

# New nomogram for extremely thin KC corneas: clinical

**Farhad Hafezi, MD PhD**

**Professor of Ophthalmology**  
University of Geneva  
Geneva, Switzerland



**Medical Director**  
ELZA Institute  
Zurich, Switzerland



**Research Group Leader**  
Lab. for Ocular Cell Biology  
University of Zurich, Switzerland



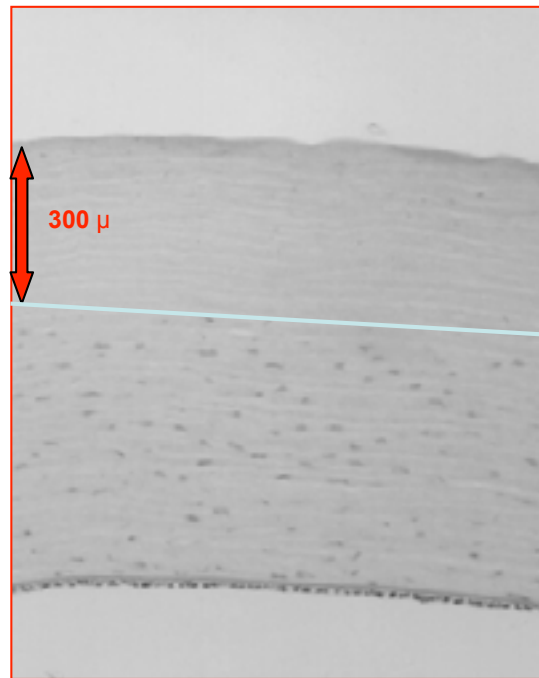
**Professor of Ophthalmology**  
Keck School of Medicine  
USC Los Angeles, USA



