A RETROSPECTIVE ANALYSIS OF THE OUTCOMES IN VISUAL ACUITY AND KERATOMETRY READINGS AFTER CORNEAL COLLAGEN CROSSLINKING IN KERATOCONUS

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A dissertation submitted to the Faculty of Health Sciences, University of the Witwatersrand, in the fulfillment of the requirements for the degree of Master of Medicine in Ophthalmology.

Johannesburg, February 2017

DECLARATION

I, Taruna Rowjee declare that this dissertation is my own work. It is being submitted for the degree of Master of Medicine in the branch of Ophthalmology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Signed:

On this _____day of _____2017

The work reported in this dissertation was carried out in the Division of Ophthalmology, Department of Neurosciences, St John Eye Hospital Unit of Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa. As well as at private practices' of Prof Mayet, Dr Daniel, Dr dos Ramos and Dr Jervis.

The project was approved by the Human Research Ethics Committee (Medical), University of the Witwatersrand, clearance certificate number M110717 (Appendix A).

DEDICATION

This dissertation is dedicated to my husband, Kalpesh. You have been my pillar of strength, my shoulder to lean on and my constant support.

To my parents, Bardev and Deya Rowjee, I am the person I am today because of your guidance, love and life skills that you have instilled into me.

To the new addition into my life, my son Vihaan, the love of my life. You have changed me as a person forever.

I love you all so very much.

PRESENTATIONS ARISING FROM THIS STUDY

Registrar presentation at the Ophthalmological Society of South Africa (OSSA) Congress, held at the Sandton Convention Centre, Johannesburg, South Africa, March 2012.

Title: A retrospective analysis of the outcomes in visual acuity and keratometry readings after corneal collagen crosslinking in keratoconus.

Presenter: Taruna Rowjee

ABSTRACT

Purpose: To evaluate if corneal collagen crosslinking carried out on patients with keratoconus, slows down or halts the progression of keratoconus. To determine which group of keratoconus patients benefited most from the procedure.

Methods: A retrospective record review of 41 eyes of 29 patients. Visual acuity and keratometry measurements were recorded for the involved eye pre-crosslinking and at 3 months and 6 months post-crosslinking. A comparison of these variables pre-crosslinking and at 6 months post-crosslinking was made to determine if there was a flattening of corneal curvature (keratometry readings) and an improvement in visual acuity.

Patients were further divided into 3 groups of keratoconus, based on their keratometry readings (measured in diopters): mild keratoconus (≤47 diopters), moderate keratoconus (48 – 54 diopters) and advanced keratoconus (≥55 diopters), to determine which group of keratoconus had the best keratometry reduction readings.

Results: After crosslinking took place on 41 eyes, the UnVA of 16(39%) eyes showed an improvement at 6 months, 17(41%) eyes showed no change and

8(20%) eyes showed a decrease in UnVA at 6 months, compared to pre-CXL values.

For BCVA, 12(29%) eyes showed an improvement at 6 months, 18(44%) eyes showed no change and 11(27%) eyes showed a decrease in BCVA at 6 months, compared to pre-CXL values.

Keratometry readings however showed that 23(56%) eyes had an average flattening of corneal curvature readings of 0.7 D and the remaining 18(44%) eyes showed more steepening (worsening) of the corneal curvature readings of 0.9 D after 6 months post-CXL.

30(73%) eyes had mild keratoconus, 7(17%) had moderate keratoconus and 4(10%) had advanced keratoconus.

19 of the 30 eyes in the mild keratoconus group (73%) showed an average flattening of corneal curvature of 0.6 D. 4 of the 7 eyes in the moderate keratoconus group (17%) showed an average flattening of corneal curvature of 0.7 D. All 4 patients in the advanced group (10%) had steepening (worsening) of their corneal curvatures with an average of 1.2 D.

Conclusion: Corneal collagen crosslinking performed on keratoconus patients at least halts the progress of keratoconus. 6 months after CXL most patients showed minimal change from pre-CXL to 6 months in both visual acuity and keratometry. However a longer follow up period and larger sample size is needed to determine if vision and keratometry readings can improve significantly.

