10 letters or more, and all other eyes remained within 10 letters of preoperative visual acuity, one year after CXL.

Corneal Topography

Maximum keratometry on the corneal topography map remains the standard topographic indicator of CXL success since it measures, in general, the severity of the KC cone. In the U.S. multicenter trial, maximum keratometry flattened by 1.6D one year post-CXL. Individually, 31% of eyes flattened by ≥ 2D, 6% of eyes steepened by ≥2D, and all other eyes remained within 2D of preoperative maximum keratometry measurements. In other studies of long-term outcomes, maximum keratometry remained stable in over 90% of adult patients (>18 years old), and 75% of pediatric patients (<18 years old).[12-14]

PHOTO CREDIT: PETER S. HERSH, MD, FACS

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Clinical Time Course

In our study of the time course after CXL, there was a significant worsening of vision and steepening of the KC cone one-month post-operation.[7] These changes appear to plateau at three months and improve thereafter. These postoperative outcomes are consistent with CXL-associated corneal haze changes over time (see below), suggesting stromal and epithelial remodeling after CXL.

Biomechanical Effects of Crosslinking

Wollensak et al.[8] reported that immediate stress measurements increased by 71.9% and 328.9% in porcine and human corneas, respectively, after CXL. In rabbit corneas, these increases in stress measurements were maintained between 69.7% and 106% at eight months post-operation.

To date, it has been difficult to quantify these biomechanical changes *in vivo.* The Ocular Response Analyzer (ORA, Reichert Inc.) and the Corvis (Oculus, Germany) are commercially available devices designed to obtain *in vivo* measurements of corneal biomechanical properties. Previous studies were able to demonstrate changes in Corvis and ORA measurements consistent with corneal biomechanical changes after CXL.[15,16] Our previous work analyzing ORA measurements after CXL did not show a significant change in biomechanical descriptors one year after CXL.[6] In the future, techniques such as Brillouin microscopy may prove to be useful in quantifying *in vivo* biomechanical changes after crosslinking.[17]

Complications

Early in the postoperative course after CXL, there are typical complications of the epithelial wound-healing process. In the U.S. multicenter trial for CXL, 22.5% of patients had a remaining epithelial defect one week after their procedure. One patient developed ulcerative keratitis three days post-CXL, which was resolved with topical antimicrobial therapy. Of 102 eyes treated in the study at one year, a corneal scar was noted in one eye, endothelial folds in another eye, and an irregular corneal epithelium was also observed. The complications after CXL for patients with post-LASIK/PRK ectasia were similar; however, one post-LASIK patient developed epithelial ingrowth, which required a flap lift and epithelial removal at that time.

Postoperative Haze

On clinical examination, corneal haze has been noted after the CXL procedure

FIGURE 3. Corneal haze after CXL.

(Figure 3). CXL-associated corneal haze appears as a dust-like change in the corneal stroma or a mid-stromal demarcation line.[18] Corneal haze has been confirmed using confocal microscopy as well and can be objectively quantified using Scheimpflug densitometry.

Similar to the time course of clinical outcomes after CXL, there appears to be an increase in haze, which peaks at one month and plateaus between one and three months.[3] Between three and six months, the cornea begins to clear and continues to return toward baseline at one year. This time course of haze and other outcomes may result, in part, from anatomic and structural changes of corneal collagen fibrils, such as compression of collagen fibrils, changes in corneal hydration, keratocyte apoptosis, changes in glycosaminoglycans, and other healing effects after CXL. It is unclear whether postoperative haze is a true complication or rather a desired wound-healing effect demonstrating the efficacy of the CXL procedure.

Outcome Predictors

The primary goal of CXL is to stabilize disease progression. We performed an analysis to determine which patients would be good candidates or contraindicated for CXL.[19] Our multivariate analyses revealed the only independent predictor of a change in postoperative best corrected vision after CXL was preoperative best corrected visual acuity. Those eyes with worse preoperative best corrected visual acuity were more likely to experience an improvement of ≥2 Snellen lines. Specifically, eyes with a preoperative Snellen visual acuity of 20/40 or worse were 5.9 times more likely to improve by two lines or more. Regarding postoperative topography, eyes with a maximum K ≥55D were 5.4 times more likely to have topographic flattening ≥2D after crosslinking compared with eyes with flatter corneas.

From the viewpoint of clinical decision-making, since no independent predictors of failure of CXL to stabilize topographic disease progression were identified, it is reasonable that all eyes with progressive KC should be considered for CXL with the goal of diminishing disease progression. With regard to postoperative best corrected vision, it might be reasonable to conclude that eyes with worse vision initially would expect the greatest chance of actual visual improvement. Furthermore, all eyes, irrespective of preoperative best corrected visual acuity, are equally likely to remain stable (within two lines of best corrected visual acuity); however, eyes with initially good vision (better than 20/40) may be somewhat more susceptible to a loss of one line of best corrected vision. Therefore, eyes with good visual acuity and progressive disease, or eyes with a high risk for progressive disease (e.g. pediatric patients), may still benefit from CXL treatment, but the practitioner should be aware of the possible complications, and the patient should be properly counseled.

Advances in Corneal Crosslinking

There are several modifications to the FDA-approved CXL procedure that are currently under investigation. Transepithelial CXL, in particular, is a variation of the standard procedure in which the corneal epithelium is not removed. This technique may offer several advantages, including faster recovery time and fewer wound-healing complications. However, early results of transepithelial CXL have been mixed.[20,21]

Multiple substances, such as benzalkonium chloride, EDTA, and sodium iodide have been used to promote riboflavin penetration through the epithelium and improve the actual crosslinking reactions. Additionally, iontophoresis and additional corneal oxygenation have been used; the former to improve the penetration of riboflavin, and the latter to improve oxygen-dependent CXL reactions with the goal of improving transepithelial CXL outcomes.

In addition to the riboflavin used for transepithelial CXL, modifications to the standard dextran riboflavin used for traditional CXL have also been made. Standard dextran riboflavin has a dehydrating effect on the corneal stroma, and frequently hypotonic riboflavin is required to swell the cornea before UV light therapy is initiated. Hypotonic forms of riboflavin, methylcellulose riboflavin, and more concentrated versions of riboflavin have all been studied.[22] Early studies appear to indicate that CXL is successful in conjunction with most of these riboflavin formulations; however, long-term and prospective studies are required to determine the optimal riboflavin composition for transepithelial CXL.

Further modifications to the CXL procedure have been suggested for thin corneas. In the FDA trial, the cornea was required to be thicker than 400 µm to perform CXL treatment. In addition to the alternative forms of hypotonic riboflavin and the transepithelial CXL approach discussed above, further modifications such as contact lens or lenticule-assisted CXL can be considered. In both cases, the epithelium is removed from the patient's cornea, and either a contact lens soaked in riboflavin or a corneal lenticule preserved from a previous SMILE procedure are used to cover the patient's cornea and modulate the depth of the CXL in the patient's stroma. Finally, algorithms are being developed to optimize the time of UVA light exposure (less than the standard 30 minutes) to customize the depth of CXL treatment, depending on the corneal thickness.

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#02 OF SERIES

KERATOCONUS and CROSS-LINKING

Practice Considerations in Managing Keratoconus and Cross-Linking

Nicole Albright, OD
Clinic Director,
Moses Eyecare Center
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KEY TAKEAWAYS

- Managing keratoconus (KC) meets patients' needs as part of a medical-model optometric practice.
- There is no global period for cross-linking; each follow-up visit is billed as an office visit.
- The progressive KC patients I have referred for cross-linking have become loyal patients.

Many optometrists are shifting towards a medical model of practice, managing chronic conditions with ocular manifestations, including dry eye, glaucoma, and diabetes. Diversifying the services you offer can better meet the needs of your patients.

Managing keratoconus (KC) is a great way to "lean in" to that more comprehensive medical model of optometric care. About 70% of KC patients first present to an optometrist's office,[1] which means that we have a unique opportunity to identify this progressive disease and refer patients for the FDA-approved iLink® cross-linking procedure in the early stages, before there is permanent vision loss. After treatment, we can continue to address the patient's vision needs over time.

Collaborating with cornea specialists in the care of KC patients has provided comprehensive patient care and strengthened my relationships with ophthalmologists in the community. When they realize that we share a common goal of helping our KC patients, it opens the door not only to specialty contact lens fitting and follow-up care after cross-linking, but to collaboration and referrals in other areas, as well.

Follow-up care after iLink® cross-linking is similar to that required for PRK, with five or more visits and one or more contact lens re-fittings in the first year being typical. After that, KC patients will continue to need vision care and annual medical eye care appointments to monitor for any further corneal changes.

While the timing and frequency of office visits may vary by patient and at the doctor's discretion, there is no global period for cross-linking. Any necessary post-treatment visits and diagnostic tests, such as pachymetry and topography, are typically billed separately.

I personally find scleral lens fitting and the management of progressive KC patients who are undergoing cross-linking to be among the most rewarding things I do as an optometrist. First and foremost, we offer them a treatment that can slow or halt KC progression. Furthermore, patients are so very appreciative when you can pinpoint the cause of and address their visual quality problems with contact lenses.

Modeling suggests that iLink® cross-linking saves the average patient nearly $9,000 in direct medical costs and nearly $44,000 in lifetime costs[2]—and that doesn't even include the impact on their mental health and well-being. In addition to the cost savings, it is very fulfilling to me to know that I can help protect a young person with early progressive KC from progressing to the advanced stages of the disease, potentially avoiding a lifetime of vision loss and the need for corneal transplant surgery. One study showed a 25% drop in corneal transplants after the introduction of cross-linking.[3]

Our KC patients are grateful for this care. They will rave about you on social media, refer family and friends—and generally become loyal patients. ■

With your medical management and cross-linking referrals, modeling[2] suggests that patients benefit:

$8,677
DIRECT MEDICAL COST SAVINGS PER PATIENT

$43,759
REDUCTION IN LIFETIME COSTS PER PATIENT

1.88
INCREASE IN PATIENT QUALITY-OF-LIFE-YEARS

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INDICATIONS
Photrexa® Viscous (riboflavin 5'-phosphate in 20% dextran ophthalmic solution) and Photrexa® (riboflavin 5'-phosphate ophthalmic solution) are indicated for use with the KXL System in corneal collagen cross-linking for the treatment of progressive keratoconus and corneal ectasia following refractive surgery.

IMPORTANT SAFETY INFORMATION
Corneal collagen cross-linking should not be performed on pregnant women.
Ulcerative keratitis can occur. Patients should be monitored for resolution of epithelial defects. The most common ocular adverse reaction was corneal opacity (haze). Other ocular side effects include punctate keratitis, corneal striae, dry eye, corneal epithelium defect, eye pain, light sensitivity, reduced visual acuity, and blurred vision.
These are not all of the side effects of the corneal collagen cross-linking treatment. For more information, go to www.livingwithkeratoconus.com to obtain the FDA-approved product labeling.
You are encouraged to report all side effects to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

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Another variation to standard CXL is accelerated CXL. In this procedure, the cornea is exposed to a higher power of UV light over a significantly shorter period of time. *Ex vivo* studies, however, have shown that despite a constant total dose of 5.4 J, increased irradiance levels result in less postoperative mechanical stiffening of the cornea compared to standard treatment. Higher irradiance levels likely cause the free radical conversion of oxygen to outpace oxygen replenishment of the cornea, resulting in less of a CXL effect. *In vivo* studies, however, have shown that accelerated CXL (for example, 9 mW/cm^2 for 10 minutes), may have similar results to the standard CXL procedure, and pulsing the UVA light may also increase oxygen replenishment in the cornea during the accelerated procedure. Moreover, despite delivering a higher power of UV light, this technique appears to be safe for the corneal endothelium because of the shorter exposure time and less penetration depth.

Further customizations of the CXL procedure include topographically "customized" treatments. Using this type of approach, the UV light is restricted to only the cone itself, rather than diffusely over the entire cornea. Biomechanical studies of the KC cornea using Brillouin microscopy suggest that the pathology in KC is limited to the area of the cone itself. Thus, limiting treatment to this area may adequately decrease progression of the disease while also improving the topographic response.

Finally, there has been increasing interest in the use of corneal collagen CXL as part of a larger treatment algorithm for patients with KC and post-LASIK/PRK ectasia. While there are many patients who may benefit from CXL alone, there are other patients who may benefit from CXL as an adjunct procedure to stabilize the cornea. Other procedures, such as intracorneal ring segments[23,24] and PRK,[25] may induce more initial flattening of steeper cones and improve the contour of the ectatic cornea; however, CXL may be required to better stabilize these changes over time.

