THE ALTERATION OF THE ALTERATI

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Financial Disclosures

• None

Let's Time Travel To The Future...

Every case of keratoconus is screened and treated **early**

A diagnosis of keratoconus **does not mean poor vision**

ZERO cases of acute hydrops

ZERO cases of cornea transplants for keratoconus

Let's talk about...



History of Keratoconus and Treatment



Current Screening Tools and Tips



Corneal Crosslinking



Co-management: Working Together



"Refractive-Plus" Procedures



Proposed Screening Protocols

Let's Start From The Beginning...

What is Keratoconus? Signs & Symptoms Historical Treatment Options

Keratoconus (kěr'ə-tō-kō'nəs)

kéras = Cornea cōnus = Cone

First Description of Keratoconus: Benedict Duddell in 1736 "Diseases of the Horny-coat of The Eye"



Early Descriptions of Keratoconus

- 1748: Burchard Mauchart described a case of keratoconus and called it "staphyloma diaphanous"
- 1854: John Nottingham described the conical cornea in "Practical observations on conical cornea"
- 1869: Johann Horner gave Keratoconus its name in his thesis "On the treatment of keratoconus"

What Is Keratoconus?



Signs:

- Thinning cornea
- Cone-like bulging
- Frequently changing glasses prescriptions

Symptoms:

- Blurry and/or distorted vision
- Sensitivity to light
- Contact lens intolerance

Keratoconus:

A sight-threatening disease

Previously estimated 1:2000 (1986 US), more recent estimate 1:375 (2017 Netherlands)

1 out of 5 people with keratoconus will need a corneal transplant

Awareness is growing





"He was getting worse, we kept going to the doctor and saying 'Hey, he is really struggling with this"

April 5, 2019

"For all his career, his life even, Steph Curry has had issues with his eyes. He said he has a condition called Keratoconus"

Survey of Ophthalmology -

1998

The Athletic - April 5, 2019



Keratoconus usually begins in the teenage years

CLINICAL SIGNS OF KERATOCONUS

Vogt's Striae

Vertical fine white folds in the posterior stroma

Fleisher's Ring

 Iron ring deposit within epithelium around base of cone (brown in color and best visualized with cobalt blue filter)

Munson's Sign

• V-shaped indentation observed in the lower eyelid when patients gaze downwards

Apical Scarring









Fig (c) Munson's sign

Fig (a). Feizi et al J Ophthalmic Vis. Res. 2012 Oct; 7(4): 328-331 Fig (b) https://en.wikipedia.org/wiki/Kayser%E2%80%93Fleischer_ring Fig (c) https://en.wikipedia.org/wiki/Munson%27s_sign



Causes of Keratoconus

- Genetic component
- Excessive eye rubbing
 - Vernal conjunctivitis
 - Allergic conjunctivitis
 - Atopy
 - Down Syndrome
- Connective tissue disorders
 - Marfan Syndrome
 - Ehlers-Danlos Syndrome

Genetic Testing for Keratoconus

- AvaGen, The Genetic Eye Test (Avellino)
- Buccal swab (non-invasive)
- Multiple genes may affect development and progression of keratoconus
- Tests for 75 known genes related to KC risk
- Gives a risk score

CONDITION TESTED	RESULT	DETAIL	EXPLANATION
Keratoconus (KC)	LOW genetic risk	22 polygenic risk score	Tested for variants within 75 genes found to be associated with keratoconus.
TGFBI Corneal Dystrophies (CD)	Negative for TGFBI Corneal Dystrophies	No pathogenic variants detected	Tested Negative for 70 known variants associate with TGFBI corneal dystrophies.





Historical Treatment of Keratoconus

- "Watch + Wait"
- Contact Lenses
- INTACS
- Cornea Transplant
 - Deep Anterior Lamellar Keratoplasty (DALK)
 - Penetrating Keratoplasty (PKP)









MOST COMMON INDICATIONS FOR PKP

Cornea Ectasia

- Keratoconus
- Pellucid Marginal Degeneration
- Post-LASIK ectasia
- Corneal Infection
- Corneal Scar





PENETRATING KERATOPLASTY

Advantages:

- No interface-related visual problems
- Ability to treat a combination of epithelial, stroma, and endothelial disease
- Easier for eyes that require anterior segment reconstruction in a single procedure
- Disadvantages:
 - Significant refractive error
 - Higher risk of vision-threatening complications