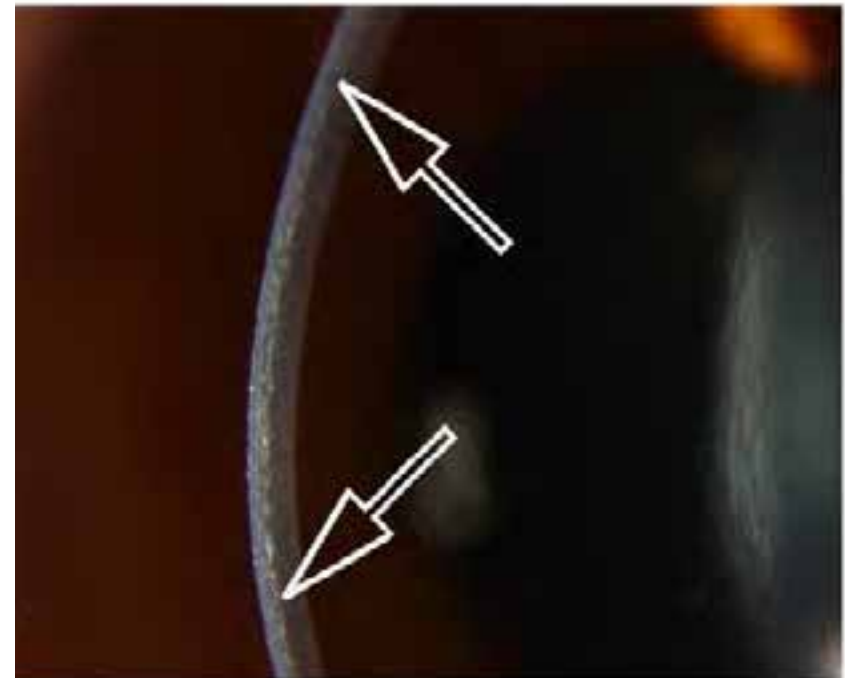
# Initial decision

- Establish irradiation parameters for minimal thickness = 400  $\mu\text{m}$

## 1. Historical



Wollensak, 1998, *Exp Eye Res*



Seiler & Hafezi, 2006, *Cornea*

# Treat thin corneas

1. Historical

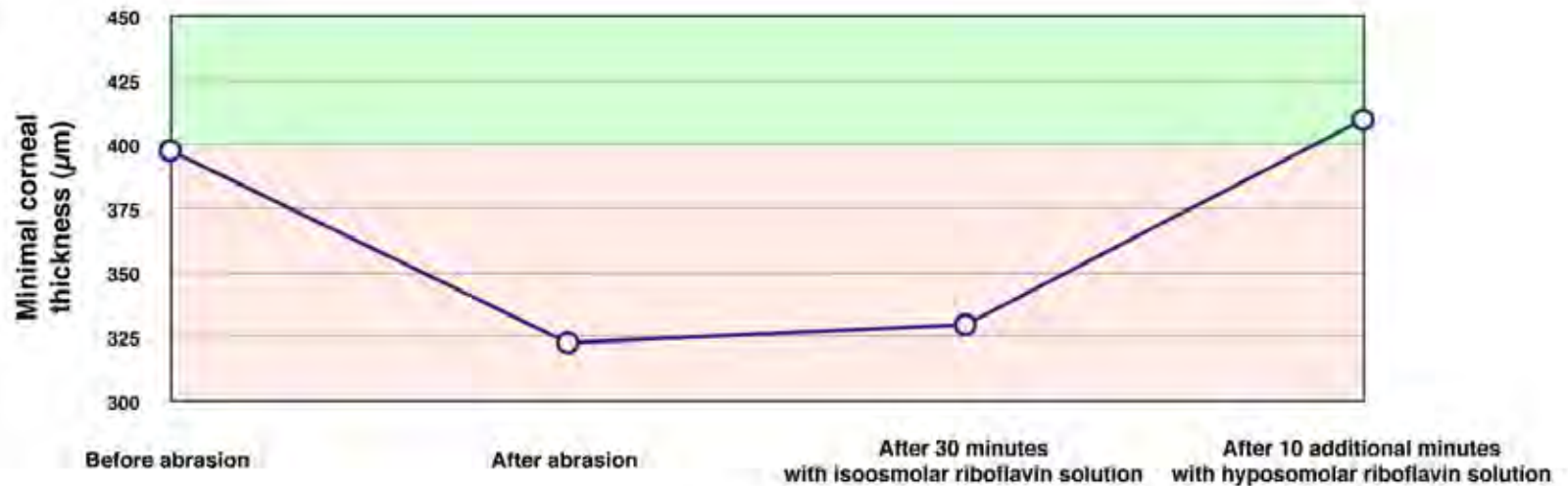
2. Hypo-osmolaric  
CXL

## TECHNIQUE

### Collagen crosslinking with ultraviolet-A and hypoosmolar riboflavin solution in thin corneas

Farhad Hafezi, MD, PhD, Michael Mrochen, PhD, Hans Peter Iseli, MD, Theo Seiler, MD, PhD

*JCRS, 2009*



# Other techniques

1. Historical

2. Hypo-osmolaric  
CXL

3. Other  
techniques

**Hypo-osmolaric CXL**

**Transepithelial CXL**

**Contact-lens-assisted**

**Epithelial island CXL**

# Factors in CXL

1. Historical

2. Hypo-osmolaric  
CXL

3. Other  
techniques

**Thickness**

**Riboflavin  
concentration**

**UV  
intensity**

**Hypo-osmolaric CXL**

**Transepithelial CXL**

**Contact-lens-assisted**

**Epithelial island CXL**

1. Historical

2. Hypo-osmolaric  
CXL

3. Other  
techniques

4. New model

# New model



**UV**  
**intensity**

- Riboflavin diffusion kinetics
- Oxygen diffusion kinetics

# Fixed fluence (5.4 J/cm<sup>2</sup>)

1. Historical

2. Hypo-osmolaric  
CXL

3. Other  
techniques

4. New model



**400 μm**



**300 μm**

1. Historical

2. Hypo-osmolaric  
CXL

3. Other  
techniques

4. New model

# Fixed fluence (5.4 J/cm<sup>2</sup>)



**400 μm**



**300 μm**

- hypo-osmolaric
- contact lens-assisted



# Adapted fluence

1. Historical

2. Hypo-osmolaric  
CXL

3. Other  
techniques

4. New model

$5.4 \text{ J/cm}^2$



**400 µm**

$3 \text{ mW/cm}^2$  for 30'

$xx \text{ J/cm}^2$



**300 µm**

$3 \text{ mW/cm}^2$  for xx'

$xx \text{ J/cm}^2$



**250 µm**

$3 \text{ mW/cm}^2$  for xx'