ACKNOWLEDGEMENTS

It is with deep appreciation that the following people be acknowledged:

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1.	BCVA	Best corrected visual acuity
2.	BSCVA	Best spectacle corrected visual acuity
3.	cm^2	Square centimeters
4.	CXL	Corneal collagen crosslinking
5.	D	Diopters
6.	EDTA	sodium ethylenediaminetetraacetic acid
7.	IOP	Intraocular pressure
8.	µm	micrometers
9.	mm	millimeters
10.	mW	milliwatt
11.	nm	nanometers
12.	ROS	Reactive oxygen species
13.	TE	Transepithelial
14.	UnVA	Unaided visual acuity
15.	UVA	Ultraviolet A
16.	vs	versus

CHAPTER 1

1.0 INTRODUCTION

1.1 LITERATURE REVIEW

Keratoconus is a progressive corneal ectasia (thinning). It is a potentially blinding condition in its advanced stages. Early diagnosis and management can prevent visual deterioration.

The cornea is made up of six anatomical tissue layers. The stroma, which is the third layer, accounts for 90% of the corneal thickness and comprises primarily of collagen fibrils. These collagen fibrils are most vulnerable to weakening, which leads to keratoconus. Collagen fibrils are an interwoven network, orthogonally orientated (horizontal and vertical) to one another.[1,2]

In keratoconic patients, this normal orthogonal orientation of collagen is redistributed due to the weak collagen fibrils.[2] In order for the stromal collagen fibrils to regain strength, a procedure called corneal collagen crosslinking (CXL) needs to be performed.

Keratoconus is one of the many corneal ectasias that is frequently seen.[3] Its progressive nature usually begins during puberty, and has a slow disease

progression until the 3rd to 4th decade.[4] Its hereditary role has not been fully determined.[4] It has been associated with many systemic disorders, such as Down syndrome, Turner syndrome, Marfan syndrome and Ehlers Danlos syndrome.[4] Ocular associations includes vernal keratoconjunctivitis, aniridia (no iris), retinitis pigmentosa and chronic eye rubbing.[3,5]

Patients with keratoconus have a reduced visual acuity because of the steep corneal curvatures that occur secondary to corneal thinning. By measuring corneal curvature (keratometry readings) in diopters (D), keratoconus can be grouped into: mild keratoconus (≤ 47 D), moderate keratoconus (48 – 54 D) and advanced keratoconus (≥55 D).[2,5]

The corneas in keratoconus patients, typically take on a conical shape in the area of most corneal thinning.[4] Classically this area of thinning is either central or paracentral.[3,5] The collagen fibrils in this thinned area are non-orthogonally arranged.[1] This is secondary to weak collagen bonds within the corneal stroma. It is also thought that the thinning is due to the increased proteolytic (breakdown) activity of collagen, rather than a decrease in synthesis of collagen thus rendering the interfibrillar bonds weak.[2,6,7]

The central or paracentral thinning can lead to tears in descemets membrane that allows aqueous humour to enter the corneal layers which leads to the

development of ‘acute hydrops’ and later, scarring.[3] When the disease has reached the hydrops or scarred stage, patients require a corneal transplant (penetrating keratoplasty) to restore vision. At this stage, corneal collagen crosslinking is no longer indicated.[7]

In order to prevent patients from undergoing a corneal transplant, the disease needs to be stopped at its initial stages, when the cornea begins to thin. Therefore the collagen within the stroma needs to be strengthened, by enhancing the collagen lamellae bonds. The procedure of choice is corneal collagen crosslinking. CXL is a procedure that increases corneal rigidity and integrity.[7,8] It is indicated in patients with structurally weak collagen binding within the corneal stroma, such as ectasias, like in the case of keratoconus and even post-lasik ectasia.