DEEP ANTERIOR LAMELLAR KERATOPLASTY

- Advantages:
 - Lower graft rejection risk
 - Minimal steroid-related complications
 - Ability to use a lower quality cornea donor
 - Better long-term graft survival
- Considerations:
 - May need to convert to full-thickness cornea transplant
 - Longer Surgery



DEEP ANTERIOR LAMELLAR KERATOPLASTY

Disadvantages:

- Interface haze
- Graft dehiscence
- Pupillary block from air/gas bubble
- Corneal stromal graft rejection
- Similar best-corrected visual acuity outcomes to PKP





Complications After Cornea Transplantation: Astigmatism

- Remove sutures
 - Selective vs. Total removal
 - Avoid suture removal before POM #3
- Prescribe correction
 - Glasses
 - Rigid Gas Permeable Lenses
 - Scleral Lenses
- LASIK or PRK (controversial)



Complications AFTER Cornea transplantation: Poor Graft centration





Complications After Cornea transplantation: Suprachoroidal hemorrhage 35 year-old male, keratoconus Planned pentrating keratoplasty Comeal surgeon

Complications After Cornea Transplantation: Keratitis



Interstitial Crystalline Keratitis (Strep. Viridans)



Fungal Keratitis (Candida spp.)

Where Are We Now?

Screening for Keratoconus Corneal Cross-Linking Epi-On versus Epi-Off Cross-Linking

EARLY DIAGNOSIS IS IMPORTANT!

- The earlier progressive Keratoconus is diagnosed, the sooner treatment can be provided that may slow the progression of the disease.¹
- Progressive disease often results in:
 - Loss of visual acuity and function
 - Decreased tolerance to contact lens wear
- Cross-linking (CXL) is an early intervention intended to slow the progression of keratoconus



1. Gelles, J. D., OD, FIAO, FCLSA. (2017, April). The Optometrist's Role in Keratoconus Management. Advanced Ocular Care.

Diagnostic imaging: Topography



Irregular Topography/Tomography

Skewed Axis or Asymmetric Bowtie











Pentacam: Belin-Ambrosio Deviation Display For Early Screening & Detection



Pentacam: Belin-Ambrosio Deviation Display For Early Screening & Detection


Pentacam: Belin-Ambrosio Deviation Display For Early Screening & Detection



Screening for KCN... Without Topography?

Irregular Mires on Placido Topography



Anterior OCT with focal thinning





WHAT IS CORNEAL CROSS-LINKING?





- Corneal collagen cross-linking combines the use of ultra-violet (UV) light and riboflavin (vitamin B2) drops
- The absorption of UVA by riboflavin generates radical riboflavin and singlet oxygen to form cross-links¹
- Shortening and thickening of the collagen fibrils
- Stiffening of the cornea²

²Beshtawi IM, O'Donnell C, Radhakrishnan H. Biomechanical properties of corneal tissue after ultraviolet-A-riboflavin crosslinking. J Cataract Refract Surg. 2013;39(3):451–62. ¹Kamaev P, Friedman MD, Sherr E, Muller D. Photochemical kinetics of corneal cross-linking with riboflavin. Invest Ophthalmol Vis Sci. 2012;53:2360–7.

Early Studies of Cross-linking

- 1990s: UV light used to induced collagen cross-linking in riboflavin soaked porcine and rabbit corneas
 - Stiffer corneas more resistant to enzymatic digestion
 - Corneas contained higher molecular weight polymers of collagen
 - Safe for the endothelium if cornea thickness exceeded 400 microns

First Human Studies

- 2003: First human studies in Dresden
 - 16 patients with rapidly progressing keratoconus
 - All patients stopped progressing after treatment
 - 70% with flattening of their steep anterior corneal curvatures
 - 65% had an improvement in visual acuity
 - No reported complications

UNITED STATES CROSSLINKING TRIAL

- Prospective, randomized, controlled clinical trial
- 208 patients with unstable keratoconus
- Two Arms:
 - Treatment group: standard CXL (epi-off)
 - Control group: riboflavin alone without removal of the epithelium
- Results:
 - Treatment group had **<u>1.6 diopters decrease</u>** in maximum keratometry after 1 year
 - Control group had progression of disease
 - **<u>Corneal haze</u>** was the most frequently reported finding with the treatment group
 - No significant changes in endothelial cell count after 1 year

United States Crosslinking Study Group. United States Multicenter Clinical Trial of Corneal Collagen Crosslinking for Keratoconus Treatment. Ophthalmology 2017 Sep;124(9):1259-70.