# New model to adapt CXL effect between 200 μm and 400 μm

1. Historical

2. Hypo-osmolaric CXL

3. Other techniques

4. New model

The oxygen concentration in the cornea  $[O_{2,c}]$  is determined by the amount of uptake by diffusion, the cellular oxygen consumption of the stroma  $Q_{O_2}$ , the production and degradation of singlet oxygen and the existence of the reduced form of riboflavin:

$$[O_{2,c}] = [O_{2,s}] + [O_{2,c}] \left( 1 + \frac{Q_{O_2}}{k_{O_2} N_A} \right) + [O_{2,c}] \left( 1 + \frac{Q_{O_2}}{k_{O_2} N_A} \right) \left( 1 + \frac{Q_{O_2}}{k_{O_2} N_A} \right) \quad (Eq. 1)$$

(Eq. 1)

where  $\Delta c_{O_2}$  is the difference in oxygen concentration between the current and the normal oxygen content in the cornea,  $[O_{2,s}]$  is the concentration of singlet oxygen,  $k_{O_2}$  is the  $O_2$  water permeability rate constant of oxygen,  $Q_{O_2}$  is the consumption of the reduced form of riboflavin,  $k_{O_2}$  is the quenching rate of riboflavin,  $k_{O_2}$  is the oxidation rate of the reduced form of riboflavin,  $Q_{O_2}$  is the atomic oxygen consumption for a given oxygen sensor  $Q_{O_2} [M]$ . The oxygen stream can be calculated from the oxygen concentration  $[O_{2,c}]$ , the molar mass of oxygen  $M_{O_2} = 32 \frac{g}{mol}$  and experimental data (Eq. 1)(2):

$$\dot{m}_{O_2} = [O_{2,c}] M_{O_2} \frac{1000 \text{ mm}^3}{1.25 \text{ g}} \quad (Eq. 2)$$

$\dot{m}_{O_2}$  is the consumption of the estimated rate of atmospheric water, i.e. collagen and non-collagenous proteins.

$$[AM] = \frac{0.18 \cdot \rho_{coll} \cdot \dot{m}_{O_2}}{M_{coll} \cdot N_A} \cdot 100 \left( [O_{2,c}] \right) \left( 1 + \frac{Q_{O_2}}{k_{O_2} N_A} \right) \quad (Eq. 3)$$

where  $M_{coll}$  is the molecular mass of collagen with a total 457 Da ( $6.75 \cdot 10^{-22}$  kg),  $\rho_{coll}$  is the density of the cornea and 0.18 is the assumed content of collagen and non-collagenous proteins in the cornea. Factor 100 is the author's estimate to describe the resolution of possible additional cross-links performed cross-link due to distorting potential binding sites.

The concentration of proteins in the cornea  $[Protein]$  is determined by the assumed UV energy along the cornea:

$$[Protein] = \frac{I_0 \cdot \Delta t \cdot \lambda \left( 1 - 10^{-\frac{I_0 \cdot \Delta t \cdot \lambda \cdot \epsilon \cdot c \cdot d}{10}} \right)}{h \cdot \nu \cdot N_A \cdot d} \quad (Eq. 4)$$

where  $\lambda$  is the spectral intensity of the UV ray,  $h$  is the wavelength,  $\epsilon$  is the absorption coefficient of the cornea stroma,  $\nu$  is the extinction coefficient of riboflavin,  $d$  is the corneal thickness,  $h \cdot \nu \cdot N_A \cdot d = 50 \mu\text{m}$  is the thickness of the riboflavin film (10) on top of the cornea in the clinical setting,  $\epsilon$  is the Planck constant,  $c$  is the speed of light and  $N_A$  is the Avogadro number.

The concentration of singlet oxygen is determined by the quantum yield of riboflavin, the singlet oxygen degradation through physical and chemical quenching and the consumption of singlet oxygen during crosslinking reaction:

$$[O_2^1] = [O_2^1] + [O_{2,c}] \left( 1 + \frac{Q_{O_2}}{k_{O_2} N_A} \right) \left( 1 + \frac{Q_{O_2}}{k_{O_2} N_A} \right) \left( 1 + \frac{Q_{O_2}}{k_{O_2} N_A} \right) \quad (Eq. 5)$$

(Eq. 5)

where  $\Phi_{O_2^1}$  is the quantum yield (16) of singlet oxygen produced for riboflavin and  $k_{O_2}$  is the collision rate of the extracellular matrix.

