Collagen Crosslinking and Management of Keratoconus

Christopher Chow, M.D.
Michigan Cornea Consultants
Oakland University William Beaumont School of Medicine
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Keratoconus

- First described in 1854
- Noninflammatory, nonvascularized progressive corneal thinning and protrusion
- Hallmark: high progressive irregular astigmatism
- No strictly defined criteria
- A clinical diagnosis
Keratoconus

- Prevalence and distribution
  - 1 per 1000-2000
  - Preponderance in women – up to 67%
  - Occurs in all races
  - 6-8% with family history
Keratoconus

- **Course**
  - Usually bilateral
    - 14.3% unilateral? – Amsler, 1961
    - Probably less – Rabinowitz, 1993
  - Onset often during puberty
  - Progression over 10 to 20 years
    - Longer?

- **Systemic Associations**
  - Atopy
  - Down Syndrome
  - Noninflammatory connective tissue disorders
Keratoconus – How Have We Treated It?

- **Mild keratoconus**: Treated with glasses/soft contact lenses to correct refractive error and astigmatism.

- **Moderate keratoconus**: Treated with RGP contact lenses, which support bulging cornea and correct refractive error/irregular astigmatism.

- **Advanced keratoconus**: Penetrating keratoplasty.
Current Treatment Options

- **Contact Lenses**
  - Gas permeable contacts are still the standard means of vision correction for keratoconus patients
    - **Pros**
      - Safe
      - No significant lifelong trauma risk
      - No rejection risk
      - Newer contact lens options – SynergEyes, KeraSoft
    - **Cons**
      - Fitting
      - Comfort – 27-37% keratoconus patients develop contact lens intolerance
      - Risk of infection
      - Contact lenses potentially exacerbate cornea thinning – contact lens-induced keratoconus
Current Treatment Options

- Collaborative Longitudinal Evaluation of Keratoconus Study (CLEK)
  - 1065 patients followed for 8 years – began in 1995
  - Conclusion – Risk factors for requiring penetrating keratoplasty:
    Gordon MO et al, AJO, 142:923, 2006
    - Younger age
    - Steeper keratometric values
    - Worse visual acuity
    - Corneal scarring
    - Contact lens discomfort
    - Poorer visual function-related quality of life
Keratoconus

- Penetrating keratoplasty
  - 4500-5000/yr penetrating keratoplasties for keratoconus
  - Up to 21% of keratoconus eyes
  - Up to 96% success rate
  - Phakic patients
Penetrating Keratoplasty for Keratoconus

**Issues**

- Slow visual rehabilitation (12-18 mos.)
- Refractive/astigmatism issues
- Suture related problems
- Infectious keratitis
- Graft rejection – 15-20%
- Transplanted corneas may develop keratoconus in 10 to 20 years, although rare
- Corneal grafts have a limited life expectancy possibly related to an accelerated rate of endothelial cell loss over time (3X normal)
- Particularly problematic for younger patients as they may require multiple transplants during their life time
Lamellar Keratoplasty

- Advantages compared to penetrating keratoplasty
  - Lower chance of graft rejection
  - Extraocular procedure
  - Less stringent requirements for quality of donor tissue
  - Less use of topical steroids
  - Better wound strength
  - Faster healing

- Disadvantages compared to penetrating keratoplasty
  - Technically more difficult and time consuming
  - Steep learning curve
  - Visual outcome usually not as good
    - Irregular/uneven dissection of donor tissue
    - Irregular/uneven dissection of host bed
    - Interface scarring
    - Interface debris
    - Stromal folds
Deep Lamellar Keratoplasty

- “Classical” technique
  - Removal of tissue layer by layer until deep stroma or Descemet’s membrane is reached

- “Big bubble” technique
  - Introduced by Anwar and Teichman in 2002
  - Injection of air into the supra-Descemet’s space to detach the membrane.
Lamellar Keratoplasty – Big Bubble Technique