Cornea Cross-linking Approval

- 2011: orphan drug status was awarded by the FDA for Avedro
- April 18, 2016: FDA approval for corneal cross-linking



Inclusion Criteria



Diagnosis of:

- Unstable keratoconus
- Pellucid Marginal Degeneration
- Post-LASIK ectasia

Minimum corneal thickness of at least 300

• Measured by ultrasound or Pentacam

At least 6 months since last corneal surgery



Severe corneal scarring that markedly affects vision

EXCLUSION CRITERIA

Pregnancy or breast feeding

Active Herpes Corneal Disease

Corneal pachymetry under 300 microns



Aim of CXL is to halt or slow disease progression.



Cross-linking is <u>not</u> a refractive procedure.



Postoperative evaluation for correction required.

STEPS TO EPITHELIAL-OFF CORNEAL CROSS-LINKING Dresden Protocol



1. Remove epithelium



2. Soak cornea Photrexa[®] (riboflavin 5'-phosphate in 20% dextran ophthalmic solution)

✓ 30 minutes



4. Once flare is observed, measure corneal thickness

✓ If corneal thickness is less than 400 um, instill 2 drops of Photrexa (riboflavin 5'phosphate in 20% dextran ophthalmic solution) until the corneal thickness increases to at least 400 µm



3. Check for flare



- 5. Irradiate for 30 minutes
- ✓ Continue applying Photrexa Viscous (*riboflavin 5'phosphate in 20% dextran ophthalmic solution*) during irradiation.



Variations in Technique

- Epithelial Debridement
 - Mechanical debridement
 - Amoils Brush
 - Alcohol-assisted Debridement
 - 100% Alcohol
 - Isopropyl Alcohol 70%
 - Direct debridement



Variations in Technique: Osmolarity

- Use of hypo-osmolar riboflavin in thin corneas with a thickness between 320 to 400 microns thick
- Helps to thicken the cornea to the minimum of 400 microns



Follow-up schedule



VISIT	PLAN
Day 1 to 1 Week	Topical antibiotic, steroid Frequent lubricants No eye rubbing Remove BCL once epithelium heals
Month 1	OCT Imaging Tomography/Topography Vision assessment Contact lens refitting evaluation
Month 3, 6, 12 (Follow ups potentially performed and billed by diagnosing physician depending on practice preference)	Continued evaluation utilizing tomography/ topography Vision assessment

Potential Side Effects

Corneal haze

- Permanent in 10%
- 90% goes away in 6 months

Persistent epithelial defect

Endothelial damage

 Risk if cornea pachymetry < 400 microns before irradiation with UV light

Punctate Keratitis

• Resolves by 1 year



Access to Cross-Linking in the U.S.

FDA APPROVED & ON-LABEL

Use of Photrexa® Viscous & Photrexa® with the KXL® system for the treatment of progressive keratoconus or corneal ectasia following refractive surgery (On-label use of a legally marketed drug)

OFF-LABEL

Use of Photrexa Viscous & Photrexa with the KXL system for any indication other than progressive keratoconus or corneal ectasia following refractive surgery (Off-label use of a legally marketed drug)

UNAPPROVED

Use of any other drug, device, or procedural protocol (i.e., epi-on) for cross-linking (Except as part of an investigational new drug (IND) study)

EPI-ON VS EPI-OFF CROSS-LINKING

EPI-ON

- 2-3 day recovery of vision versus 2-3 months
- Less discomfort
- Lower risk of corneal infections
- Lower risk of corneal haze

EPI-OFF

- Better absorption of therapy
- More corneal flattening
- Decreased risk of progression of ectasia post-treatment

Wen D, Song B; Li Q et al. Comparison of Epithelium-Off Versus Transepithelial Corneal Collagen Cross-Linking for Keratoconus: A Systematic Review and Meta-Analysis. Cornea 2018. 37:8 1018-1024.



Summary

- Patients with progressive keratoconus should be educated regarding risks and benefits of CXL.
- Referring ophthalmologists and optometrists are a critical part in ensuring early diagnosis, monitoring, and continuing care of these patients.