The concentration of the riboflavin radical pair  $[RFR^*]$  is given by:

$$[RFR^*] = [RFR^*] + [AM] \left( 1 + \frac{Q_{O_2}}{k_{O_2} N_A} \right) \left( 1 + \frac{Q_{O_2}}{k_{O_2} N_A} \right) \left( 1 + \frac{Q_{O_2}}{k_{O_2} N_A} \right) \quad (Eq. 6)$$

(Eq. 6)

where  $\Phi_{RFR^*}$  is the quantum yield of riboflavin crossing for riboflavin and  $k_{O_2}$  is the quenching rate of the riboflavin radical.

1. Historical

2. Hypo-osmolaric  
CXL

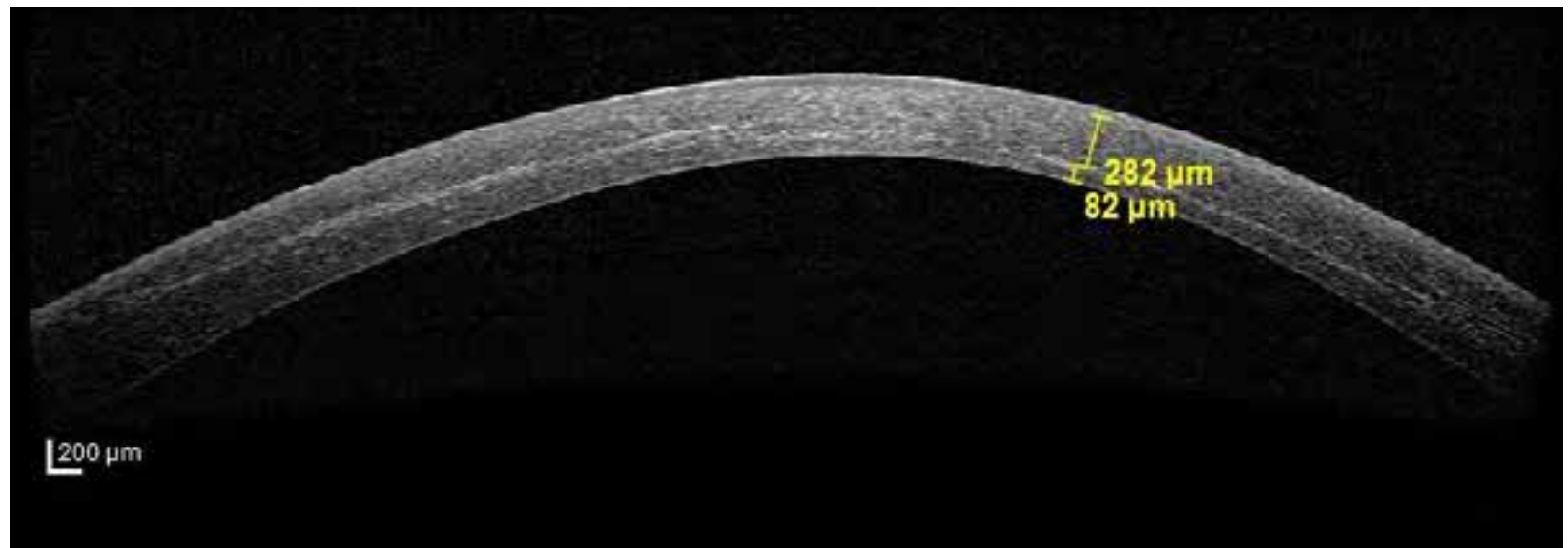
3. Other  
techniques

4. New model

5. Clinical study

## Treat corneas thinner than 400 $\mu\text{m}$

- Prospective study, ELZA Zurich
- Currently 14 eyes
- Depth of demarcation line at 1 month



- Treated so far: 245  $\mu\text{m}$  to 395  $\mu\text{m}$

# Conclusions

1. Historical

2. Hypo-osmolaric  
CXL

3. Other  
techniques

4. New model

5. Clinical study

6. Conclusions

- The future: customized settings for every corneal thickness
- Use one single riboflavin solution: no more confusion with multiple different riboflavin solutions
- Can the CXL effect stabilize a 250  $\mu\text{m}$  cornea?