Corneal crosslinking is a unique treatment to stabilize and even improve the visual acuity and topography of patients with KC and ectasia. In the future, faster and more precisely guided UV light delivery systems, new forms of riboflavin, and algorithms to customize treatments will continue to improve the safety and efficacy of this procedure.

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#01 OF SERIES

KERATOCONUS and CROSS-LINKING

Optometry's Role in the Patient Journey

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KEY TAKEAWAYS

- Cross-linking with the only FDA-approved iLink™ System can stop or slow progressive keratoconus.
- Early diagnosis and treatment are essential to preserve as much vision as possible.
- Optometrists are uniquely positioned to change lives and protect vision by identifying at-risk patients in the mild stages of the disease.

Keratoconus (KC) is a degenerative condition with onset in early adolescence. It is characterized by gradual thinning of the corneal stroma, causing a cone-shaped protrusion and worsening vision. As doctors of optometry, our top priority with these patients should be to manage their disease—and only secondarily to correct their vision.

A referral for corneal collagen cross-linking, which has been shown to halt progression in 92%-100% of cases[1], may be able to preserve vision. As with any surgical procedure, there is the potential for complications and cross-linking may not be right for everyone. After treatment, patients will still need regular optometric care. Follow-up care is similar to that required for PRK. However, there is no global period, so each follow-up visit is charged as a regular exam.

Without cross-linking treatment, progressive KC typically continues to worsen until around age 40 (and sometimes longer), with 10%-20% of cases requiring a penetrating keratoplasty (PKP).[2] When patients reach the advanced stages of keratoconus, it becomes a debilitating disease that affects every aspect of their lives. Worsening KC severity is associated with significant declines in reading, mobility, and emotional well-being quality of life (QoL) scores.[3] The impact on QoL can be even greater than that of retinal diseases and can be felt even when one eye still has good vision[4] so it is important that patients get help as early as possible.

In the U.S., when cross-linking is performed with the iLink™ platform (Glaukos), the only FDA-approved cross-linking system, it is generally covered by insurance for 96% of those with commercial insurance. In a recent simulation model, treatment with iLink™ was found to be highly cost effective, resulting in a 26% reduction in PKPs and patients spending 28 fewer years in the advanced stages of KC.[5] Young patients who can be treated early while their vision is still good have the most to gain.

That's where optometrists' role becomes so critical. Our awareness of early progressive KC signs and risk factors can be nothing short of life changing for that young myope in our chair. There is no need to wait until a patient has lost vision or has slit lamp signs (e.g., thinning or striae) to refer for a more in-depth KC evaluation. It is standard of care to intervene with cross-linking upon detection of progression.[6]

Advanced tomography/topography provides the most sensitive and accurate diagnostic information. However, there are a number of signs and symptoms that should heighten suspicion of KC and prompt further testing, either in the practice or by referral. These include myopic shift, rapidly changing astigmatism, vision that won't correct to 20/20 (with no other known reason), distorted mires on manual keratometry, and scissoring or an irregular retinoscopy reflex. Patients with a history of eye rubbing, connective tissue disease, Down syndrome, or a family history of KC are also at higher risk.

By promptly referring these patients for further testing and, if warranted, iLink™ cross-linking treatment, optometrists are uniquely positioned to protect and preserve patients' vision over their entire lifetime. ▪

With Cross-Linking[5]

26% fewer PKPs | **28 fewer years in late-stage KC**

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Surgical Management of Keratoconus

By Steven A. Greenstein, MD[*,†] and Peter S. Hersh, MD, FACS[*,†]

Historically, there were three treatment options for keratoconus (KC) management to achieve visual correction. Patients with mild KC were prescribed spectacles or standard soft contact lenses. In more moderate cases, when the vision was not adequately corrected with spectacles or soft contact lenses, a specialty contact lens (historically, a corneal rigid gas permeable lens) was fitted. Ultimately, if a patient could not be fitted or tolerate a specialty contact lens or did not achieve adequate visual correction with the lens, then a full-thickness penetrating keratoplasty was required.

Modern KC management requires a comprehensive approach, which can be individualized to each patient. This approach can be broken down into three key steps. While not every KC patient requires a surgical procedure, it is important to consider these steps when evaluating KC patients.

The first step in modern KC management is ensuring corneal stability with corneal crosslinking (CXL). Currently, in the U.S., iLink (KXL, Photrexa, Photrexa Viscous, Glaukos, USA), with removal of the corneal epithelium, remains the only FDA-approved CXL procedure for patients with progressive KC.[1] While CXL does appear to stabilize the KC cornea, there is only a modest amount of corneal flattening and visual improvement expected after

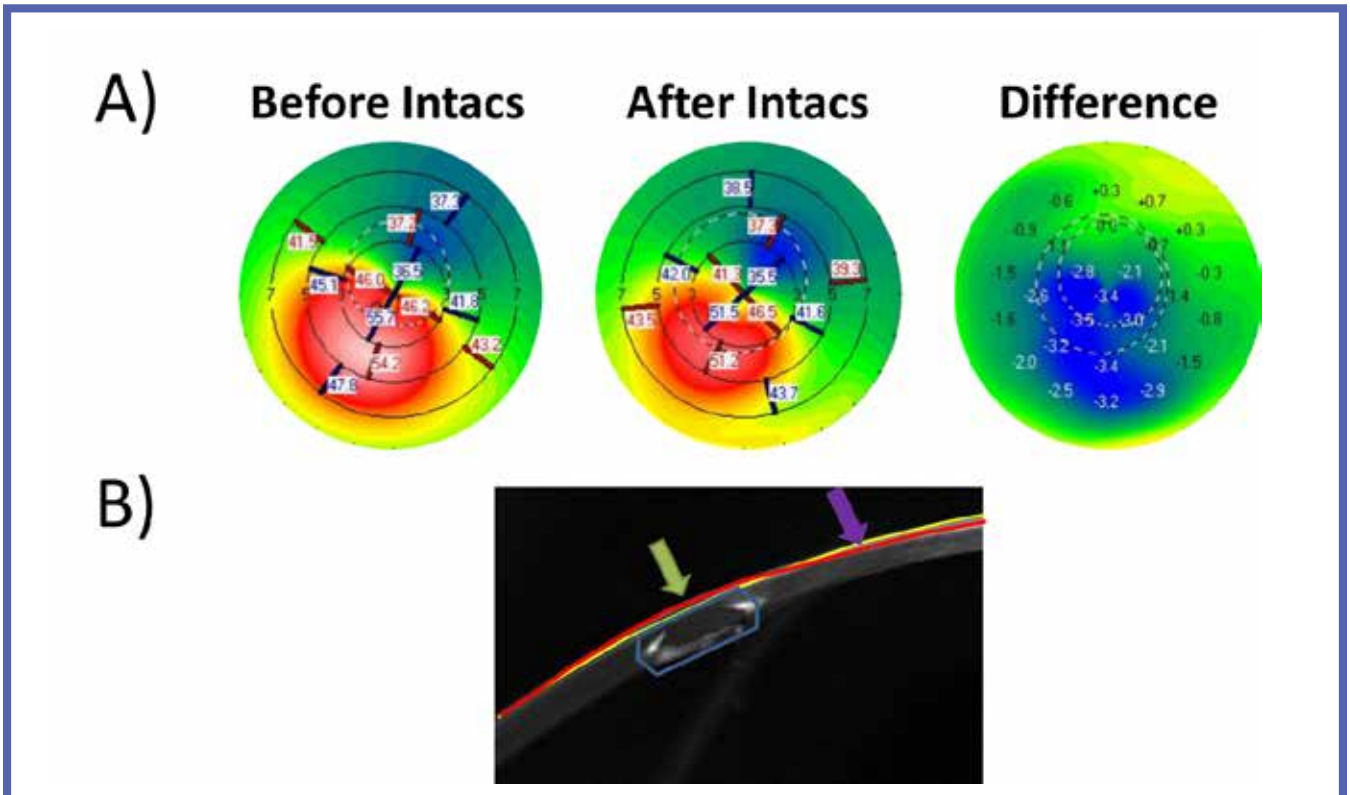

Figure 1. A) Axial topography maps before and after Intacs placement. B) Scheimpflug image after Intacs placement. The yellow and red lines represent the preoperative and postoperative corneal curvatures, respectively. The green arrow indicates the elevation of the postoperative cornea over the Intacs segment, and the purple arrow shows the flattening inside of the Intacs segment.

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CXL alone.[2] It is important to counsel the patient that the goal of CXL is to decrease KC progression, not improve visual acuity. Therefore, the second step in the modern surgical management of KC includes an evaluation of each patient for further improvement of their corneal topography or tomography. This improvement can be achieved with procedures such as intracorneal ring segments, topography-guided excimer laser, conductive keratoplasty, and in more advanced cases, lamellar or penetrating keratoplasty. Some of these procedures can be performed simultaneously with CXL, while others may benefit from a sequential approach. Finally, the third step in KC management is best visual correction. In most cases of KC, specialty contact lenses are still required to achieve best-corrected vision for patients; however, after stabilization of the cornea, and improving corneal topography, an increasing number of our KC patients can achieve adequate visual correction with further excimer laser or intraocular lenses (IOLs).

Topography-Altering Procedures

Intracorneal Ring Segments

Worldwide, there are multiple intracorneal ring segments available for the treatment of patients with KC. In the U.S., Intacs (Corneagen, USA) are the most commonly used intracorneal ring segment. Intacs were originally FDA approved for the indication of myopia and were later approved under a human device exemption for KC.[3,4] Intacs likely provide a modest structural support to the keratoconic cornea, and each segment induces topographic flattening inside of the segment itself (Figure 1). Proper placement of these segments around the cone is critical to achieve optimal results. It is also important to select a segment of the appropriate thickness to modulate the necessary flattening for adequate topographic improvement. Most eyes with KC only require placement of one segment to achieve adequate results. Furthermore, Intacs can be performed simultaneously with CXL to achieve topographic improvement and stability of the cornea at one time.[5w]

In our practice, we performed a randomized prospective study of 198 eyes with KC.[5] Intacs placement resulted in improvement of uncorrected and best spectacle corrected visual acuity, flattening of maximum keratometry (K_{max}), and improvement of corneal symmetry (I-S value). On average, K_{max} flattened by -2.5D, the average maximum flattening in the cornea was -7.5D, and the average I-S value improved by -3.9D. Uncorrected visual acuity improved by 2 LogMAR lines, and best spectacle-corrected visual acuity improved by 1.1 LogMAR lines six months after Intacs and CXL were performed. Furthermore, higher order aberrations and subjective visual outcomes improved six months after Intacs/CXL.[6]

Now, with more treatment options available to improve corneal topography, Intacs are primarily indicated to improve uncorrected and best spectacle corrected visual acuity. Intacs can also be placed before ultimately performing topography-guided photorefractive keratectomy (TGPRK) or conductive keratoplasty to further improve vision. Caution should be used when performing Intacs to improve vision with contact lenses or ease contact lens fitting. In some cases, Intacs placement can make specialty contact lens fitting more challenging. Bearing down or rubbing of the lens on top of the Intacs segment may result in contact lens discomfort, and resulting tissue damage can lead to complications such as extrusion of the segment. Collaborative care with the surgeon and contact lens practitioner is imperative to discuss the goals of Intacs surgery and contact lens wear after surgery to ensure proper expectations for postoperative outcomes.

It is also important to counsel patients that some Intacs segments may require future removal. In our center, we reviewed 593 Intacs that were placed in patients with KC,[7] and 6.1% of these patients required Intacs explantation. A total of 23 eyes (3.5%) required explantation for subjective visual complaints, including increased glare, halo, or worsening subjective vision. A total of 15 eyes (2.6%) required explantation for medical complications, including both infectious and non-infectious keratitis, and extrusion of the Intacs segment.

Topography-Guided Photorefractive Keratectomy (TGPRK)

Topography-guided excimer laser (Contoura, Alcon, USA) was originally approved for LASIK.[8] TGPRK in KC is an off-label use of this procedure. Unlike conventional or wavefront-optimized excimer procedures, which use a refraction to guide the laser ablation pattern, TGPRK uses Placido disc imaging to create a customized ablation pattern to improve postoperative corneal symmetry. This technology may improve LASIK outcomes for certain patients with myopia and astigmatism,[9] and now this technology can also be used to treat irregular corneal astigmatism in patients with KC.[10] Transepithelial topography-guided PRK, in which the epithelium is not removed initially, can be used in patients with KC to treat more advanced cases (Figure 2), and to limit the potential myopic shift that may be induced in many of these cases.