Dr Gregor Wollensak introduced CXL, in a 3year long pilot study (started in 1998) carried out in Dresden, Germany.[9] He was inspired by the widespread polymer industry that used crosslinking to stabilize tissue. This was evident in the collagen based bioprosthesis used for heart valves and physical crosslinking by Ultraviolet A light which is often used in dentistry to harden teeth fillings.[10,11,12] Individuals who are ’protected’ against developing keratoconus are, diabetics and the aged, as crosslinking of collagen occurs by advanced glycation endproducts for diabetics and the naturally occurring age-related crosslinking process that takes place in the aged.[10]

Over the last decade, CXL has become a procedure of choice for the management of keratoconus and other corneal ectasias. The aim of CXL is to stop or slow down the progression of corneal ectasias. This then reduces the need for corneal transplantation. The mechanism of CXL is combining Riboflavin (Vitamin B2) 0.1% and Ultraviolet A light (UVA). This leads to strengthening of the interlamellar and intralamellar collagen fibril adhesions between adjacent collagen lamellae.[8]

Ribloflavin has a triple action; it acts as a photosensitiser to produce free oxygen radicals or reactive oxygen species (ROS), it absorbs the UVA irradiation and it lubricates the cornea at the same time.[13] It is non-toxic and easily penetrates the cornea in the absence of an epithelium.[11] It is available in the form of a topical (eye drop) preparation.

The free oxygen radicals cause photo-oxidative damage of cells i.e. apoptosis (death) of keratocytes and induces chemical covalent crosslinkage bonds between collagen fibrils via the lysyl oxidase pathway.[8] In this manner, collagen fiber diameter increases and the mechanical strengthening of collagen takes place.[13] Wollensak et al, describes an average increase in collagen fiber diameter of 12.2% in the anterior stroma and a 4.6% increase in the posterior stroma of treated corneas.[12,13]

The UVA light on the other hand causes an increase in intra and interfibrillar covalent bonds by photosensitized oxidation.[14] Normally, the cornea would absorb 30% of the UVA light and 50% is absorbed by the lens. When combining a photosensitiser like riboflavin, as much as 95% of UVA light is absorbed within the cornea. This enhances the mechanism of collagen strengthening and at the same time protects the posterior structures (corneal endothelium, lens and retina) from irradiation.[14,15] Most changes take place within the anterior 300 µm of the cornea, accounting for a 328% increase in the tensile rigidity after CXL.[8]

Apart from increasing corneal strength, the effect of combined riboflavin/UVA prevents viral and bacterial replication.[14] There are many indications for this procedure, but this research will focus on CXL for keratoconus patients.

Specific criteria needed for the crosslinking procedure are: [8,12,16]

- Patients under the age of 35 years
- Best corrected visual acuity (BCVA) worse than 6/7.5
- Corneal thickness > 400 µm

Screening parameters that studies looked at prior to CXL, included: [7,9,11,12,18,20]

Best corrected visual acuity (BCVA), corneal topography (corneal curvature), intraocular pressure (IOP) measurement, keratometry measurements (K1 and K2), central corneal endothelial cell density, corneal photography, slit lamp

examination, fundus examination and preoperative pachymetry (corneal thickness more than 400 µm is required).

Postoperatively the same parameters were assessed as outcome measures of the procedure.

The technique of CXL is simple and easy to perform: [8,9,10,12,14]

- CXL is a sterile procedure, carried out preferably in an operating theatre.
- Instillation of 4 drops of Ofloxacin 0.3% (antibiotic) and 2 drops of Pilocarpine 2% into the treatment eye.
- Topical anaesthetic drops are applied.
- Pachymetry is carried out in 5 consecutive measurements, on the thinnest part of the cornea ensuring that it is not less than 400 µm.
- Debridement of the central 7.0 - 9.0 mm of the corneal epithelium.
- Iso-osmolar Riboflavin 0.1% solution (10mg riboflavin-5-phosphate in 10ml dextran T-500 20% solution) is applied to the cornea every 4-5 minutes for 30 minutes.
- After the first 30 minutes, ultrasound pachymetry is repeated to ensure the stroma is still 400 µm thick. If it is less than 400 µm, then 0.1% riboflavin in hypo-osmolar saline solution is used instead and applied every 4-5 minutes for 30 minutes. The pachymetry is rechecked after this.

- Penetration of riboflavin into the anterior chamber is viewed by performing slit lamp biomicroscopy and looking for a ‘yellow’ flare in the anterior chamber.[14]
- Irradiation with UVA light of 370nm is applied for 30minutes to the eye at a working distance of 54mm with an irradiance of 3mW/cm^2.
- During the UVA treatment, 0.1% riboflavin solution is instilled every 4-5 minutes, and topical anaesthetic is instilled when necessary.
- After treatment, antibiotic ointment/drops are administered and a bandage contact lens is applied to the eye.