Deep Anterior Lamellar Keratoplasty

- Complications
  - Descemet’s membrane perforation – 9-30%
    - If conversion to penetrating keratoplasty is necessary a second, healthier donor cornea may be needed
  - Pseudo-anterior chamber
  - Descemet’s folds/interface opacification
  - Stromal graft rejection – 1.4-3.1%
INTACS

- Arc-like PMMA segments inserted into the deep corneal stroma to flatten the central cornea
- Originally designed and approved by the FDA in 1999 to treat mild myopia (-1.00 to -3.00 D)
- Colin 2001 – first published use of INTACS for keratoconus patients
- 2004 - approved by FDA under humanitarian device exemption for use in contact lens-intolerant keratoconus patients
How Do INTACS Work?

Arc-shortening model
INTACS


Table 1. Change in Visual Acuity—All Eyes

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>%</th>
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<tbody>
<tr>
<td>BSCVA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved ≥ 2 Lines</td>
<td>33</td>
<td>45</td>
</tr>
<tr>
<td>No change</td>
<td>38</td>
<td>51</td>
</tr>
<tr>
<td>Worsened ≥ 2 Lines</td>
<td>3</td>
<td>4</td>
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<tr>
<td>Total</td>
<td>74</td>
<td>100</td>
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“Doctor, isn’t there anything you can do to keep my keratoconus from getting worse??”
Crosslinking

- Crosslinking – hardens and stabilizes materials
  - Tanning leather
  - Egyptian mummies
  - Garden hose
  - Automobile lacquers
Crosslinking

- Crosslinking – hardens and stabilizes materials
  - Dentistry – UVA crosslinking to harden filling materials
  - Pathology – formaldehyde to preserve tissue specimens
  - Heart valves – glutaraldehyde crosslinking to enhance durability, resistance to enzymatic degradation and reduce immunogenicity
  - Dermatology – tighten collagen in sagging skin
  - Aging – arterial hardening, stiffening of joints, wrinkling of skin
  - Cataract – UV crosslinking of lens crystallins
Corneal Crosslinking

- Crosslinking the Cornea
  - Natural crosslinking of aging cornea through glycation
  - Diabetics – lower incidence of keratoconus due to natural crosslinking from high glucose and UV light
  - Concept proposed by Theo Seiler in 1996 at ARVO
  - Clinically reported by Wollensak in 2003
  - UVA at 370 nm used to excite photosensitizer riboflavin to generate reactive oxygen species which reacts further with other molecules to induce covalent bonds between collagen fibrils
  - Approved in all 26 European Union nations by 2006
Corneal Collagen Crosslinking
Corneal Collagen Crosslinking

Creates chemical bonds between fibers
Collagen Crosslinking

- Laboratory studies
  - Increased corneal rigidity of 329% - Wollensak et al, AJO, 135: 620, 2003
  - Crosslinking effect present for depth of 300 μm
  - Rabbit anterior stroma – collagen fiber diameter increased by 12%
  - Rabbits – keratocyte apoptosis up to 300 μm
Collagen Crosslinking

- Dual role of riboflavin
  - Absorption of UVA
    - Wollensak G, et al, 2003. Riboflavin increases absorption of UVA by the cornea to 95% compared to 32% without
  - Photosensitizer
    - Production of oxygen free radicals to induce cross-linking of collagen fibers
  - No cytotoxic effect on keratocytes
Collagen Crosslinking

- **Technique**
  - Topical anesthesia
  - Debridement of central 8-9 mm epithelium
  - 0.1% riboflavin in 20% dextran applied every 2-5 minutes for 30 minutes
  - Slit lamp evaluation to assess penetration of riboflavin
  - Pachymetry
  - Irradiation with UVA 370 nm for 30 minutes. Continued application of riboflavin every 2-5 minutes
Collagen Crosslinking

