Basics on cornea and keratoconus, relevant facts for crosslinking (CXL)

CXL stiffens the keratoconic cornea by instilling riboflavin in combination with exposure to a UVA light source. The procedure is designed to halt progression of keratoconus.

1. Snapshot of keratoconus
2. Biomechanics of the cornea
3. Progression of ectasia
4. Management of keratoconus

Snapshot of keratoconus:
- Prevalence: 86 patients per 100,000 residents
- Typical presentation: young man in his teens or twenties
- Asymmetrical involvement: one eye more than the other
- Natural course: onset at puberty, progression until the 3rd or 4th decade when it usually stabilises spontaneously

Snapshot of keratoconus: clinical features
- Fleisher ring
- Hydrops
- Thinning and protrusion
- Subepithelial scarring
- Vogt striae

Snapshot of keratoconus: Scheimpflug tomography
- Typical patient at first presentation:
  - teenager
  - recent decrease DCVA
  - increase in astigmatism
  - clear corneas

Relevance to clinical crosslinking
- The risk of progression to corneal transplant (10 to 20%) is higher when the age at presentation is lower and the degree of steepening is higher.
- Closer follow-up of young patients or CXL at presentation (<20 y old)
**Relevance to clinical crosslinking**

- Self limiting disease with very different end points of keratoconus evolution: from a very mild undetected form to advanced stages with severe thinning and scarring

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not every keratoconus needs CXL
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43 y old: Detection at genetic screening.
47 y old: CL dependent for more than 25 years
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**Keratoconus: etiology**

- Complex disease:
  - genetic predisposition
  - environmental factors (sex hormones at puberty and during pregnancy)
  - risk-conferring behaviours (rubbing, relationship with allergy)

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STOP rubbing, treat allergy!
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**Keratoconus: pathogenesis**

- Mechanism? tissue degradation and or slippage of fibrils and lamellae

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-> final common pathway: focal abnormality in the biomechanical properties of the stroma
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**Corneal biomechanics and UVA crosslinking**

CXL aims to change the biomechanical characteristics of the cornea thereby stabilizing progressive keratoconus

Foundations of the biomechanical response:

- Corneal architecture
- Corneal material properties

**Corneal architecture**

Physical strength, stability of shape, and biomechanical characteristics of the cornea are attributable to the anatomic and biochemical properties of the stroma.

- Collagen is the primary structural component of the corneal stroma and Bowman’s layer (type I and smaller amounts of types III, V and VI).
- Keratocytes secrete procollagen molecules that are assembled into collagen fibrils.

**Corneal architecture**

- Collagen fibrils show a highly organised arrangement and are braced apart by a proteoglycan matrix that maintains uniform interfibrillar spacing (Maurice, 1998).
Corneal architecture

- The fibrils are arranged into flat bundles, or lamellae, approximately 300 centrally to 500 at the limbus.

Anterior lamellae run obliquely and randomly across the cornea, often starting at the limbus and terminating at Bowman's membrane where they interweave with the collagen of the Bowman's membrane.

Posterior lamellae are thicker and have an ordered limbal to limbal arrangement, running preferentially in the inferior-superior and medial-lateral meridians.

Enzymatic crosslinking is part of the normal physiology of the cornea: Lysyl oxidase (LOX) transforms amino groups into aldehyde groups that form covalent bonds between collagen molecules.

- Keratoconus: possible gene defect of this enzyme
- Corneal wound healing and scarring: upregulation of this enzyme

Crosslinks are part of the normal anatomy of the stroma.

Relevance to clinical crosslinking

- Non-enzymatic crosslinking
  - Sugar aldihydes (Advanced Glycation End products AGE) lead to increased crosslinking and increased rigidity of the cornea with ageing and in diabetes mellitus
  - Photochemical crosslinking or photopolymerization as in riboflavin / UVA clinical crosslinking

Corneal biomechanics and UVA crosslinking

CXL aims to change the biomechanical characteristics of the cornea thereby stabilizing progressive keratoconus

Foundations of the biomechanical response:

- Corneal architecture
- Corneal material properties
Corneal material properties

• Stress & Strain: Basic concepts of biomechanics

- Stress can cause deformation, tensile stress causes elongation.
- As the elongation depends on the original length a dimensionless value is introduced:
  \[ \epsilon = \frac{\text{elongation}}{\text{original length}} \]
- Relationship between stress \( \sigma \) and strain \( \epsilon \) depends on the type of material and the magnitude and type of the stress.

