

Epi-on versus Epi-off in cross linking

Essay

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Abbreviation

UVA	Ultra violet A
CXL	Cross linking
Epi-on	Epithelial on
Epi-off	Epithelial off
Na	sodium
K	potassium
BAK	Benzal konium chloride
CDVA	Corrected distance visual acuity
K-Reading	Keratometry reading
D	diopter
BSCVA	Best spectacle corrected visual acuity
ICR	Intra corneal rings
TE CXL	Trans epithelial
PTA	Placido disk based topography
RSB	Residual stromal bed
PACK-CXL	Photoactivated chromophore corneal collagen cross linling
ROS	Reactive oxygen species
PRK	Photo refractive keratectomy
MRSA	Methicillin resistant staph aureus

PBK	Pseudophakic bullous keratopathy
SE	Spherical equivalent
UCVA	Uncorrected visual acuity
I-CXL	Iontophoresis cross linking

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INTRODUCTION

Collagen crosslinking is a treatment for ectatic corneal conditions. The treatment combines riboflavin and ultraviolet A (UVA) light, allowing the formation of reactive oxygen species, with the goal of halting the progression of corneal disease. (Asri et al., 2011)

Collagen crosslinking is used for the treatment of:

- Keratoconus;
- Forme fruste keratoconus;
- Pellucid marginal degeneration;
- Forme fruste pellucid marginal degeneration;
- Post-LASIK ectasia;
- Post-radial keratometry with diurnal vision changes;
- Infectious keratitis.

For riboflavin to act as a catalyst in this process, it must first be absorbed into the corneal stroma. Because the corneal epithelium acts as a barrier to riboflavin absorption, it can be removed before application of the riboflavin.

The Dresden technique, or "epi-off" crosslinking, is initial removal of the central 9 mm of epithelium, followed by 30 minutes of riboflavin administration. Subsequently, UVA light is applied for 30 minutes, followed by bandage

contact lens placement. Epi-off crosslinking can be effective in reducing keratometry readings.(**Asri et al., 2011**)

The potential risks of this procedure include initial worsening of vision in the first month, pain, haze, corneal melting, and infection.

Dr. Brian Boxer Wachler was the first to perform transepithelial crosslinking, or "epi-on" crosslinking, in 2004. Because the epithelium is not removed, riboflavin loading requires more time than with epi-off techniques. Epi-on crosslinking has several distinct advantages: faster visual recovery; reduced pain; and reduced risks for delayed epithelial healing, infection, and visually significant corneal haze. (**Baiocchi et al., 2009**)

Today epi on cxl is performed using a two step application approach. The first is application of paracel which helps in loosening the epithelium bands. The second step is application of riboflavin which then easily passes to the stroma. This has the advantage of decreasing the application time needed.

The efficacy of the transepithelial approach has been challenged, specifically on the basis of whether sufficient riboflavin penetrates the cornea and whether the epithelium absorbs too much UV light, thus diminishing the effects of crosslinking. For these reasons, epi-on crosslinking remains controversial. (**Baiocchi et al., 2009**)

ANATOMY OF THE CORNEA

In the average adult, the horizontal diameter of the cornea is 11.5 to 12.0 mm **[Rüfer et al., 2005]** and about 1.0 mm larger than the vertical diameter. It is approximately 0.5 mm thick at the center and gradually increases in thickness toward the periphery. The shape of the cornea is prolated flatter in the periphery and steeper centrally-which creates an aspheric optical system. Corneal shape and curvature are governed by the intrinsic biomechanical structure and extrinsic environment. Anterior corneal stromal rigidity appears to be particularly important in maintaining the corneal curvature. **[Müller et al., 2001]** Organizational differences in the collagen bundles of the anterior stroma may contribute to a tighter cohesive strength in this area and may also explain why the anterior curvature resists change to stromal hydration much more than the posterior stroma, which tends to more easily develop folds. Stromal hydration also appears to affect the cornea's response to strain and shear forces.**[Simon and Ren 1994]** The human cornea consists of 6 recognized layers.