- Wollensak G et al. AJO, 135:620, 2003
  - 23 eyes with moderate or advanced progressive keratoconus treated and followed for 3 years
  - Progression of keratoconus stopped in all eyes
  - 16 eyes – flattening by 2 diopters
  - 15 eyes – improved BCVA

  - 60 eyes
  - Keratoconus progression stopped in all
  - Flattening by up to 2.87D
  - BCVA improved by a mean 1.4 lines
Collagen Crosslinking

Collagen Crosslinking

  - French National Reference Centre for Keratoconus
  - 142 eyes with progressive keratoconus
  - Halted keratoconus progression or improved max keratometry value in 89.9% at 12 months
  - CDVA stabilized or improved in 87.6% at 12 months
  - 3.5% with 2 or more lines of vision lost
Collagen Crosslinking

  - 241 eyes, 7 year results
  - Decrease in maximum keratometry
    - 2.7D at 1 year
    - 2.2D at 2 years
    - 4.8D at 3 years
  - Visual acuity improved 1 line per year for 3 years in 57%
  - No lines of lost BCVA
  - 2 patients with progression of keratoconus – repeat CXL
  - Such confidence in procedure – no control group
Collagen Crosslinking

- Siena Eye Cross Study – Caporossi A et al, AJO, 149: 585, 2010
  - 44 pts with keratoconus and documented progression had one eye treated.

<table>
<thead>
<tr>
<th></th>
<th>1 yr</th>
<th>2 yrs</th>
<th>3 yrs</th>
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<tbody>
<tr>
<td>Treated eyes: Keratometry</td>
<td>-1.96 D</td>
<td>-2.12 D</td>
<td>-2.24 D</td>
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<tr>
<td>Untreated eyes: Keratometry</td>
<td>+1.2 D</td>
<td>+2.2 D</td>
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<tr>
<td>Effective change with treatment:</td>
<td>-3.16 D</td>
<td>-4.32 D</td>
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Collagen Crosslinking

- Subjective outcomes
  - Brooks NO et al., JCRS, 38:615, 2012
    - 107 eyes treated in 76 patients
    - 71 eyes with keratoconus, 36 eyes with post-LASIK ectasia
Managing Expectations with CXL

- MUST set proper expectations with patients
- 98%: Stop progression of Keratoconus
- 60-80%: Improved/Reduction in Corneal steepness
- 60-80%: Improvement in BCVA
  - 1-2 lines
  - NOT a refractive procedure – will likely still need glasses or contact lenses

Who Should Get Crosslinking?

- Young keratoconus patients
- Keratoconus patients older than 35 – only if progressing
- Progressive ectasia
- Pellucid marginal degeneration
- Post-RK visual fluctuation
What Are the Risks and Complications of CXL?

- Treatment Failure
- Loss of best-corrected visual acuity
- Corneal edema
- Stromal Haze/Scarring
- Postoperative infection
- Increased IOP
- Carcinoma?
Risks and Complications of CXL

- Treatment failure
  - Defined as progression of keratoconus
  - Perhaps about 7-8%
  - Possible risk factors
    - Age >35
    - Spectacle correction better than 20/25
    - Max keratometry >58.00D
Risks and Complications of CXL

- Loss of BCVA
  - Transient loss is common
  - Permanent loss of 2 or more lines of Snellen acuity is considered a complication in assessing refractive procedures.
    - 5% considered acceptable?
  - Koller T et al, JCRS, 35:1358, 2009
    - 3 out of 105 patients = 2.9%
      - Remember – this is not an elective refractive procedure
      - Risk factors: age > 35, CDVA of 20/25 or better
  - Other studies – less
Risks and Complications of CXL

- Corneal edema
  - Spoerl E, et al, Cornea, 26:385, 2007
  - Corneal endothelial risk and edema in cornea with thickness <400 microns
Collagen Crosslinking