Resources for patients

- Livingwithkc.com website
 - Informational videos
 - Q&A for patients
 - Insurance coverage
- National Keratoconus Foundation (NKCF)
 - www.nkcf.org
- Facebook groups for Keratoconus

Shaping Our Future

Pipeline Treatments "Refractive-Plus" Screening Protocols

Pipeline Treatments

Photoactivated chromophore for infectious keratitis (PACK-CXL)

- Proposed Mechanisms:
 - 1) Destroy pathogens
 - 2) Halt replication
 - 3) Stronger covalent bonds among collagen fibers
- Knyazer et al.: PACK-CXL associated with faster healing time in bacterial ulcers
- Also found to be effective in fungal, parasitic, and herpes keratitis

"Refractive-Plus" Procedures



"Refractive-Plus" Procedures

- Cross-linking + refractive procedure
- Off-label
- Refractive results less predictable

Corneal Cross-linking (CXL) and Photorefractive Keratectomy (PRK)

- Kanellopoulous et al. looked at CXL + PRK compared to CXL followed by PRK
- Same day cross-linking + PRK advantageous
 - Better BCVA and UCVA
 - Greater mean reduction in keratometry
 - Less corneal haze

Athens Protocol

- 1. Place topical anesthetic and aspirating lid speculum
- 2. Perform 6.5mm, 50 micron phototherapeutic
- keratectomy (PTK) to remove the corneal epithelium
- 3. Apply partial topography-guided PRK treatment
 - a. Effective optical zone diameter 5.5mm
 - b. 50 µm maximum ablation depth for approximately
 - 70% treatment of cylinder and sphere
- 4. Apply a cellulose sponge soaked in mitomycin C (MMC)
- 0.02% solution over the ablated tissue for 20 seconds
- 5. Irrigate with 10mL of chilled balanced salt solution

- 6. Collagen cross-linking procedure
 - a. Apply 0.1% riboflavin sodium phosphate ophthalmic solution every 2 minutes for 10 minutes
 - b. Start UV-A irradiation with of mean 370-nm wavelength and 3 mW/cm2 radiance at a distance of 2.5 cm from the cornea for 30 minutes
- 7. Place bandage contact lens

Other "Refractive-Plus" Procedures

- Phakic IOLs
 - Used for both iris-fixated lenses and posterior chamber lenses
 - Placed 6-12 months after CXL to establish corneal and refractive stability
- LASIKxtra
 - Accelerated CXL immediately after laser ablation
 - One drop of riboflavin soaks in the stroll bed for 60-90 seconds
 - LASIK flap replaced prior to radiating the cornea
 - 3 minutes of 10 mW/cm2 OR 60-90 seconds of 30 mW/cm2 of UV-A light
 - Not meant for eyes with keratoconus but as a preventative measure
- Conductive Keratoplasty (CK) unclear benefit

Customized Cross-linking

- Treatment area just directed to cone
- Advantage:
 - Smaller epithelial defect
 - Faster recovery
 - Less Haze
- Disadvantage
 - Unclear efficacy
 - Unclear safety profile
 - Not FDA-approved



Accelerated Cross-linking

- Similar to FDA-approved Dresden Protocol but with higher powers
- Use a higher powered light source (greater than standard 3.0 mW)
- Possible advantages:
 - Increasing stiffening effects
 - Increasing the flattening effects
- Possible drawbacks:
 - Unclear benefit (no information on outcomes and safety)
 - Possible short and long-term side effects (endothelial damage)
 - Not FDA-approved

"WHAT ARE THE BARRIERS FOR SCREENING OUT EVERY CASE OF KERATOCONUS?" Protocol Equipment Manpower Community Awareness



HOW AND WHEN DO WE SCREEN? - IN-OFFICE OR SCREENING EVENTS?

EQUPPENT



EQUIPPENT COST VS EFFICACY



- MANUAL KERATOMETRY? - AUTOREFRACTION? - STANDARD TOPOGRAPHER? - PENTACAM?














Epithelial debridement

1. Using topical anesthesia, debride the epithelium to a diameter of approximately 9 mm using standard aseptic technique.

Induction

2. Instill 1 drop of Photrexa® Viscous topically on the eye every 2 minutes for 30 minutes.

Check Flare and Corneal Thickness

- 3. Observe eye for yellow flare
 - If the yellow flare is not detected, instill 1 drop of **Photrexa Viscous** every 2 minutes for an additional 2 to 3 cycles. Repeat until yellow flare is observed.
- 4. Corneal thickness of 400 μ m,
 - Swell the cornea using hypotonic **Photrexa**[®] every 5 to 10 seconds until the corneal thickness increases to at least 400 μm.

UV Irradiation

5. Irradiate the eye for 30 minutes using the **KXL[®] System.** Continue instillation of 1 drop of **Photrexa Viscous** topically on the eye every 2 minutes for 30 minutes.