In a retrospective review of 25 eyes with KC that received transepithelial TGPRK, we found that uncorrected visual acuity significantly improved by 3.5 LogMAR lines, and best spectacle-corrected visual acuity improved by almost 1.5 LogMAR lines (although this BSCVA

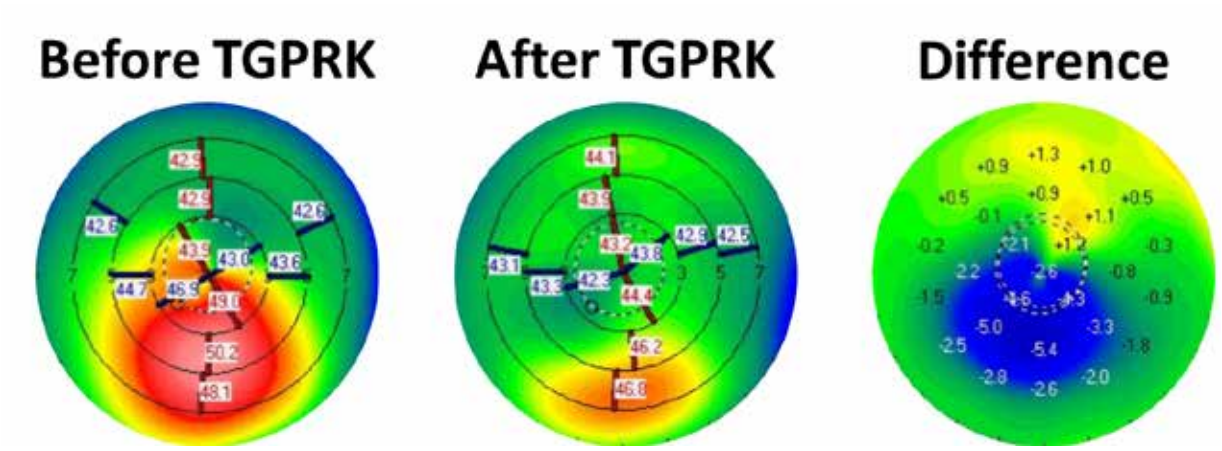

Figure 2. Axial topography maps before and after transepithelial topography-guided PRK.

improvement did not reach statistical significance).[11] On average, 39 microns of stromal tissue was ablated and maximum keratometry flattened by -4.7D. All patients were treated with CXL.

Adjunctive crosslinking is important since TGPRK is an ablative procedure, and the resulting corneal pachymetry is thinner postoperatively. Thus, CXL is usually indicated as an adjunctive procedure to stabilize the treated corneas over time. Whether CXL should be performed simultaneously[12] or sequentially[13] is still under investigation. In addition, TGPRK can be used after Intacs placement or other corneal inlays to further improve a patient's uncorrected and corrected vision.

Corneal Transplantation

Even with the advancement of modern surgical management, corneal transplantation still plays an important role in improving corneal topography and vision. Currently, the most common indication for KC corneal transplantation is corneal scarring. The preferred method of corneal transplantation in KC is deep anterior lamellar keratoplasty (DALK); however, patients with corneal endothelial pathology may still benefit from a full-thickness penetrating keratoplasty. With modern contact lens technology, it is rare for a KC patient to require corneal transplantation for contact lens intolerance or inability to wear contact lenses based on corneal curvature limitations.

In general, the number of penetrating keratoplasties performed in the U.S. has decreased since 2010.[14] This is primarily due to the increase in endothelial keratoplasties performed. Specifically, corneal ectatic diseases are now the second most common indication for penetrating keratoplasty, and there has been a 56% reduction in the number of penetrating keratoplasties performed for ectasia patients since 2016.[14] This is the same year that CXL was FDA approved in the U.S. During the same time period, there has also been an increase in the number of DALKs performed in the U.S., with corneal ectasia being the most common indication for this procedure.

There are multiple potential benefits of DALK since KC is primarily a stromal disease and corneal transplantation is typically required at a younger age than other corneal pathologies. Additionally, eyes with KC usually have healthy endothelium, which can be preserved with a DALK procedure. Postoperatively, sutures can be removed earlier after DALK, and there appears to be fewer intraocular complications, including glaucoma and cataract formation. A meta-analysis comparing DALK and penetrating keratoplasty (PKP) showed significantly better postoperative endothelial cell count and improved postoperative spherical equivalent in post-DALK patients. There was a trend toward better corrected visual acuity, topographic cylinder, and refractive cylinder in patients with PKP; however, these trends did not reach statistical significance.[15]

Despite this analysis, many corneal surgeons still prefer full-thickness keratoplasty, given the technical difficulty of deep lamellar procedures in corneas with severe thinning and scarring. DALK is a technically more challenging procedure than PKP. Multiple techniques such as manual dissection, "big bubble,"[16] and "groove and peel,"[17] have been proposed to make the DALK procedure more reproducible. Each of these techniques have certain advantages and disadvantages to performing this procedure. Modern instrumentation and femtosecond laser technology[18] will hopefully continue to improve our ability to perform reproducible DALK procedures.

Future Procedures

The future of KC surgical management includes the use of fresh,[19] preserved,[20] and bioengineered[21] corneal tissue to create corneal inlays, and Bowman layer transplants.[22] These inlays can be created manually or with a femtosecond laser, and they frequently can be used in more severe cases of KC than TGPRK or Intacs procedures. In addition, corneal tissue inlays offer improved biocompatibility, potentially fewer long-term complications, and a more customizable procedure for specific corneal topography.

Special Considerations/Acute Hydrops

Acute hydrops can be a devastating complication for patients with advanced KC. Frequently, hydrops will result in extensive scarring of the cornea, which if located over the visual axis, may result in significant worsening of visual acuity. Historically, observation was the initial management of these cases, waiting for corneal edema to resolve, and resultant scarring to form. If scarring is visually significant, then a PKP may be performed, and if not, then a specialty contact lens can be refitted for the patient. Resolution of corneal edema can take months, significantly impacting a patient's quality of life during that time.

More recently, surgical options such as gas or air tamponade,[23] suturing of the Descemet's break,[24] and mini DMEK[25] have been suggested to accelerate the recovery process. This may allow a patient to return to their contact lens wear sooner and may decrease postoperative visually significant scarring. Additionally, there are some case reports of performing a primary DALK in cases of acute hydrops to improve visual outcomes more rapidly.[26]

Vision Correction Procedures (Non-Topography Altering)

Once a KC cornea has been stabilized with CXL and topography has been optimized, then one must decide how to improve the remaining correctable vision for each patient. In some cases, this can be done with glasses or specialty contact lenses. In other cases, this can be done surgically with a refractive excimer laser procedure (PRK) or phakic/pseudophakic IOL. Those who benefit most from these surgical procedures are typically patients with adequate spectacle or soft contact lens correction.

In cases of adequate spectacle correction, PRK can be performed in a more traditional refractive approach to achieve improved uncorrected visual acuity. It is important to make sure that the cornea has an adequate stromal thickness for such an ablation. Additionally, a KC patient can also benefit from a phakic IOL, which can be placed in the anterior chamber or in the sulcus.[27] The most common phakic intraocular lens used in the U.S. is the Implantable Collamer Lens (ICL, STAAR Surgical, USA). This can be placed in the sulcus to improve myopia and astigmatism. In these cases, the advantage of a phakic intraocular lens is there is no further ablation performed on the cornea, and therefore, corneal pachymetry does not factor into placing the phakic IOL. Adequate anterior chamber depth and endothelial cell count is required to safely place these IOLs.

Similar to phakic IOLs, pseudophakic IOLs can be used to improve uncorrected vision for presbyopia or cataracts. In general, cataract surgery in patients with KC can be particularly challenging.[28] Accurate biometry measurements can be difficult to obtain. The axial length measurement can be complicated by the decentered apex in KC corneas, and difficulty measuring the axial length along the true visual axis is common. Accurate anterior keratometry measurements can also be difficult to measure, and many current IOL formulas do not adequately account for the posterior curvature of the KC cornea. Certain formulas such as the Barrett and Kane formulas have developed specific KC adjustments, which may help in choosing an IOL more accurately.[29]

In all cases, one must be prepared for postoperative refractive surprises and for an IOL exchange if needed. With modern KC management, and the three-step approach outlined above, all KC patients with a visually significant cataract should be evaluated for topography-altering surgery to offer an additional opportunity to improve visual results after IOL placement. With adequate spectacle correction or regular topographic astigmatism, toric IOLs can be very helpful in many cases. However, placement of a toric IOL will require fitting of a front surface toric contact lens in patients who still require a contact lens postoperatively. Therefore, in our practice we usually limit our use of toric lenses to patients with symmetric corneal astigmatism congruent to their refractive

The future of keratoconus surgical management includes the use of fresh, preserved, and bioengineered corneal tissue to create corneal inlays.

cylinder. Also, given the multifocality of the KC cornea, extreme caution is required when considering multifocal or extended depth of focus IOLs in KC.

The ability to stabilize the cornea with CXL has created the opportunity to surgically improve corneal topography/tomography and both corrected and uncorrected visual acuity. Many of these patients can benefit from the ability to wear spectacles for more functional vision after topography-altering surgery. A specialty contact lens may be fit to achieve best corrected visual acuity, and these patients can choose to wear spectacles during times of less visual demand. This may decrease contact lens intolerance and preserve the ability to wear specialty contact lenses for times of higher visual demand throughout their lives.

Additionally, diagnosing KC early remains critical to stabilize the cornea prior to disease progression. Modern surgical treatments can then be performed to improve corneal topography and both uncorrected and corrected vision. When necessary, modern technology has also improved corneal transplantation, in particular, deep anterior lamellar keratoplasty procedures. New surgical procedures, such as corneal tissue derived intracorneal ring segments, may offer the opportunity to treat patients with a more customized, topography-altering surgical treatment for improved visual correction in KC.

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OVERVIEW

Managing patients with keratoconus can be challenging—but research in the field is rapidly bringing more opportunities for improved outcomes into eye care clinics. Marked by thinning and bulging of the cornea, keratoconus can lead to severe blurring and visual distortions, making early diagnosis crucial for appropriate management.

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- Create strategies to accurately diagnose patients and classify their severity of keratoconus
- Explain the safety and efficacy data supporting currently available keratoconus therapies
- Evaluate clinical trial data for treatments being investigated for the management of keratoconus
- Describe optimal approaches to patient-centered keratoconus care that incorporate their individual characteristics and goals

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Specialty Contact Lenses for Keratoconus

By Melissa Barnett OD, FAAO, FSLS, FBCLA[*], Gloria Chiu OD, FAAO, FSLS[†]
John D. Gelles, OD, FAAO, FIAOMC, FCLSA, FSLS, FBCLA[‡, §]

PHOTO CREDIT: SOLSTOCK

In order to improve quality of life for patients with keratoconus (KC), early detection, diagnosis, and management of KC are essential. The key to KC management is stopping progression of the disease and then addressing the patient's refractive needs. For each patient there is a unique combination of options that will provide the optimum visual outcome after progression has been addressed. This may be achieved with corneal surgical interventions, such as intracorneal ring segments, excimer laser surface ablations, or keratoplasty, or optical interventions, such as spectacles, contact lenses (CLs), or intraocular lenses. The following describes non-surgical optical correction with CLs.

First, it is important to take into account patient considerations and evaluate the patient's motivation, dexterity, their expectations of vision, and their willingness to compromise vision and comfort. Additionally, understanding their contact lens history, such as what they have been fit with in the past, may inspire the doctor to use a different modality.

Contact Lenses and Keratoconus

Contact lenses, specifically those made of rigid materials, have historically been the mainstay for visual correction of KC. The CL should provide good comfort and vision without compromising ocular health. A common misconception is that CLs treat or prevent KC progression; however, this has been disproven.[1] It is important to address this long-standing misinformation with patients, making them aware that contact lenses do not stop or prevent the progression of KC. They simply can be used to correct refractive error, and it is vital that patients are monitored regularly for corneal changes and overall corneal health for the duration of lens wear. There is no such thing as a perfect lens that will work for all cases, thus it is important for practitioners to be well versed in a variety of contact lens options for KC.

Early in the course of the disease, when optical performance is only mildly

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impacted, spectacle lenses (glasses) and conventional soft CLs may be utilized to correct refractive error.

In mild KC, glasses correction may be used solely or be used in addition to CLs. Vision may be limited since glasses do not correct for irregular astigmatism. There are myriad viable options that include commercially available soft CLs, custom soft CLs, specialty KC soft CLs, corneal gas permeable lenses (GPs), hybrid lenses, piggyback lens systems, and scleral
lenses. In early KC, soft CLs are a viable option.