Corneal material properties

• Elastic behaviour

- Linear elastic behaviour:
  - linear relationship between stress and strain
  - expressed by Hooke’s law \( \sigma = E \times \epsilon \) and \( E = \) Young’s modulus of elasticity

Corneal material properties

• Non-linear elastic behaviour:
  - Non-linear relationship between stress and strain, description by exponential functions
  - Deformation is completely reversible, no hysteresis

Corneal material properties

• Viscous materials

- Viscous damping
  - The resistance to an applied force depends primarily on the speed at which the force is applied.
**Corneal material properties**

- Human corneal tissue is a composite visco-elastic structure
  - Deformation is reversible
  - Hysteresis between loading and unloading

**Corneal material properties**

- The cornea is anisotropic i.e. displays different physical properties when stress is applied in different directions.
  - E-modulus varies between vertical and horizontal meridian; in the vertical meridian the cornea is stiffer in the upper part
  - Anterior part is 25% more rigid than posterior part
  - Cornea stiffer in the periphery than in the center
- Biomechanical properties are not constant but change with advancing age, corneal pathology and level of hydration.

**Measuring corneal biomechanics in vitro**

- Tissue strips:
  - Stress-strain measurements
  - Stress-relaxation measurements
  - Creep measurements
  - Fracture measurements
- Shell model:
  - The cornea is fixed on a pressure chamber and the IOP is varied; the strain is measured in 2 dimensions by holo- and videography.

**Measuring corneal biomechanics in vivo**

- Main difficulty is to distinguish between the biomechanical properties of the cornea and the effect of IOP.
- Ocular Response Analyser

**Relevance to clinical crosslinking**

- Efficacy of crosslinking is demonstrated by stress-strain measurements, using an extensometer.

**Measuring corneal biomechanics in vivo**

- Different response of normal versus keratoconic cornea

**Measuring corneal biomechanics in vivo**

- Detection of keratoconus? Effect of CXL?
Measuring corneal biomechanics in vivo

- CorVis-ST: air puff combined with a high speed Scheimpflug camera that captures the deformation of a section of cornea in real time.

More reading on corneal biomechanics

Measuring corneal biomechanics in vivo

- Brillouin light scattering: arises from the interaction of incident light with propagating thermodynamic fluctuations (acoustic phonons) in the corneal tissue → frequency shift related to the elastic modulus.

Diagnosis and follow-up of keratoconus: topography and tomography

Specular reflection keratometry is still valid, but...

Scheimpflug imaging goes beyond measurement of the anterior surface.

Placido corneal topography: cone morphology

4 maps refractive display of a keratoconus eye
To document progression look at Scheimpflug maps of:
- anterior curvature
- pachymetry
- posterior elevation
  - least influenced by outside forces (warpage by contact lenses!)
  - keep the reference surface constant (initial exam = baseline)

Preferably data that are less dependent of fixation/alignment
  - K max, pachymetry at the thinnest point

Supported by patient age, BSCVA, refraction

Relevance to clinical crosslinking

Management of keratoconus

- Most patients present with complaints of loss of visual acuity
  - They need both stabilisation of the conus and optical correction of their refractive error
  - Contact lenses and crosslinking are complementary

NB rigid lenses do not stabilize keratoconus!

Management of keratoconus: RGP contact lenses

- Rigid gas permeable contact lenses have been the mainstay for correction of refraction:
  - very efficient and safe, easily adjustable
  - only drawback is discomfort and intolerance

Management of keratoconus: specialty lenses

- All you need to know about contact lenses as a refractive surgeon
  - RGP lenses, soft lenses, specialty lenses, etc.

3 point touch fitting of a corneal RGP lens

Sunday 6th September 17.00 h
Management of keratoconus

Progressive keratoconus or not?
Yes R/ crosslinking

Need for optical correction?
Yes R/ contact lens trial

Good tolerance for CL

Intolerance for CL

R/ contact lenses

R/ refractive surgery

If best lens corrected VA remains < 0.5 transplant surgery