GLAUK

MA-01789C



- 1. Power on the device
- 2. Press "Start New Treatment" button
- 3. Confirm treatment parameters
- 4. Scan treatment activation card
- 5. Sync remote



O Scan Activation Card



- Place the activation card in the RFID reader until the system emits a beep.
- After a multi-use activation card has been scanned, the display will show the number of treatments remaining on the card.
- Single-use cards may be discarded after the treatment is complete.



Activation card scanned ...

This is the fnal treatment allowed for this activation card

GLAUK S

Cancel Session

MA-01789C

Sync the Alignment Remote

- A window is displayed prompting user to sync remote (for 15 seconds)
- Press the "S" button on the remote to synchronize the remote during that time frame.
- If remote goes out of sync, a pop-up message will notify the user.





Common Procedure Supplies

Equipment

KXL System Procedural Microscope Ultrasound Pachymeter Treatment Activation Card Wastebasket Tray/Mayo Stand Clock Timer

Medications

Photrexa Viscous (orange label) Photrexa (green label) Topical Anesthetic Post-operative Drops (patient's)

Tray Supplies

Lid Speculum (e.g. Lieberman/solid blade) Epithelial removal supplies 4 x 4 Gauze Surgical spears (e.g. Weck-Cel) BSS Solution

Other Supplies

Betadine Prep Swabs Surgical Gloves Surgical Bonnet Surgical Tape Bandage Contact Lens Table Drape



O Tray example



MA-01789C

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Step 1: Epithelial Debridement

- Method 1:
 - Soak cornea light shield in alcohol
 - Apply for 10-12 seconds
 - Use a combination of Weck-cell sponges, micro-hoe, crescent blade, or PRK spatula to remove loose epithelium
- Method 2:
 - Apply 8mm well on the cornea
 - Inject alcohol into the well
 - Let sit for 10 seconds
 - Use Weck-cell sponges to soak up the alcohol then remove the well from the eye
 - Use a combination of Weck-cell sponges, micro-hoe, crescent blade, or PRK spatula to remove loose epithelium



Step 2: Induction

- 1 drop of Photrexa viscous every 2 minutes
- Machine will signal when to put in the next drop
- If cornea thickness < 400, can use Photrexa (non-viscous)







Every 2 minutes, the status bar illuminates in orange and displays the "Apply Riboflavin" reminder and the system beeps.



The treatment stops automatically after the treatment timer expires.

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Step 3: UV Irradiation

- Check for Flare
 - If no flare use Photrexa viscous every 2 minutes until flare detected
- Check pachymetry
 - OK to proceed if > 400 microns
 - DO NOT PROCEED if < 400 microns
 - 1) Photrexa every 5-10 seconds
 - 2) BSS drops every 5-10 seconds
- Place speculum to open eye
- Align Crosshairs of UV lamp
- Continue riboflavin eye drops every two minutes





- Align the Optical Head over the patient eye, positioning the "X & Y Axis" crosshair at the center of the pupil.
- Align the "Z Axis" crosshair to the center of the "X & Y Axis" crosshair by moving the optical head up and down.
- Fine tune the alignment using the remote.







MA-01789C

O Post-op Considerations

- A bandage contact lens should be applied.
- Surgeons may apply their standard of care for postoperative management of PRK patients.
- This may include:
 - Antibiotic
 - Steroid
 - NSAID
 - Lubricating drops



• As always in the practice of medicine, it is up to the physician's discretion regarding the most appropriate care for their patients.

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- Press "Power Off"
- Confirm
- Toggle Main switch to "Off" position on the base of the KXL system above the power cord

MA-01789C

GLAUK S

Today's Wetlab

- Affix the pig eye to the styrofoam block
- Set up the cross linking machine
- Step 1: Epithelial Debridement 8-9mm
- Step 2: Induction Photrexa drop every 2 minutes
- Check pachy, flare
 - What do you do if pachymetry is under 400 microns?
 - What do you do if you do not see flare?
- Step 3: UV Irradiation center crosshairs, riboflavin drop every 2 minutes

STEPS TO EPITHELIAL-OFF CORNEAL CROSS-LINKING Dresden Protocol



1. Remove epithelium



2. Soak cornea Photrexa[®] (riboflavin 5'-phosphate in 20% dextran ophthalmic solution)

✓ 30 minutes



4. Once flare is observed, measure corneal thickness

✓ If corneal thickness is less than 400 um, instill 2 drops of Photrexa (riboflavin 5'phosphate in 20% dextran ophthalmic solution) until the corneal thickness increases to at least 400 µm



3. Check for flare



- 5. Irradiate for 30 minutes
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