In moderate to advanced cases, rigid corneal gas permeable, piggyback, hybrid, and scleral lenses enhance vision by masking the irregular corneal astigmatism. Effectively, the surface of the CL becomes the first refractive surface of the eye. As KC severity progresses, spectacles no longer provide adequate visual acuity, and specialty CLs are required for vision restoration. The CL selection can often be successful in patients who would otherwise require a penetrating keratoplasty.[2,3]

When selecting a CL modality for KC, it is essential to consider the corneal shape. In early KC, ectasia is minimal with regular or mildly irregular astigmatism. Traditional soft toric lenses, in select designs, can correct cylinder up to -5.75D and may be appropriate in these cases.

Toric Lenses

As corneal ectasia and astigmatism increase, custom soft toric lenses can be considered. If vision is acceptable on manifest refraction, custom toric lenses can accommodate sphere power ranges from -25.0D to +25.0D, cylinder powers up to -8.00D, and axis in one-degree steps. When mild to moderate ectasia and irregular astigmatism are present, custom soft lenses with broad parameters and increased center thickness can be used. The increased lens thickness and rigidity help to mask surface irregularity and higher-order aberrations.

Patients with early or mild KC may do well in commercially available toric and extended-range soft CLs, as parameters are readily manufactured. As KC progresses and if decreased acuity or lens decentration is noted with commercially available soft CLs, numerous manufacturers offer custom soft CLs with greater power ranges and parameter availability. These custom-made lenses may provide improved vision, a better fit, and greater comfort as they are tailored specifically for the patient. With advanced KC, soft CLs are limited as they tend to contour and assume the irregular KC cornea.

Gas Permeable Lenses

Masking front surface corneal irregularity necessitates a neutralizing tear lens under

a smooth refractive plane, which may be achieved with a GP.[4] Specialty soft contact lenses for KC exhibit characteristics similar to a GP and mask low amounts of corneal irregularity, as they are lathed in higher modulus (more stiff) materials or are designed with greater lens center thicknesses. Many KC soft CLs are available in silicone hydrogel materials or utilize fenestrations to minimize corneal hypoxia. With increasing corneal ectasia and irregular astigmatism, custom soft lenses may not be able to provide sufficient optics or may not be able to contour the ocular surface properly. This is when corneal rigid GP lenses can be considered.

GP lenses do not drape over the cornea like soft designs and tend to provide better optics with their rigid optical surface and tear lens; these lenses can provide adequate vision even in moderate disease with central corneal scarring. Corneal GPs remain the initial lens of choice when fitting an irregular cornea.[5] Fitting goals for a corneal GP lens are to minimally vault over the corneal apex to avoid epithelial disruption, provide mid-peripheral alignment, and moderate peripheral clearance. An ideal fit is easier to obtain in early KC. In moderate to advanced KC, it is more difficult to obtain an optimal fit due to corneal irregularities. Smaller diameter corneal GPs are successful in KC corneas with central or paracentral cones – these are sometimes referred to as "nipple" cones. Corneas with larger cone diameters are referred to as "oval" cones; decentered cones fare better in medium or large diameter corneal GPs. A poor-fitting GP may be uncomfortable and compromise ocular health. Flat-fitting GPs with associated corneal staining are a known risk factor for corneal scarring.[6] Additionally, eyes fit with flat-fitting GPs also experience more lens discomfort and put patients at a higher predisposition for corneal transplantation.[7] Proper centration and movement are essential to achieve optimal fit with good comfort and vision.

Piggyback Systems

A piggyback system containing a soft CL under a corneal GP may be a viable solution that maintains ocular health, while simultaneously improving both lens fit and vision. In advanced KC, poor corneal GP centration, lens discomfort, and ejection with blink are often experienced. Although alternative options such as a hybrid or scleral lens are preferred, at times these are not an option due to patient-related issues, such as lens handling. Utilizing a plus-powered soft CL will not only act as a bandage but will also provide a centralized convex surface to aid GP centration. Approximately 20.9% of the SCL power contributes toward the entire refractive error correction.[8] Using a low-powered, well-fitting silicone hydrogel lens of high Dk will minimize GP power modifications. Independent lens movement should be exhibited by both the soft CL and corneal GP to allow adequate tear exchange and facilitate debris removal. A piggyback system may be complicated as it requires the proper care and handling of two different sets of CLs. Prescribing a daily replacement SCL will simplify the process.

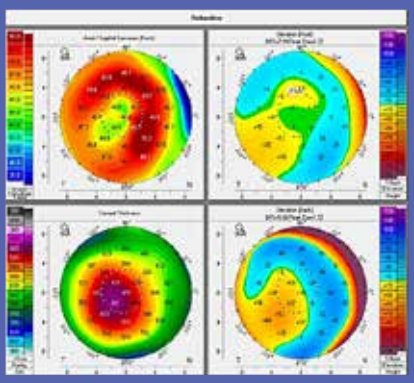

FIGURE 1. Corneal tomography demonstrating the effect of hybrid contact lens wear on corneal shape in KC. While central thinning and posterior elevation are appreciated, the anterior curvature is not consistent with the typical ectatic keratoconic shape.

Hybrid Lenses

Hybrid lenses may be considered in mild to moderate KC. The rigid center contributes to improved optics in the irregular cornea, and the soft skirt helps with stabilization. Hybrid lenses consist of a corneal GP bonded with a soft peripheral silicone hydrogel skirt. These lenses are a good lens option for those who are intolerant of corneal GPs and have difficulty handling scleral lenses. The central GP lens provides crisp optics and offers ultraviolet protection, while the soft skirt enhances lens comfort, stability, and centration when compared to a GP. It is important to describe hybrid lenses as such, as many patients have the misconception that a hybrid lens will provide the comfort of a soft lens, and thus they will have unrealistic expectations of the lens. An ideal fitting hybrid lens should vault over corneal irregularities and move freely, ensuring adequate tear exchange.

Scleral Lenses

In advanced KC with significant ectasia, thinning, and scarring, GP and hybrid lenses may not stabilize properly. This may lead to lens decentration and frequent lens loss. In these cases, a scleral lens can be utilized. Scleral lenses are large diameter GP lenses that vault the cornea and land on the scleral conjunctiva.[9] Scleral lenses are the first type of CL and were made of blown glass shells in the late 1800s.[10,11] The correction of corneal irregularity for KC was described by Fick and Kalt.[10,11] In the early 1900s, scleral lenses were manufactured from polymethyl methacrylate (PMMA) material with impression molding. Limitations of conventional scleral lenses were reproducibility, hypoxia, and design restraints. Interest in modern scleral lenses has continued to expand. Current scleral lenses have highly oxygen permeable materials, are incredibly reproducible with repeatable computer assisted

lathes, and are highly customizable with sophisticated designs. Fluid in the post-scleral lens fluid reservoir corrects corneal irregularities and provides continuous corneal lubrication and ocular protection. The beauty of scleral lenses is that they offer visual improvement and neutralize irregularities of the corneal surface. Scleral lenses have improved centration and stability compared to corneal lenses. Additionally, scleral lenses are less likely to mechanically reshape the cornea and cause corneal warpage compared to corneal GP lenses. There is improved comfort and less lens awareness since scleral lenses do not touch the cornea. In a recent study, significantly improved comfort was reported for scleral lenses compared to RGP lenses.[12] The use of scleral lenses in the management of corneal ectasias has been published extensively.

Effects of Contact Lens Wear on Cornea

In addition to selecting a CL based on corneal shape presentation, it is also important to understand the effects of CL wear on the cornea itself. Specialty lenses that rest on the cornea, such as RGP and hybrid designs, may contribute to corneal molding effects.[13] A lens that strongly bears on the surface may lead to temporary corneal flattening (see Figure 1), as well as increased risk of scarring. Practitioners should aim to fit RGP and hybrid lenses with adequate centration and movement and as close to alignment as possible to minimize corneal molding changes.

Interestingly, while scleral lenses do not typically rest on the cornea, studies have shown a flattening effect on the cornea with wear in KC patients and even in those with intracorneal ring segments. After corneal crosslinking,[14-16] the average magnitude has been reported to be about a 1D decrease in Kmax. Average pachymetry has also been reported to be 2.5% higher.[14]

Soft hydrogel toric lenses have also been shown to contribute to regional corneal swelling under the location of thicker stabilization zones within the design, as well as slight flattening of the anterior corneal surface.[17]

Effects of lens wear on corneal shape are particularly important to consider when monitoring for progressive disease or when calculating measurements in preparation for ocular surgery. It may be helpful to discontinue CL wear prior to corneal imaging to obtain the most accurate measurements in KC patients.

Methods of Contact Lens Fitting

Traditionally, CLs for KC have been fit by

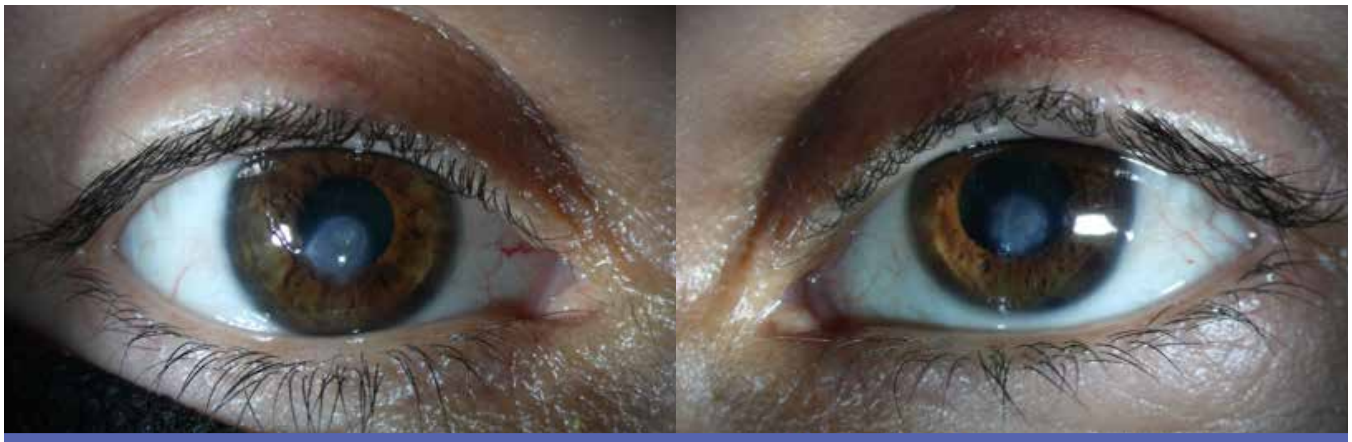

FIGURE 2. Central corneal scars in KC patient with 30-year history wearing RGPs.

application and examination of diagnostic lens sets. More recently, the use of device-driven, ocular impression-driven diagnostic lens selection, and lens design software have been utilized. The use of Placido-based corneal topography and corneal Scheimpflug tomography can be used for corneal-based lens applications, such as customized corneal GP design and selection of hybrid designs. Scleral lenses use rasterstereography and Scheimpflug-based profilometry to capture the geometry of the cornea and sclera to either aid in first diagnostic lens selection or design of a scleral lens. These systems can aid in improving CL fitting and reduce the number of lenses needed to be successful, but practitioners should have appropriate expectations as these lenses will still require modifications – they are not perfect, and thus the ability to recognize and modify a lens is still paramount.

Optical Problem Solving

In some cases, the use of specialty CLs will only improve vision to a point. This can be due to the cornea – such as posterior corneal irregularities, corneal scarring, or the CL itself by decentration, asphericity, or optic zone size. If we consider an eye as a refractive lens system and focus on the cornea, the cornea has two refractive surfaces – the anterior and posterior corneal surfaces. The anterior surface has a large index of refractive change, which occurs between air and the cornea with overlaying tears. The posterior corneal surface is where a small index of refractive change occurs between the cornea and aqueous. A CL masks the anterior surface with the CL and an interface fluid such as natural tears or saline. This makes the largest index change happen between air and the surface of the lens with overlying tears. Thus, the anterior corneal contribution to the optical quality is reduced, but not altogether eliminated, leading to residual aberrations. These can be addressed with wavefront-guided optics, which can reduce residual higher-order aberrations by approximately 50%, resulting in a one to two line improvement in visual acuity.[18-20] To learn more, refer to the Optics section.

Occasionally, a rigid lens with spherical optics will not actually improve a patient's vision compared to their refraction. This may be partly due to the compensation of anterior and posterior corneal aberrations in keratoconic corneas.[21] In these cases, a soft lens may be more beneficial, as the lens will drape to the anterior corneal surface, allowing the posterior corneal compensation to continue. Fitting a CL over a corneal scar can have variable visual results, typically impacted by the location and density of the opacity. No matter how bad the scarring appears, a rigid lens over-refraction is appropriate to assess potential visual acuity.

