Pentacam topographic changes after collagen cross-linking in patients with keratoconus

Thesis

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List of Abbreviations

BCVA	: Best Corrected Visual Acuity
CXL	: Corneal Collagen Cross-linking
D	: Diopter
DALK	: Deep anterior lamellar Keratoplasty
HR	: High Resolution
IOL	: Intra-occular Lens
KC	: Keratoconus
kDa	: Kilo Dalton
mm	: Millimeter
mW	: Milliwatt
nm	: Nanometer
NSAID	: Non Steroidal Anti-Inflammatory Drug
PAS	: Periodic Acid Schiff
PKP	: Penetrating Keratoplasty
PMD	: Pellucid Marginal Degeneration
PRK	: Photo Refractive Keratectomy
PTK	: Photo Therapeutic Keratectomy
SB	: Symmetric Bowtie
UCVA	: UnCorrected Visual Acuity
UVA	: Ultra Violet A
µm	: Micrometer
IOP	: Intraocular pressure

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Introduction

Keratoconus is a condition of cornea characterized by asymmetric, bilateral, progressive and non inflammatory ectasia due to the instability of cornea *(Salman, 2013).* Its incidence in the general population is reported to be approximately one in 2000. It seems to occur in all populations throughout the world, although it may occur more frequently in certain ethnic groups. The exact cause of keratoconus is uncertain, but it has been associated with detrimental enzyme activity within the cornea. A genetic link seems likely, as the incidence rate is greater if keratoconus or atopic phenotypes have been diagnosed in a family member *(Asri et al., 2011).*

KC leads to progressive corneal thinning and steepening with paracentral reduction of biomechanical strength of cornea and stromal thinning which results in irregular astigmatism and progressive myopia and this eventually leads to a decrease in visual acuity *(Caporossi et al., 2006).*

Treatment modalities are based on refractive correction with spectacles, contact lenses, and intrastromal corneal rings to correct astigmatism and restore visual acuity. Such modalities do not stop ectatic progression and further visual deterioration, which ultimately necessitate corneal transplantation in 10% to 20% of patients *(Raiskup and Spoerl, 2013)*.

Corneal collagen crosslinking (CXL, X-linking) is a recently introduced treatment for addressing progressive keratoconus. Cross-linking is a low-invasive procedure designed to strengthen the corneal structure and stop the progression of keratoconus *(Raiskup and Spoerl, 2013).*

In recent times, evidence has shown that collagen cross-linking (CXL) with riboflavin drops increases the biomechanical strength and stability of the cornea. *(Sharma et al., 2012)* In this procedure on the cornea, additional cross-links can be induced within or between the collagen fibers using ultraviolet A (UVA) light and the photo-mediator riboflavin *(Hafezi et al., 2009).*

Scheimpflug imaging is considered among the most prevalent modalities in the diagnosis, staging, and follow-up of keratoconus patients. It is based on a rotating camera and a monochromatic slit-light source, which rotate together. In addition to pachymetry and topographic imaging, Scheimpflug devices provide elevation maps of the anterior and the posterior corneal surfaces *(Labiris et al., 2012).*

Aim of The Work

The aim of this study is to document and monitor corneal changes as measured by pentacam and changes in visual acuity after corneal collagen accelerated cross linking in cases of keratoconus.

Chapter 1

Anatomy and histology of the normal cornea

The cornea is a highly specialized structure which possesses the following vital functions: a clear refractive interface, tensile strength, and protection of the intraocular contents from the external environment. It has an elliptical shape with the dimensions 10.6 mm vertically and 11.7 mm horizontally *(Weng & William, 2005).*

Histologically the cornea consists of six layers (figure 1.1):