- Use of hypo-osmolar riboflavin for thin corneas
  - Raiskup F and Sproel E, AJO, 152:28, 2011
  - 32 eyes of 29 patients with progressive keratoconus and stromal thickness of less than 400 microns
  - Treated with hypo-osmolar riboflavin every 2 min for 30 minutes before CXL
  - At 1 year – no progression of keratoconus, no scarring
Risks and Complications of CXL

- Stromal haze
  - 14/163 (9%) patients with visually significant stromal haze
  - 5/44 (11%) patients with visually significant stromal haze
  - Extends 60% into stroma
  - Greatest at 1 month, often will resolve over time (12 months)
    - Koller T et al, JCRS, 35:1358, 2009
      - Grade of haze decreases from 0.78 to 0.006
  - Worse with thinner corneas and higher keratometry readings
  - DLK reported when treating post-LASIK ectasia
Risks and Complications of CXL

- Postoperative Infection
  - Reports of bacterial keratitis - pseudomonas, E. coli
  - Reactivated herpes simplex keratitis
  - Acanthamoeba keratitis
  - Some apparently related to contaminated riboflavin
Risks and Complications of CXL

- Increased Intraocular Pressure
  - Several studies have shown increased IOP of about 2mm Hg
  - Uncertain accuracy of IOP readings due to change in corneal rigidity
Risks and Complications of CXL

- Carcinoma
  - Ultraviolet light as risk factor
  - Total UV dose per treatment = 5.4 joules/cm² in Dresden protocol
    - About the same as 30 minutes on a sunny summer day at the beach
    - Some studies using higher irradiance
What to do with the Epithelium?

- Epithelium off vs. epithelium on
  - Epi on would be simpler
  - Epi on would have fewer risks – infections, ulcers, scarring, infiltrates
  - Epi on would have less pain and faster visual recovery
    - Days vs. weeks/months
  - How to get riboflavin to penetrate?
    - Can take much longer
    - Disrupt epithelium – preservatives (BAK), topical anesthetics, 20% alcohol, scratching/epithelial disruptors
    - Different riboflavin preparations
  - Overall – epi-on may be about 20% less effective than epi-off
Collagen Crosslinking

- Variations
  - Dresden protocol
  - Athens protocol
    - CXL + topography-guided PRK
  - CXL + INTACS
    - Riboflavin into INTACS channel
  - Pulsing of UV light
    - Allows replenishing of oxygen reserves
  - Keraflex (Avedro Inc.) microwave pulse + CXL
    - Microwave pulse raises temperature to 149F, shrinking and flattening the anterior 150 microns of central cornea
  - TRXL (Seros Medical) continuous wave infrared laser + CXL
    - Shrinks anterior stroma
  - CXL + phakic IOLs
Collagen Crosslinking

- Other applications for Crosslinking
  - Role in treating infections?
    - UV light alone kills bacteria, fungi, viruses and protozoa
    - UV light and riboflavin interaction forms cytotoxic free oxygen radicals
    - Enhancement of corneal resistance to enzymatic degradation
    - Makdoumi K et al, Cornea, 2011 – 7 eyes treated
  - Corneal edema
  - Corneal melt
  - “LASIK extra”
    - Incidence of ectasia after LASIK = 1 in 10,000?
    - Riboflavin to stromal bed, replace flap, 10 min UV
    - Results in interweaving of stroma to flap
Questions and Future Directions

- Epi-on vs Epi-off and establishment of protocol variations
- LED lamp technology
- Titration of treatment – increase of irradiance with decrease in treatment time
- Establish how much stiffening is needed. 2x? 4x? 8x?
- Alternative crosslinking agents
  - Glycolaldehyde
  - Beta-nitro alcohols
  - Flash linking – hydrogel substrate polyvinyl pyrrolidone
  - Riboflavin with alternate preparations
- Premature aging of cornea – other sequelae?
  - Keratocyte and dendritic cell risks
  - Tear function
  - Stem cell effects
- Standard of Care
Thank you!