Additionally and specifically, scleral lenses have been shown to reduce or resolve some corneal opacities with time.[20,22] For lenses with small optic zone diameters, aberrations can be induced when the transition zone is within the pupil, such as for patients with large pupils or decentered lenses whose optic zone bisects the pupil. For these patients, increasing the optic zone size – whether by modification or design/modality change – will improve the quality of vision.

Ocular Health Considerations

Aside from corneal shape, ocular health and the condition of the ocular surface must be evaluated before fitting any type of CL. Baseline presentation should be documented, including details of the eyelids, conjunctiva, and cornea, including neovascularization, thickness and clarity, tear film, and previous surgeries. Anterior segment photography, corneal pachymetry, and corneal topography or tomography should be acquired. Scleral and other types of CL wear have been shown to alter the ocular surface in KC patients,[14-16,23,24] so practitioners need to be prepared to adjust parameters, change lens modalities, or even discontinue lens wear if necessary to

optimize ocular health. Lens wear should be avoided in most cases of active infection or acute inflammatory events.

Most KC patients are first evaluated for and fit with specialty CLs in their teens or 20s, when the diagnosis is typically made.[25] While normal age-related eye diseases are typically not present, KC patients often suffer from atopic conditions, including asthma, eczema, and allergic conjunctivitis and ocular allergies.[26,27] To enhance CL comfort and success, care should be taken to treat dry eye disease and ocular allergic conjunctivitis prior to lens fitting. Additionally, patients should be educated to address chronic ocular allergies, which may be exacerbated by CL wear.

While the particular lens modality is frequently chosen based on KC severity, practitioners may choose to switch lens modalities to optimize ocular health. Soft CLs tend to be most comfortable, even with concurrent ocular allergies, but may not provide adequate vision and comfort in moderate and advanced KC. GPs may provide better optics, but they continuously rub on the cornea. Over time, this constant friction may lead to central corneal scarring and decreased vision (see Figure 2).[13] GPs may also contribute to giant papillary conjunctivitis[28] and eyelid ptosis[29] due to frequent interaction with the upper eyelids and palpebral conjunctiva.

While scleral lenses may not be indicated for improved vision in mild or even moderate KC, this larger diameter modality has the benefits of constant lubrication from the fluid reservoir, less lid interaction given better stability of the design, and no corneal rubbing or touch. However, the larger size and coverage make them more challenging to handle and create a greater hypoxic environment compared to other lens designs.[24]

Considerations in Post-Surgical Keratoconus Contact Lens Fitting

Crosslinking

Crosslinking (CXL) is a procedure that aims to slow or halt progression of KC by utilizing riboflavin and UV-A light to strengthen the corneal tissue and has been shown to be very effective over the years.[30] It is important to reiterate that CLs do not slow or stop the progression of KC. A documented temporary effect of CXL is the transient appearance of corneal haze in the first few months.[31,32] This is not inflammatory haze nor scarring, but it is rather a change in the microarchitecture and repopulation of keratocytes after the procedure, and it may transiently affect visual performance. After epithelium-off CXL, established CL wearers can resume CL wear once the epithelium is healed and smooth, typically two to four weeks after

the procedure. New fits can be initiated at the same two to four weeks post-operative time frame. In addition to a strengthening effect, there is a subtle curvature flattening effect,[33] which may slightly impact CL fittings. As the changes are small and predominantly flatter at the point of maximum keratometry, on average, about 1.7D,[34] typically wearing the same lens as prior to CXL will not be a problem. The flattening effect may even enhance fitting. For lenses that rest on the cornea, such as soft, hybrid, and GP, very mild changes in base curve or power may be indicated.[35] For scleral lenses that vault the cornea, lens shape may not require much modification, but a prescription change may be necessary.[36]

Contact lenses, specifically those made of rigid materials, have historically been the mainstay for visual correction of KC. The CL should provide good comfort and vision without compromising ocular health.

Intracorneal Ring Segments

Intracorneal ring segments (ICRS) are rigid arc-shaped PMMA implants that are implanted within the peripheral posterior corneal stroma. These segments aim to flatten the cornea shape inside the segment by elevating the mid periphery to create a more regular curvature. This may allow for improved best-corrected vision through glasses or soft CLs. If the surface remains too irregular for soft lenses, specialty CLs may still be required.[37] However, GP or hybrid lens fitting may be challenging due to the mildly elevated rigid bands caused by the added segments. After implantation, epithelial remodeling occurs over the segment and the epithelium thins. Thus, any significant rubbing over the segment may lead to an epithelial breakdown, as most ICRS are implanted in the mid-peripheral cornea where GP and hybrid lenses rest. The preferred lenses for corneas with ICRS are either scleral lenses to vault the entire cornea, or soft lenses that gently rest or conform to the cornea. Occasionally, a piggyback lens system can be effective, as the soft lens will cushion the force of the GP on the cornea. Individuals with large pupils may occasionally notice more glare, particularly at night when the pupil size is larger, due to reflections off the ICRS. Lens design or prescription adjustments may not be able to overcome these optical aberrations. If the glare becomes too disruptive, the ICRS may need to be removed.[38] Approximately 3.5% are removed for refractive or topographic considerations.[39]

Surface Ablation

Using excimer laser procedures in the form of surface ablation is becoming a more common surgical option for patients with KC. This is partly due to CXL and device-guided ablations, such as topography or wavefront-guided excimer laser platforms. Unlike a traditional photorefractive keratectomy (PRK), which removes stromal tissue evenly across the central surface of the normal cornea to correct refractive error, the typical goal of PRK for KC is to improve corneal symmetry with tissue-sparing techniques, by removing minimal amounts of tissue from select regions of the cornea. Generally, the targeted areas are over the cone to locally flatten the apex, and outside the cone in the adjacent flat portion of the cornea to steepen the flat portion of the cornea and create a more symmetric corneal shape. This results in a cornea that is generally more optically correctable. The cornea can effectively be strengthened by using CXL, either sequentially or concurrently. Removing a controlled small amount of tissue in select cornea regions with CXL is safe, effective, and demonstrates long-term stability.[40,41] Considerations for CL fitting in this population is that there will be an improvement in symmetry and a flattening over the corneal apex. Similar to CXL, established CL wearers can resume CL wear once the epithelium is healed and smooth, typically two to four weeks after the procedure. As the changes are typically significant, modification or refitting is generally necessary. On occasion, the more symmetric shape can allow for a less complex design to be utilized.

Corneal Tissue Addition

Corneal tissue addition is a new procedure showing great promise for KC. In this procedure, allograft stromal tissue is custom shaped and implanted into the cornea via femtosecond laser techniques to provide a determined amount of corneal flattening. As the procedure is extremely customizable, the results can produce large changes to corneal curvature, some on the order of 30D. This allows for significant improvement in uncorrected and best spectacle-corrected vision. As the changes to corneal curvature and elevation are large, contact lens refitting is indicated, and the ability to utilize a less complex design is more common than other procedures.

Intraocular Lenses

The population affected by KC may have undergone surgeries to address myopic refractive error with a phakic implantable

collamer lens (ICL) or cataract surgery, like the rest of the population. These intraocular implantable lenses may have a cylindrical correction. Considerations in patients with toric implants are to address these refractive errors with CLs capable of addressing internal astigmatism. These options include soft and scleral lenses. However, some corneal GP designs can incorporate toric correction, and if the corneal GP displays exceptional stability, this may be an answer. Otherwise, for lens designs only available with spherical optics, the use of glasses with cylinder correction can be employed to address residual astigmatism.

Keratoplasty

When central corneal scarring becomes very dense and limits best corrected vision even in specialty CLs, corneal transplantation may be required. A full thickness penetrating keratoplasty or deep anterior lamellar keratoplasty can remove the affected and scarred corneal tissue. However, while post-graft corneas are clear centrally, irregular astigmatism may still be present, requiring specialty lenses for correction.[42] All lens wear decreases oxygen flow to the cornea to some degree and may contribute to edema, graft failure, or graft rejection. Care should be taken to use materials with higher Dk and optimize fits to maximize oxygen flow to the cornea. Extended wear should be avoided; patients should be instructed to never sleep or nap in their lenses. At times, topical steroids may need to be used to maintain good health and prevent corneal graft rejection. When fitting GPs, the lenses should move adequately and not rub excessively on the graft, which could cause staining and compromised health. When fitting scleral lenses, the vault should clear the cornea but be minimized, high Dk materials should be utilized, lens thickness should be minimized, haptic design should be aligned, and fenestrations or channels may be considered. Graft edema with scleral lens wear has been well documented in patients with penetrating keratoplasty.[43-45] Monitoring tomography, specifically global corneal pachymetry, is pertinent for changes in corneal transplants.

Additionally, a scleral lens challenge (several hours of in-office wear to gauge corneal response to lens wear) may be appropriate in patients with questionable graft health. Findings of a cornea with a poor physiologic response to lens wear include epithelial microcysts and bullae formation, corneal edema with stromal folds, and endothelial microcysts. These patients may complain of a rainbow effect around lights (Sattler's veil), decreasing vision, or increasingly cloudy vision over the day with lens wear. For those with these responses, limiting wear time can be helpful. These effects are not exclusive to scleral lenses. Any CL could affect the cornea in this manner; thus, frequent follow-up is appropriate. Keep in mind that grafts do not last forever. Repeat corneal transplant has been among the top three indications for corneal transplants for years (according to the Eye Bank Association of America annual report), so it may simply be time for the cornea to be replaced.

Specialty CL prescriptions are not simply placing a piece of plastic on an eye. They are used as part of the comprehensive management of ocular pathology. Ongoing evaluation of the health and integrity of the ocular surface is essential. Technology has improved our understanding of ocular surface contour and has improved our ability to manufacture lenses that more closely align to that contour to provide good vision and comfort while maintaining ocular health.

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Collaborative Care in Keratoconus

By Mitch Ibach, OD, FAAO,* and John Berdahl, MD*

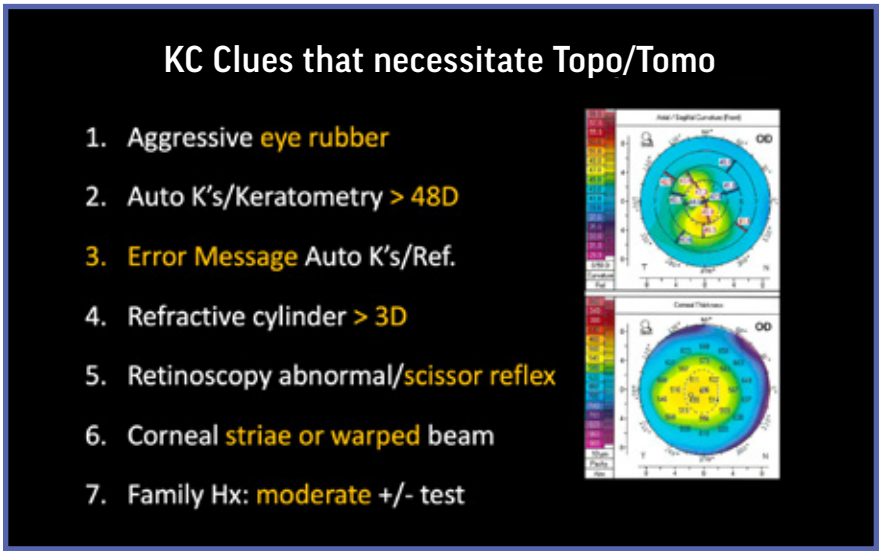


FIGURE 1. Keratoconus clues that necessitate topography/tomography

Keratoconus (KC) is an ideal condition for collaborative care between optometrists and ophthalmologists since the disease has a progressive lifecycle. A first-class KC management protocol focuses on earlier diagnosis, prioritizes arresting disease progression, and promotes visual rehabilitation with optical and surgical techniques.

Optometrists play a key role in KC management as gatekeepers of primary eye care and disease monitoring and champions of optical correction, including glasses, contact lenses, and medically necessary contact lenses. Ophthalmologists, often cornea specialists, provide specialized surgical care for KC, such as corneal collagen crosslinking (CXL), intracorneal ring segments (Intacs), excimer laser treatments, deep anterior lamellar keratoplasty (DALK), and penetrating keratoplasty (PKP). A symbiotic mentality, coupled with open communication, fosters collaborative care – all to the benefit of patients with KC.