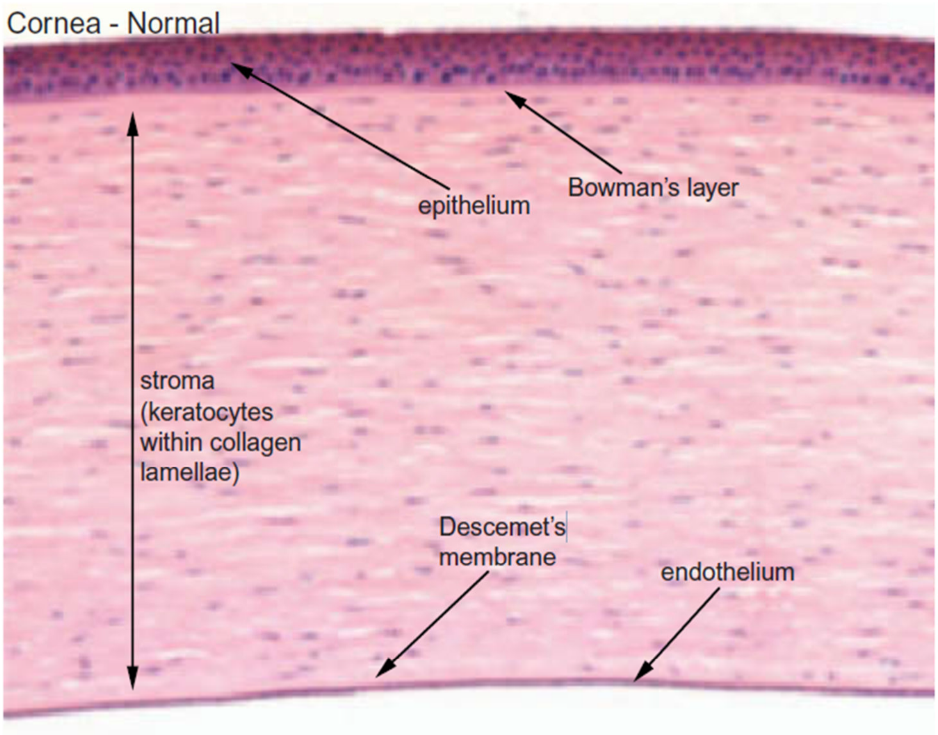

Figure 1.1 The constituents and relative thicknesses of the layers of a normal cornea. (Weng & William, 2005)

1. *Epithelium* (50 µm): consisting of five or six layers. These layers are divided into(figure 1.2):

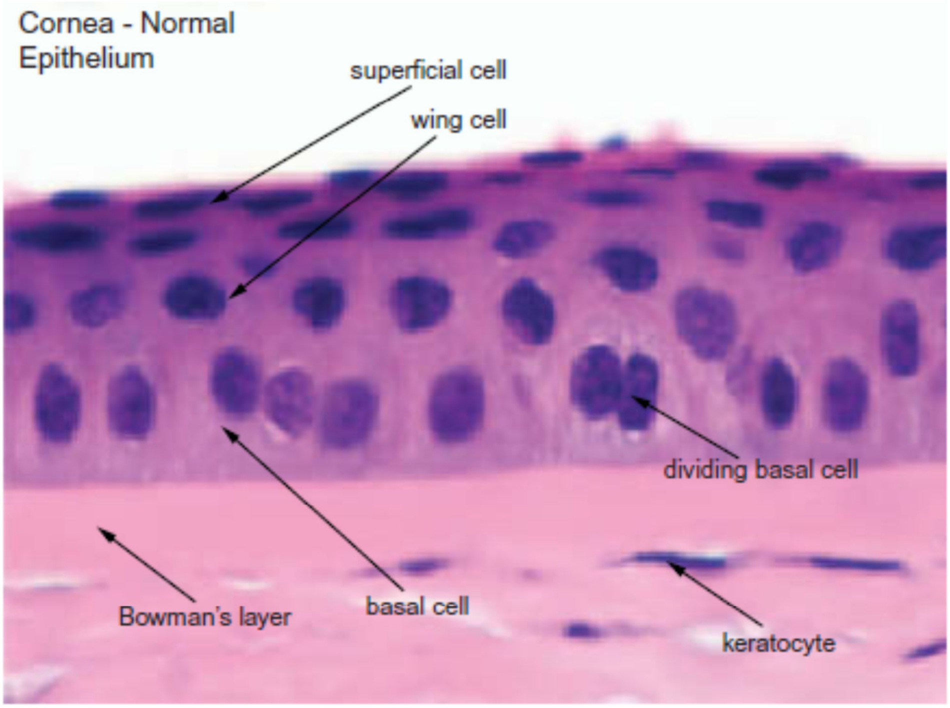

Figure 1.2 In an H&E section, Bowman's layer is homogeneous and is distinct from the stroma in which there are keratocytes between the collagenous lamellae. The spaces between the lamellae are due to an artefact. (Weng & William, 2005)

a) Basal cell layer: cuboidal cells where cell division occurs.

b) Wing cells: the second layer is wing shaped to fit over the rounded anterior surface of the basal cells

c) Superficial cells: the next three layers become increasingly flattened as they progress towards the surface due to mitotic activity in the basal cell layer. The most superficial cells detach from the surface as a normal process of "wear-and-tear". The cells of the epithelium are attached by desmosomes and the basal layer is attached to Bowman's layer by an anchoring complex *(Weng & William, 2005).*