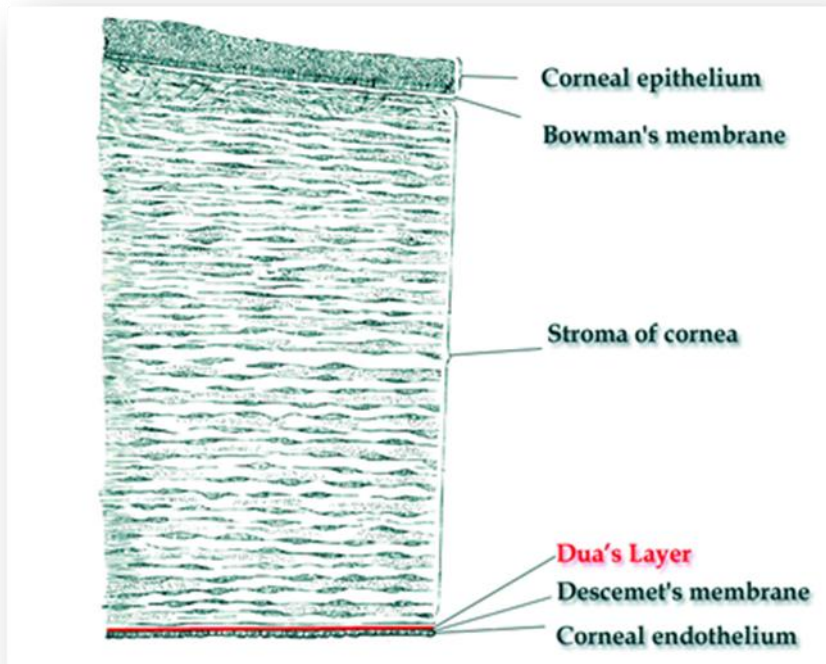


Figure (1): Histology of the cornea showing different layers including Dua's layer (**Dua et al., 2013**)

Epithelium

The epithelial surface of the cornea creates the first barrier to the outside environment and is an integral part of the tear film–cornea interface that is critical to the refractive power of the eye. It is a stratified, non-keratinizing squamous layer characterized by extreme uniformity from limbus to limbus.

Corneal epithelial cells have an average lifespan of 7 to 10 days [**Hanna et al., 1961**] and routinely undergo

orderly involution, apoptosis (programmed cell death), and desquamation. This process results in complete turnover of the corneal epithelial layer every week as deeper cells replace the desquamating superficial cells in an orderly, apically directed fashion. The most superficial corneal epithelial cells form a mean of 2 to 3 layers of flat polygonal cells. These cells have extensive apical micro-villi and microplicae, which in turn are covered by a fine, closely apposed, charged glycocalyceal layer. **[Farjo et al., 2008]** This layer's apical membrane projections increase the surface area of contact and adherence between the tear film's mucinous layer and the cell membrane.

As discussed earlier, this is critical for a smooth and clear optical system. These surface cells maintain tight junctional complexes between their neighbors, which prohibit tears from entering the intercellular spaces. This can be demonstrated clinically by observing a healthy epithelial surface's ability to repel dyes such as fluorescein and rose bengal. This barrier also prevents toxins and microbes from entering deeper corneal layers. Beneath the superficial cell layer and just anterior to the deepest basal layer of the epithelium are the supra-basal or wing cells. This layer is 2 to 3 cells deep and consists of cells that are less flat than the overlying superficial cells but possess similar tight lateral intercellular junctions.

The deepest cellular layer of the corneal epithelium is the basal layer, which comprises a single cell layer of columnar epithelium approximately 20 μm tall. Besides the stem cells and transient amplifying cells, basal cells are the only corneal epithelial cells capable of mitosis. [Wiley et al., 1991] They are the source of wing and superficial cells and possess lateral intercellular junctions characterized by gap junctions and zonulae adherens. The basal cells are attached to the underlying basement membrane by a hemidesmosomal system. This strong attachment is what prevents the epithelium from separating from the underlying corneal layers.

Bowman Layer

Bowman layer (or Bowman membrane) lies just anterior to the stroma and is not a true membrane but rather the a cellular condensate of the most anterior portion of the stroma. This smooth layer is approximately 15 μm thick and helps the cornea maintain its shape. When disrupted, it will not regenerate and can form a scar.

Stroma

The corneal stroma provides the bulk of the structural framework of the cornea and comprises roughly 80% to 85% of its thickness. The collagen fibers are arranged in parallel bundles called fibrils, and these fibrils are packed in parallel

arranged layers or lamellae. The stroma of the human eye contains 200 to 250 distinct lamella.[**Maurice 1970**] The peripheral stroma is thicker than the central stroma, This highly organized network reduces forward light scatter and contributes to the transparency and mechanical strength of the cornea. This variation in stromal organization also accounts for the differences in response to corneal edema. Descemet folds are the result of asymmetric swelling of the posterior stroma imposed by the structurally more rigid anterior cornea and structural restriction imposed by the limbus.[**Gipson and Joyce 2008**] Stromal swelling is therefore directed posteriorly and results in relative flattening of the posterior surface, which can push Descemet membrane into multiple folds that become visible as striae.

Dua layer

Dua's layer, according to a 2013 paper by Harinder Singh Dua's group at the University of Nottingham, is a layer of the cornea that had not been detected previously. [**Dua et al., 2013**] It is hypothetically 15 micrometres (0.59 mils) thick, the fourth caudal layer, and located between the corneal stroma and Descemet's membrane. Despite its thinness, the layer is very strong and impervious to air. [**Bourne et al., 1997**]

Descemet Membrane