Earlier Diagnosis

The incidence and prevalence of KC continues to rise.[1,2] A 2012 article states that up to 70% of KC patients present to optometric practices.[3] These two statistics combine to highlight the importance and growing opportunity for early detection of KC by optometrists. There is a surfeit of advanced technologies to make the definitive diagnosis of KC, but we believe the first step for diagnosis by optometrists and ophthalmologists is to both recognize and act on KC "red flags." Utilizing tools in every practice such as an autorefractor/keratometer, phoropter, and retinoscopy, and noticing an increase in astigmatism or reduced quality of best corrected vision, are other signs and symptoms to garner ectasia suspicion – which is a great start. (Figure 1). An example of this would be keying in on a 14-year-old's refraction with subjective blur and a manifest cylinder of 3.75D, guiding you to order a corneal topography in your practice or referring out for one.

Arresting Disease Progression

Once a practitioner has either recognized KC "red flags" that require definitive diagnosis, or has diagnosed KC in their practice, the next step in our proposed process is referred to as arresting disease progression. Communication with a targeted and detailed referral note is beneficial in any handoff, especially a surgical one, and KC is no outlier here. In preparation for referring a KC patient, two practices will serve your patients well. First, educate them against eye rubbing and treat the underlying contributing factors (ie. allergic conjunctivitis, blepharitis, etc.). Second, treat any preexisting ocular surface disease. Dry eye syndrome can mimic KC on anterior elevation mapping, and if the patient proceeds with epithelium-off CXL, a pristine tear film aids in epithelialization. If the KC cornea is unstable (most are) and progressing, then the first step is halting disease worsening. The primary treatment is epithelium-off CXL. In its current form, CXL is on-label and best

Vance Thompson Vision, Sioux Falls, South Dakota

reimbursed by insurance companies when disease progression can be shown. Because of this, a thorough referral note with all refractive values and keratometric data is a best practice, and documented progression is very helpful.

Note: defining progression by insurance carriers is not one size fits all, but a guideline from the FDA CXL clinical trial is: steepest keratometry [Kmax]>1.00D increase, >1.00D increase in refractive astigmatism, >0.50D increase in myopic spherical equivalent, and decrease >0.1mm in back optical zone radius of curvature in rigid lenses.

Outside of disease stabilizing, the other bucket for KC surgical procedures focuses on refractive improvement. When referring for these procedures, clearly outlining patient goals (less dependence on specialty contact lenses vs. gaining functional uncorrected vision) and setting realistic expectations are two pillars for success.

Follow-Up Patient Management

After surgery, the next handoff in collaborative care for the KC patient is follow-up management. Whether the procedure was indicated for arresting disease progression or improving vision quality, the patient is often best served by their long-term eye care provider.

First, focusing on epithelium-off CXL, the follow-up mirrors that of a surface keratectomy (PRK/PTK). If a one-day post-op is performed, areas of focus are: confirming the bandage lens (BCL) is in position, reviewing post-op medications, and discussing pain management. In our practice, the first visit after CXL is commonly four to seven days post-op and revolves around corneal epithelialization and the decision of removing the BCL. Of resounding importance is remembering that CXL currently does not have a global period, and co-managing practitioners will want to bill office visit CPT codes. After BCL removal, a common next follow-up appointment is one month post-CXL. Routinely, this visit includes an updated glasses refraction and soft contact lens dispense when appropriate. In our practice algorithm, after the one-month post-op visit, patients are scheduled for a three-month post-op visit that centers around a specialty contact lens fit. Of course, many patients achieve keratometry flattening past three months, and optical correction may need to be updated.

An important next visit is nine to 12 months post-CXL. That visit is where we put the most stock into confirming the success of CXL, which is defined as halting keratometric steepening. After this visit, practitioners can make the next follow-up (six to 12 months later) based on the patient's progression risk post-CXL. Patients should continue to undergo topographic/tomographic scans to confirm stability, because despite being very effective, CXL is not a "set it and forget it" procedure. (Figure 2)

In refractive procedures for KC, a similar follow-up schedule can be used, but visual acuity is used as the success marker at these visits. In the case of topography-guided PRK (TGPRK), a BCL removal is needed, and ocular surface disease management is paramount. In the postoperative setting of acrylic intracorneal rings, the immediate focus is preventing infectious keratitis, while the focus later shifts toward warding off corneal melts. These scenarios are both very rare, but potentially visually compromising. The future looks promising for advancements in both CXL with a refractive or topographic planner, as well as intracorneal ring inserts derived from human tissue.

A final category of KC surgical care is keratoplasty. In our practice, we save keratoplasty for a patient who has exhausted medically necessary contact lenses and doesn't have candidacy for other vision-improving surgical procedures. An example would be a patient post-corneal hydrops with a large central scar. In this scenario, a keratoplasty is likely the last option. DALK and PKP are the mainstream options. A DALK removes and transplants the anterior corneal layers (epithelium, Bowmans, and stroma) but leaves the posterior tissue in place. A PKP is a full thickness tissue removal from the patient, and a full thickness corneal button

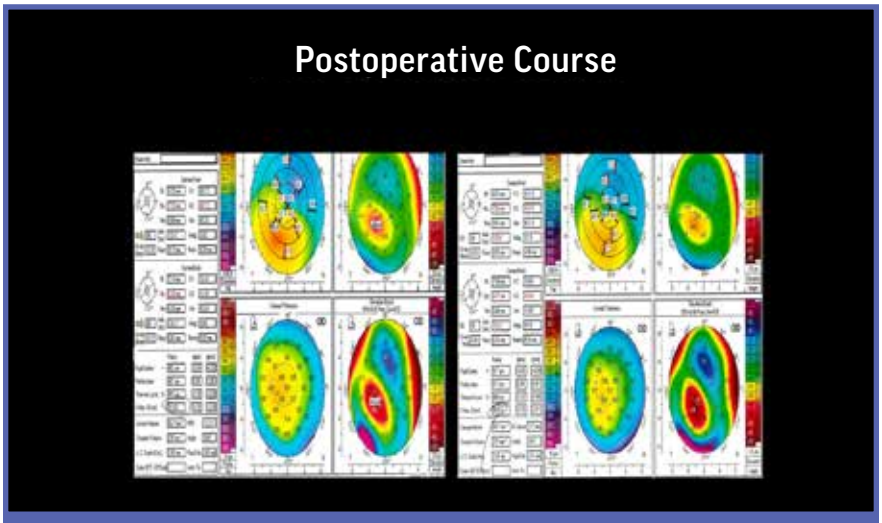
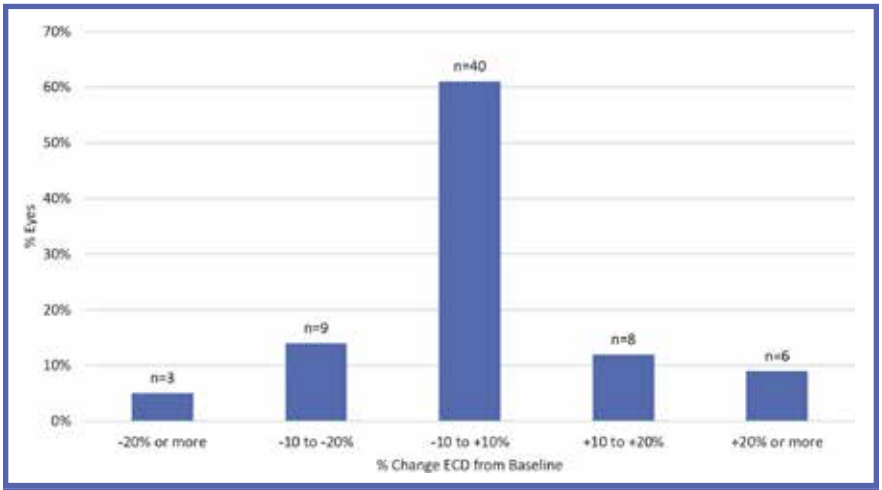


FIGURE 2. Postoperative patients should continue to undergo topography/tomography.



Bar graph showing the change in endothelial cell density (ECD) between baseline and 12 months after corneal collagen crosslinking.

is sutured back into place.

If the KC management protocol follows the steps of an early diagnosis, halting disease progression, and optimizing visual quality, then a collaborative care model fits beautifully. We see this collaborative care model as a win-win-win. It is a win for optometrists because they can concentrate on being excellent diagnosticians and rehabilitating the ectatic eye with spectacle and contact lens devices. It is a win for surgically oriented practices, as they can see more patients that need specialized care. Most importantly, the patient wins because collaborative care with excellent communication and an interventional mindset in KC aims to preserve visual quality and, in many cases, improve acuity, and in turn, quality of life.

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Clinical Pearls for Communicating with Keratoconic Patients

By Melissa Barnett, OD, FAAO, FSLS, FBCLA[*], Katie Greiner, OD, MS, MBA, FAAO[†]
S. Barry Eiden, OD, FAAO, FSLS[‡]

PHOTO CREDIT: THOMAS NORTHCUT

Communication is always a two-way street. It is imperative that we, as eye care professionals, clearly inform our patients about all aspects of their disease (etiology, comorbidities, genetic and environmental influences, natural course, medical management, surgical management, and vision optimization options). It is equally important that the patient fully comprehends this information in order to make the most informed and appropriate decisions regarding treatment.[1] Often, we think we have done a great job in communicating to our patients, but the patient has not processed the information as intended.

All efforts need to be made to ensure that our patients clearly understand all aspects of their keratoconus (KC) condition and its management. In this regard, it is helpful to ask the patient questions pertaining to the information we have provided so that we understand how they have processed it. Further, it is important to always ask the patient (or others who accompany them) if they have any questions or concerns, and give them the option to reach out at a later time with any questions (via phone, e-mail, text, etc.).

It is not unusual for patients who have been diagnosed with KC to have been told by other practitioners that

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their disease is expected to necessitate a corneal transplant if not treated properly. Experienced KC practitioners know very well that this is not necessarily the case, and in fact, many KC patients only progress to a certain level and then naturally stabilize with variable degrees of vision loss.[2] Furthermore, it is the minority of KC patients who will go on to require a corneal transplant, even if not crosslinked (although that number is significantly reduced if patients undergo crosslinking).

The importance of early KC diagnosis and corneal collagen crosslinking (CXL) to halt disease progression must be clearly communicated to the patient.[3] This is not only true for the patient but also for family members who may be at risk of developing the disease. Educating patients about genetic risk, genetic screening, advanced technologies for early diagnosis, and the efficacy and importance of CXL is a critical part of patient management. Part of a comprehensive KC history should include asking about family history of KC, and even if negative, finding out if the patient has siblings and/or children who would be at risk for developing KC – and would then need to be screened for the disease.

Environmental impact on KC is also very important. Communicating the need to avoid mechanical corneal trauma that could lead to disease progression (such as vigorous eye rubbing), while the comorbidity and impact of atopy and ocular allergy are key discussion points as well.[4]

Finally, it is important to clarify that there are two primary elements of KC management that both need to be addressed: disease progression control with medical and surgical treatment (CXL, frequent and continuous follow up, keratoplasties, etc.) and visual optimization (contact lenses, corneal ring segments/inlays, laser corneal reshaping, such as topography-guided PRK, etc.). Addressing KC in such a comprehensive manner will result in best practices and results.[5] Communicating these issues is imperative to achieve success.

Resources for Keratoconus Patient Education

Utilization of resources beyond one-on-one doctor and patient communication is highly effective. Some examples of such resources include:

1. *Support staff:* A highly educated and trained group of support staff can have a great impact on our ability to educate our KC patients. This includes all staff: administrative staff, ophthalmic technicians, and opticians.
2. *Print materials:* Production of a "KC Folder" is an excellent way to distribute information about KC to our patients. Included may be materials pertaining to general KC information, genetic testing, CXL, contact lens options, and surgical methods, among others. This is also an opportunity to market a KC specialty practice by highlighting advanced technologies and treatments provided by the practice.
3. *Website and Blogs:* Having a practice website section devoted to KC is highly effective, and discussing various topics on a blog is also an excellent way to educate patients.
4. *Support groups:* For practices with a larger KC patient population, creation of a KC support group can provide opportunities for individuals to share experiences and understanding.
5. *KC Patient-Centric Organizations:* The National Keratoconus Foundation (NKCF) is the largest organization dedicated to patient education and support. Additionally, there are a number of online KC patient groups. Warning should be given to our patients about participation in the online groups since information provided is not screened, not fact-checked, and can often be misleading. However, the sharing of experiences is often very impactful.

Frequently Asked Questions . . . and Answers

Patients with KC are typically diagnosed at a young age, which makes the disease that much scarier to both the patient and their family. The diagnosis is often shocking, since patients have so much of their lives ahead of them, and they never imagined having an impaired ability to see the world, their kids, their work, and their future.

All efforts need to be made to ensure that our patients clearly understand all aspects of their keratoconus condition and its management.