2. *Bowman's layer:* a thin homogeneous layer which serves as a base for the epithelial anchoring system. Once destroyed,

this layer is never replaced. Its absence indicates previous trauma or ulceration *(Weng & William, 2005).*

3. *Stroma* (average 500 µm): the keratocytes are spindle cells with long branching interconnecting processes which are never visualized in routine histological sections. These cells lie between lamellae which contain bundles of uniformly spaced collagen fibrils. The interfibrillar spacing is such that any light scattering is cancelled by interference with light rays from adjacent fibrils and is the basis for one of the theories to explain corneal transparency. The orientation of the fibrils varies by 60 degrees between lamellae and this provides structural strength *(Weng & William, 2005).*

4. *Descemet's membrane:* a thin elastic membrane possessing high tensile strength and containing proteoglycans and glycoprotein in addition to collagen. The membrane stains intensely pink with the PAS stain. At the ultra structural level, two zones can be identified – an anterior banded zone which is formed in fetal life and a posterior non-banded zone which increases in thickness throughout adult life *(Weng & William, 2005).*

5. *Endothelium:* this monolayer is flattened in section. The endothelial cell population declines with age and this process can be accelerated by certain disease states or surgical intervention. Ultra structural examination reveals thin inter-digitations between cells which increases the surface area available for fluid transport. Examination of the posterior surface by scanning electron microscopy reveals that the endothelial cells are arranged in a uniform hexagonal pattern *(Weng & William, 2005).*

6. *Dua's Layer:* Located between corneal stroma and descemet's membrane. The mean thickness is 10.15 microns (range 6.3 to 15.83). The Dua's layer is made of collagen bundles organized as tightly packed thin lamellae numbering 5-8. By electron microscopy the anterior surface shows parallel bundles of collagen regularly arranged while the posterior surface shows a smooth pleated pattern made of coarse bundles of collagen *(Dua et al., 2014)*.

Corneal Collagen Networks:

The major constituent of the corneal stroma, and the cornea as a whole, is collagen, which accounts for approximately 71% of the dry weight of the cornea. The corneal stroma consists of many different types of collagen but mostly collagen type I. *(Gipson et al., 2005)*

The collagen fibrils are highly organized into 200 to 250 parallel and stacked lamellae. The fibers are evenly spaced and have a relatively uniform diameter, ranging from 27 to 35 nm. The small, uniform size of the collagen fibrils and their close spacing is important for corneal transparency. Generally the primary functional role of collagen is acting as a supporting tissue. Collagen is a structural protein which is organized in fibers. Those fibers are responsible of limiting tissue deformation and preventing mechanical breaks *(Ashwin et al., 2010).*

The keratocytes are cells interspersed within the stroma, can be considered stromal fibroblasts. They synthesize and maintain the corneal collagen and other components of the extracellular matrix. Keratocytes also have considerable regenerative capacity; they are able to replenish their numbers if an insult to the cornea occurs *(Spoerl et al., 2007).*

Aggregated forms of the collagen monomers are strengthened by intermolecular cross-links. This process happens as a part of maturation, ageing and disease. Collagen fibrils cross-link naturally as a part of their maturation process. When these fibrils are secreted, they have short segments at either end of the collagen chains (telopeptides) that do not assume the triple-helical conformation. The hydroxylysine residues in these end chains participate in cross links formation. The cross-links are formed by oxidative deamination of the e-amino group of this single lysine or hydroxylysine in the amino and carboxy telopeptides of collagen by the enzyme lysyl oxidase. The aldehyde thus formed reacts with a specific lysine or hydroxylysine in the triple helix to form divalent bonds that link the molecules head to tail. Then they spontaneously convert during maturation to trivalent cross-links. A second cross-linking pathway occurs during ageing involving a non-enzymatic reaction termed glycation *(Ashwin et al., 2010).*

Stabilization of those collagen molecules are related to the interactions between the 3 helics and are due to Hydrogen links, Ionic links and intra-chain reticulations (cross-links). The stroma, composed mainly by collagen lamellae, gives the cornea 90% of its thickness. Between the lamellae, keratocytes can proliferate, migrate and turn into their active state. Integrity of corneal epithelium for the switch of keratocytes (resting cells) in fibroblasts (active cells) is very important *(Pinelli, 2009).*

The most important mucopolysaccharide present in corneal stroma is Keratansulphate type I which plays an important role for the orientation of collagen mashes and lamellae (corneal clarity, tensile strength) and for corneal hydration (corneal edema) *(Pinelli, 2009).*