Oftentimes these individuals present with a rapidly changing prescription – especially increasing astigmatism – that leads to multiple glasses remakes. It is typically when the best-corrected visual

PHOTO CREDIT: ERIC AUDRAS

acuity starts to decline that eye doctors react with topographies, pachymetry measurements, and maybe even a rigid lens trial to confirm the diagnosis of KC.[6] If you happen to be that eye doctor to confirm the diagnosis (and sometimes it takes several opinions or referrals to come to this conclusion), that is when questions from the patient (and sometimes even more so their loved ones) begin. Will I go blind? How do we treat it? Will it require surgery? Can it get better or will it worsen for the rest of my life? Why don't glasses provide clear vision? Why did I get this? Will my children get this too? What did I do wrong?

It may take several discussions with the patient to allow them to understand this condition that most likely many of them have never heard of before. There are a few key points to cover early on after assuring them that they will not go blind from KC. One important point is that while there are no eye drops or medications to prescribe for this disease, the patient is fortunate to live at a time when CXL is FDA approved to slow down and even halt the progression of the disease before it would necessitate a corneal transplant. After CXL, the patient can be fitted into specialty contact lenses with much improved quality of vision compared to spectacles.

Another important topic to cover from the start is that eye rubbing can play a role in both the development and worsening of the condition and should be avoided at all costs.[4] The patient should have their family members screened for the disease and educate them to avoid eye rubbing.[7] While the disease cannot improve from the onset of diagnosis, the technology today allows those with KC to live fulfilling lives with the potential for very functional vision. Even without CXL, an important discussion point for those with KC needs to be around the natural crosslinking that occurs in the cornea as early as their fourth decade of life. This can help in making patients comfortable with the fact that the disease is not going to progress forever. Being transparent with the patient when answering their questions and educating them on the advances in KC care can shed a hopeful light on a condition that can often cause fear and depression.

What Personality Traits Are Common in Keratoconic Patients?

The literature neglects to substantiate a unique "keratoconic personality," even though those with KC tend to score differently on personality scales compared with controls.[8] It has been hypothesized that the stage of life at which KC usually presents plays a crucial role in personality and the development of coping mecha-

nisms that significantly affect behavioral patterns and relationships with caregivers.

A study of 109 subjects used a standardized personality inventory to measure 20 personality scales, both normal and pathologic. Subjects were divided into three age-matched groups: patients with KC, patients with other chronic eye diseases, and normal controls.[9] Although chronic eye disease (including KC) did have an impact on personality functioning in young and middle-aged adults, no specific complex of personality characteristics attributable to KC could be identified. Those with KC were less conforming and more passive-aggressive, paranoid, and hypomanic. Individuals with KC tended to more have disorganized patterns of thinking and scored higher on substance abuse indicators.

A study assessed the prevalence of psychiatric disorders in individuals with KC and the effect of clinical parameters and psychiatric morbidity on quality of life in this patient group.[10] In this study, 94 subjects (mean age 23.9 ± 4.8 [range, 18-40] years) with KC underwent a complete ophthalmic and psychiatric examination. Of these subjects, 35 (37.2%) had a psychiatric diagnosis, 13 (13.8%) had moderate-severe depression, and 20 (21.2%) had moderate-severe anxiety, according to the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) questionnaires, respectively.

Technology today allows those with keratoconus to live fulfilling lives with the potential for very functional vision.

The possibility of having a psychiatric disorder was higher with more severe KC. Individuals with a psychiatric diagnosis scored lower on physical functioning, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, and pain subscales of the Short Form-36 (SF-36).

National Eye Institute Refractive Error Quality of Life (QoL) Instrument-42 questionnaire scores were not affected by having a psychiatric diagnosis or a psychiatric disorder. There was high psychiatric morbidity among individuals with KC, and having a psychiatric disorder was associated with lower QoL. Thus, as practitioners, we have the responsibility to provide empathy, support, and resources for individuals with KC.

How Do You Manage Patient Expectations?

Once the diagnosis of KC is made, the eye care provider should help set realistic expectations for the patient when it comes to their vision. These expectations can be shaped by making sure the patient understands what irregular astigmatism is and where it is coming from in KC, namely the protruding and thinning of the cornea. It should be explained to the patient that not only is the surface of the eye not completely round, but it is actually curved in multiple directions at varying angles, which leads to light being focused on the retina in multiple places. Glasses are not helpful to correct these varied curved rays of light because through a flat plane, these multiple light rays cannot be aligned to a single point of focus inside the eye. When specialty contact lenses negate the irregular curvature, light can again be more properly focused. Today's specialty lenses allow for more customized shapes, as well as molded and 3D-printed options, to better fit the eye and properly focus light, allowing for improved quality of vision.[11]

Frustratingly enough for patients with KC, cataract surgery does not provide the same type of positive refractive outcomes afterwards as it might in those who do not have KC. Since general cataract surgery does not change the curvature of the cornea, KC is still present after the surgery is performed. While an intraocular lens implant can likely reduce the nearsighted or farsighted component of the prescription, while also allowing more light to enter into the eye, the irregularity of the cornea causing irregular astigmatism still remains. These patients continue to benefit from corneal correction, such as specialty contact lenses after the surgery for best corrected acuity and quality of vision.

Another important topic to cover from the start is that eye rubbing can play a role in both the development and worsening of the condition.

In terms of premium IOL options, the vast majority of surgeons would agree that the array of multifocal intraocular lens designs are contraindicated in this population. The already aberrated surface of the cornea does not lend itself well to the design of these IOLs and will lead to increased higher order aberrations post-operatively.[12] It is highly debated whether or not a KC patient should have a toric IOL implanted at the time of cataract surgery. With advancements in technology and surgical procedures, surgeons are more willing to implant a toric IOL in those with stable, mild corneal ectasias. However, placement of a toric implant may preclude standard contact lens use because of the internal astigmatism now negating the corneal astigmatism, as discussed below. Therefore, expectations have to be placed that this implant may not correct the vision to the degree the patient finds satisfactory, and glasses or specialty contact lenses may still be needed.[12]

When a toric IOL has been implanted into a patient with moderate to advanced levels of corneal ectasia, it is very likely that the patient will still need a specialty contact lens for best acuity after surgery.[13] In this situation, the practitioner should be prepared to fit a front toric contact lens. The toric IOL is designed to counteract the patient's corneal astigmatism, but so is a specialty contact lens. What remains in this situation is residual astigmatism that comes from the lenticular astigmatism generated from the toric IOL. For best corrected acuity, this then needs to be corrected as a front toric contact lens design (usually high powered), or in over-spectacles. This is not an ideal situation for the patient or the practitioner.

Monofocal IOLs have traditionally performed the best in these patients, especially when the expectation that corrective eyewear – likely specialty contact lenses – will still be needed after surgery, just as it was before surgery.

You know your KC patients best. Make sure to communicate with the cataract surgeon on the patient's goals, needs, and successes or failures with contact lenses, and most importantly, their expectations. Commence the specialty lens refitting process about a month after surgery. Communication and co-management of these patients when cataract surgery is performed is key.

DR. KATIE GREINER is CEO of Northeast Ohio Eye Surgeons located in Stow, Kent, Akron, Canton, Medina, and Wadsworth, Ohio. Her focus is on comprehensive eye care, as well as specialty contact lens fittings, refractive surgery evaluations, and administrative duties. Dr. Greiner obtained both her Doctorate of Optometry and Masters in Vision Science from The Ohio State College of Optometry in 2009. She then went on to complete a Surgical Co-Management and Contact Lens Residency at Davis Duehr Dean, where she discovered her true passion for specialty contact lens fits. With three corneal specialists in her current practice, she was quickly able to establish a premier center for hard-to-fit contact lenses and has added four fitters since the start of the program 10 years ago. She mentors a fourth year OSU optometry student on specialty fitting at Northeast Ohio Eye Surgeons each semester. Dr. Greiner is active in the optometric community, serving as the past Membership Chair for the Ohio Optometric Association, recent past Zone 3 Governor, a Visionary and an Allied Eye Professional Co-Chair on the East West Eye Committee, and she provides RealEyes health and safety education to grade school students. She completed a Health Care MBA program at Baldwin Wallace University in 2019 to further her administration skill set in the field of eye care.

DR. S. BARRY EIDEN is President and Medical Director of North Suburban Vision Consultants, Eye Care Specialties of Illinois, and Keratoconus Specialists of Illinois, a multi-specialty group practice in the Chicago area. He is President and Co-Founder of the International Keratoconus Academy of Eye Care Professionals, an organization providing education and research to the eye care professions. Dr. Eiden is also Co-Founder and President of EyeVis Eye and Vision Research Institute, which is dedicated to clinical research and the development of technologies in the eye care field. Dr. Eiden is an Assistant Clinical Professor at the University of Illinois at Chicago Medical Center in the Department of Ophthalmology, Cornea and Contact Lens Service, and he is an Adjunct Faculty Member of the Indiana, Illinois, Midwestern, Salus, SUNY, and UMSL Colleges of Optometry. He is on the editorial board of numerous professional journals and frequently publishes in professional literature. Dr. Eiden is Past Chair of the American Optometric Association's Contact Lens and Cornea Section. He is a Fellow of the American Academy of Optometry and a Fellow of the Scleral Lens Education Society. Dr. Eiden is a research consultant for numerous contact lens, technology, and pharmaceutical companies and lectures extensively both nationally and internationally.

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Coding and Billing for Keratoconus: Medically Necessary Contact Lenses

By Clarke D. Newman, OD, FAAO, FBCLA, FSLS, FNAP*

There are two elements when discussing billing for medically necessary contact lenses. First, what service and material charges are appropriate for this patient, and second, who will pay for these services and materials. It is up to the practitioner to determine what services you provide to your patient, not contracted payers. The payers can only tell you who will pay for those services and at what rate.

It is of the utmost importance to thoroughly evaluate payer contracts to decide if they make sense for your practice. Several plans reimburse at a rate that will not even cover material costs and also don't allow for the balance to be billed to the patient. If a payer has a poor reimbursement policy, then you should not contract with that payer.

Coding and Reimbursement

The first element in reimbursement is establishing medical necessity. That begins with a chief complaint that is rational to keratoconus (KC), such as decreased acuity. Thorough, detailed documentation regarding the medical and ocular history, visual acuity, habitual contact lens history, and family history is necessary.

Each diagnostic test must be rational to the chief complaint; it must be ordered, the test must be interpreted, and that interpretation must affect your clinical decision-making. Be mindful that claims for an examination to rule out KC because of a family history of the condition may be rejected. There should be a proximal complaint to the specific patient, such as decreased visual acuity.

The next element of correct coding is the proper ICD-10-CM diagnosis code. These codes are as follows:

It is best practice to avoid the "unspecified eye" codes whenever possible, regardless of the diagnosis code. CPT rules require the provider to use the highest level of speci-

ICD-10-CM Diagnosis Codes	
H18.61	Keratoconus, stable
H18.611	right eye
H18.612	left eye
H18.613	bilateral
H18.619	unspecified eye
H18.62	Keratoconus, unstable
H18.621	right eye
H18.622	left eye
H18.623	bilateral
H18.629	unspecified eye

*Plaza Vision Center, Dallas, Texas

ficity that is practicable. Use the *H18.61x: Keratoconus, stable* codes for disease that is documented as not progressing. Another time to use the stable codes is for the "Emerging/Mild" category when billing EyeMed. Use the *H18.62x: Keratoconus, unstable* codes for disease that is documented as progressing, and for the "Moderate/Severe" category when billing EyeMed. (Check the EyeMed "Medically Necessary Contact Lens Benefits" policy.)

Billing for Services Related to Lens Prescribing and Materials

The CPT service code for prescribing lenses when the diagnosis is KC is *92072: Fitting of contact lens for management of keratoconus, initial fitting.* The plain language of the code rules. The descriptor is "fitting of contact lens for the management of keratoconus." This code only covers the diagnostic evaluation visit, or fitting, of the medically necessary lenses. It does not cover the ancillary testing or the original eye examination.

Three sub-text instructions apply only to the 92072 code. They are, in order: 1. For subsequent fittings, report using evaluation and management services or general ophthalmological services; 2. Do not report 92072 in conjunction with 92071; and 3. Report the supply of lenses separately with 99070 or the appropriate supply code.

The ambiguity of "initial" and "subsequent" was cleared up by CPT Assistant, September 2017. "If the lens needs to be changed because it no longer fits the patient's needs, the fitting of a new lens is considered an initial fitting." All other visits required to achieve success are billed according to the sub-text instructions.

Evaluate payer contracts to decide if they make sense for your practice. Several plans reimburse at a rate that will not even cover material costs and also don't allow for the balance to be billed to the patient.

Resources

Regarding the billing to vision care plans, the best advice is to follow the rules for each plan. At the website, under the "Resources" tab, is a tab for the "Coding and Billing" module. In that module, you can find several helpful resources. First, is a two-hour lecture with a handout regarding the coding and billing for specialty lenses.

The two-hour lecture contains a step-by-step guide for finding and using the policies for the various vision care plans regarding specialty lens prescribing. I encourage you to read and print the rules for each vision care plan which you contract. Follow their rules specifically, as their rules are uniquely different from each other and from the Principles of CPT.

Using these resources will guide your decision-making process to ensure correct coding and billing for reimbursement. Remember to carefully review payer contracts and select payers that will provide appropriate reimbursement in order to provide patients with the best care.

DR. CLARKE NEWMAN is a 1986 graduate of the University of Houston College of Optometry, and he has been in private practice in Dallas, Texas, since. His practice specializes in the visual rehabilitation of patients who have had corneal diseases, failed refractive surgeries, or corneal trauma. Dr. Newman is a Past President of the Texas Optometric Association (TOA), served as Chair of the American Optometric Association (AOA) Federal Relations Committee for four years, currently serves on the Evidence Based Optometry Committee, and is a long-time member of the AOA's Cornea and Contact Lens Section (CCLS). Dr. Newman is a Diplomate in the Section on Cornea, Contact Lenses, and Refractive Technologies of the AAO, and is currently the Immediate Past Chair of the Section. He is a Distinguished Practitioner in the National Academies of Practice and he is a Fellow in the British Contact Lens Association and the Scleral Lens Educational Society. He serves on the FDA Medical Devices Advisory Committee – Ophthalmic Devices Panel. He has won numerous awards, including the TOA Young OD of the Year, the TOA OD of the Year, the TOA Distinguished Service Award, the AOA CCLS Luminary Award for Distinguished Practice, the AOA CCLS Legends Award, the AOA Advocate of the Year, and the CLMA GPLI Practitioner of the Year. He writes and lectures frequently on a wide range of anterior segment and contact lens related topics.

Coding and Billing for Keratoconus: Corneal Collagen Crosslinking

By Janet Cox, CPC*

PHOTO CREDIT: COURTNEYK

Corneal crosslinking (CXL) is an approved procedure for the treatment of progressive keratoconus (KC) and the treatment of corneal ectasia following refractive surgery. The procedure codes that are used to submit CXL claims are 0402T and J2787. CPT code 0402T is a Category III code, CXL of cornea, including removal of the corneal epithelium and intraoperative pachymetry. HCPCS code J2787 is to bill the medication: Riboflavin 5' – phosphate, ophthalmic solution, up to 3 ml. HCPCS code J2787 requires two units when billing for the medication.

Medical Policy and Insurance Carriers

Simply knowing how to bill and submit a claim for CXL is not enough. It is important to understand the medical policy of the different insurance carriers to see what documentation is required to show progressive KC. Some policies want to see at least one of the following – an increase of 1.00D in the steepest keratometry value, an increase of 1.00D in regular astigmatism by a subjective manifest refraction, a myopic shift of 0.50D on subjective manifest refraction, or a decrease ≥ 0.1 mm in the back optical zone radius in rigid contact lens wearers where other information is not available. Some insurance carriers will not cover CXL for ectasia if refractive surgery is not a covered service. It is important to notify the patient what their coverage is or if they will not have any coverage. Having this clearly outlined in your documentation is also very helpful if the insurance company is requesting records.

Understanding the medical policy for the procedure is key. However, knowing what the medical policy is for required testing for the examination is also important. When a patient comes in for their corneal exam, we bill for an office visit and any necessary testing. Corneal topography is a common test, which is CPT code 92025. Corneal topography can be considered medically necessary for patients who need CXL with a diagnosis of corneal ectasia or KC. Coverage for corneal topography may also vary by insurance carrier. There are some carriers that have a different medical policy and only cover it if it is done for the initial diagnosis of KC and for monitoring of the disease when there is a change in vision. We have also seen where some insurance carriers do not cover corneal topography. In this case, a financial waiver can be used to notify the patient that they would be financially responsible for the testing. If the charge for corneal topography is denied, a practice could also try to appeal with documentation to see if the insurance company would reconsider their denial.

Vance Thompson Vision, Sioux Falls, South Dakota

Reimbursements

Once the CXL procedure has been done and the claim has been submitted and paid, it is essential to review the reimbursement. Our team reviews paid claims to ensure they are paid appropriately and according to our contract. If you find that your reimbursement is low, it is important to first verify if the payment is consistent with the contract. You may have a contract that has been in place for years and is outdated. If that is the case, reach out to the insurance company to discuss this with their contracting department to review the low reimbursement. You may need to set up a peer-to-peer call to work with the medical director. We have had success with explaining what CXL is and comparing the cost of CXL to the cost of a corneal transplant. We also outline the costs associated with the procedure and how their reimbursement compares to other carriers.

Being aware of the medical policies and monitoring the reimbursements helps set your practice up for success. We have seen that a lot of positive changes take place with crosslinking. It has been an exciting journey with many providers and practices doing their part to help patients get the care they need and being properly reimbursed for the care they provide.

JANET COX is the Revenue Cycle Director at Vance Thompson Vision and has been with Vance Thompson Vision since 2006. She is responsible for managing coding, billing, collections, payment posting, contracting, and provider enrollment for seven clinic locations and four ASCs. Cox attended the University of Sioux Falls where she received her Bachelor's Degree in Business Administration. In the past, Cox was an Adjunct Instructor for Colorado Technical University. With over 20 years of experience in the medical field, she has been a trusted consultant to multiple companies for medical reimbursement. She has lectured nationally and regionally, and she is a member of the Amecan Academy of Professional Coders (AAPC) and the American Society of Ophthalmic Administrators (ASOA).

Resources

Everything You Need to Manage Keratoconus and Where to Find It

John D. Gelles, OD, FAAO, FIAOMC, FCLSA, FSLS, FBCLA and Melissa Barnett, OD, FAAO, FSLS, FBCLA

Keratoconus (KC) management requires a comprehensive understanding of the disease. In its simplest terms, KC is a progressive corneal disease that requires early diagnosis, treatment to stop progression, and continuous monitoring. Vision can be corrected with a variety of contact lenses and surgical options. The most important management part is collaboration among providers to ensure the best outcome. Various educational resources beyond this supplement should be used to gain additional knowledge. Many of these resources will overlap with the *Scleral Lens Education Initiative,* which can be viewed here.

Books

These books will be vital to aid in your clinical success.

Cornea, 2-Volume Set, 5th Edition

Editors: Mark Mannis and Edward Holland

The most comprehensive corneal disease manual is available in its fifth edition. Additionally, surgical procedures are covered to understand surgical co-management better.

Clinical Manual of Contact Lenses, 5th Edition

Editors: Edward S. Bennett and Vinita A. Henry

A classic among contact lens practitioners, this book covers all modalities of contact lenses and is helpful for all aspects of keratoconus management.

Keratoconus

Editors: Luis Izquierdo, Maria Henriquez, Mark Mannis

Keratoconus, Elsevier, 2023, ISBN 9780323759786

This easy-to-read guide offers concise, practical clinical guidance for early diagnosis and effective management of keratoconus.

Keratoconus: Recent Advances in Diagnosis and Treatment

Editor: Jorge L. Alió

Springer International Publishing Switzerland 2017

A comprehensive book focused exclusively on keratoconus, covering imaging,

Peer-Reviewed Journals

Understanding the research aids practitioners in applying new evidence-based medicine in clinical practice. These peer-reviewed journals contain information relevant to keratoconus, contact lenses, cornea, ocular surface disease, and experimental research.

- Cornea
- Journal of Cataract and Refractive Surgery
- Contact Lens & Anterior Eye
- Eye & Contact Lens
- Investigative Ophthalmology and Vision Science
- Optometry and Vision Science

Professional Publications

Professional publications are a great way to learn from key opinion leaders about keratoconus applications. These are generally more conversational and provide a distilled and sometimes opinionated view of peer-reviewed research.

- Contact Lens Spectrum
- Review of Cornea & Contact Lens
- Cataract & Refractive Surgery Today (CRST)
- CRST Europe
- Corneal Physician
- Review of Optometry
- Review of Ophthalmology

Crosslinking

- Glaukos - iLink CXL treatment
- Glaukos Provider Locator

Symposia

Attendance at these meetings will ensure collegial interaction among peers and offer many opportunities to ask questions and interact with experts. For auditory, visual, and hands-on learners, this is the best way to gain valuable education in a compressed time frame.

International Keratoconus Academy Annual Meeting

Organized by the International Keratoconus Academy, this collaborative optometry and ophthalmology meeting exclusively focuses on all aspects of keratoconus management.

CXL Experts

This is primarily an ophthalmology meeting focused entirely on novel crosslinking applications and innovations and new treatments and management of keratoconus and corneal ectasia.

CLEI Education Refractive Surgery and Keratoconus Management Symposium

This annual meeting focuses on keratoconus and refractive surgery, providing information on comprehensive keratoconus care and refractive surgery.

American Society of Cataract and Refractive Surgery Annual Meeting

An ophthalmology meeting with a primary focus on refractive and cataract surgery, a large amount of research and lectures are presented on keratoconus treatments and management.

European Society of Cataract and Refractive Surgery Annual Meeting

The European counterpart to the ASCRS meeting, this meeting primarily focuses on refractive and cataract surgery with featured lectures on keratoconus.

The Association for Research in Vision and Ophthalmology Annual Meeting

A research-based meeting that brings together researchers and practitioners alike. It is a great way to understand the evolution from research to clinical application.

Global Specialty Lens Symposium

Symposium focused entirely on specialty contact lenses of all varieties, featuring sections on research and clinical applications, industry innovations, and practical, hands-on wet labs.

International Congress of Scleral Contacts

This two-day, highly interactive global meeting is dedicated solely to scleral lenses.

The Summit

The Summit is the only specialty contact lens meeting in Europe that brings together key opinion leaders to share their experiences, research, and cutting-edge ideas.

Professional Societies

These societies, academies, and associations provide excellent continuing education opportunities and organized resources for practitioners. Many have archives of webinars available for viewing at any time.

- American Academy of Optometry: Cornea, Contact Lens, and Refractive Technology
- American Optometric Association: Cornea and Contact Lens
- British Contact Lens Association
- Contact Lens Society of America
- Eye and Contact Lens Association
- Gas Permeable Lens Institute
- International Keratoconus Academy
- Optometric Cornea Cataract and Refractive Society
- Scleral Lens Education Society
- The Association for Research in Vision and Ophthalmology
- American Society of Cataract and Refractive Surgery
- European Society of Cataract and Refractive Surgery
- Cornea Society

Blogs and Podcast

- Mastering Keratoconus-Mastering Keratoconus Healio Blog
- Chang Reaction Podcast

Diagnostics

Comprehensive keratoconus management relies on the ability to diagnose and monitor the disease. Relevant devices include topography, tomography, aberrometry, and biomechanics.

- CSO
- Essilor Instruments
- Haag-Streit
- Heidelberg Engineering
- Medmont
- Marco
- Nidek
- Oculus
- Ovitz
- Reichert
- Topcon
- Tracey Technologies
- Visionix
- Zeiss
- Ziemer

Genetic Testing

- Avellino AvaGen

Patient Information, Support, and Advocacy

- National Keratoconus Foundation

Contact Lens Manufacturing Laboratories

Contact lenses have been the mainstay of vision correction in keratoconus. Each design has unique features that can address the needs of each unique cornea. As there is no such thing as the best lens, it is important that practitioners learn multiple designs. Choosing a manufacturing laboratory is entirely based on practitioner preference and design needs. The manufacturing laboratory should be considered your partner who is invested in the success of you and your patients. Laboratory consultants are vital to the fitting process and offer years of experience to aid in lens selection and modification. Additionally, many laboratories have created extensive resource libraries to provide education on their specific designs.

- ABB Optical Group
- AccuLens
- Advanced Vision Technologies
- Art Optical Contact Lens
- Bausch + Lomb SVP
- BostonSight
- CooperVision SEC
- Custom Craft Lens Service
- Essilor Custom Contact Lens Specialists
- EyePrint Prosthetics
- Gelflex
- Kerasoftlens
- Metro Optics
- SynergEyes
- SpecialEyes
- Tru Form Optics
- United Contact Lens
- Valley Contax
- Visionary
- Visionary Optics
- X-Cel Specialty Contacts

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KERATOCONUS 2023

A COMPREHENSIVE GUIDE TO THE MODERN MANAGEMENT OF KERATOCONUS

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