The method of CXL described above is known as the ‘epi-off (epithelium off) CXL or classic CXL’ proposed by Gregor Wollensak.

More recently there has been literature published on CXL not involving the removal of the central epithelium, also known as ‘epi-on (epithelium on) CXL or transepithelial CXL’. The difference with this type of CXL is the use of transepithelial riboflavin (riboflavin TE or Ricrolin TE) specially formulated with trometamol (Tris-hydroxymethyl aminomethane), 0.01% sodium ethylenediaminetetraacetic acid (EDTA) and occasionally 0.3% gentamicin and benzalkonium chloride.[17,18,19] Ricrolin TE solution is thought to enhance the penetration of riboflavin through the epithelium without debridement of the central epithelium. The exposure time remains the same at 30minutes with a 3mW/cm^2 of UVA exposure.

In view of not having to debride the epithelium, this technique has been favoured in the paediatric population and those with a corneal thickness of ≤ 400 µm.[17,18] The postoperative management is similar to the epi-off CXL technique. It differs only because there is no insertion of a bandage contact lens after the epi-on procedure.

The postoperative follow-up proposed by Jankov II et al, for epi-off CXL suggest that visits take place on day 1 and 5, then at 1, 6 and 12 months.[14] On day 1 topical antibiotic is prescribed. It is used 4 times a day for 1 week. Topical steroid use immediately postoperatively is debatable and surgeon dependant. Jankov II et al further describes, removing the bandage contact lens on day 3 postoperatively and the patient is then instructed to use a topical steroid on day 3, which will be tapered over the course of 2 months.[14]

Outcomes demonstrated by Wollensak et al over a period of 4 years showed that the best corrected visual acuity (BCVA) improved by an average of 1.26 snellen lines (visual acuity) and the average flattening of keratometry readings were 2.01 diopters.[9] The Siena Eye Cross Study performed in Italy, were able to show comparable outcomes after their 5 year follow up post CXL. They demonstrated a mean keratometry reduction of 2 diopters, a mean best spectacle corrected visual acuity (BSCVA) improvement of 1.9 snellen lines and an unaided visual acuity (UnVA) improvement of 2.7 snellen lines over 5 years.[20]

It is evident that CXL is a relatively safe and minimally invasive procedure for the treatment of keratoconus with promising outcomes. It is frequently indicated in the early stages of keratoconus. CXL can be beneficial in preventing future corneal transplantation and assist with potentially minimising the waiting lists for corneal transplants. A South African study by Makgotloe and Carmichael revealed that easier payment for corneas favour its distribution to the private rather than the public sector, due to the lack of procurement programmes for corneal donations in public hospitals.[21]

Thus if CXL is performed at the earlier stages of keratoconus, it can reduce the need for future corneal transplants, and perhaps reduce the burden of long waiting lists for corneal transplants in the public sector due to affordability issues.

1.2 RESEARCH AIM

The aim of this research report was to analyse the visual acuity and keratometry readings in keratoconus patients before and after classic ‘epi-off’ CXL in order to establish the efficacy of crosslinking in halting or slowing down the progression of keratoconus.

1.3 RESEARCH OBJECTIVES

a) To compare the outcomes of visual acuity and keratometry readings (corneal curvature flattening) before and after CXL.

b) To determine the degree of improvement in visual acuity and degree of corneal curvature flattening after performing CXL.

c) To determine which group of keratoconus patients benefitted most from the procedure.

CHAPTER 2

2.0 METHODOLOGY

2.1 STUDY DESIGN

The study comprised a retrospective review of the pre-CXL and post-CXL visual acuity and keratometry readings of patients with keratoconus who underwent CXL in the period, January 2009 to July 2011at private practices of four ophthalmologists. Patient records were the source of the relevant data captured.

2.2 DATA COLLECTION

The data collected was a review of patient records from four private ophthalmologists.

Consent for data collection was given by each ophthalmologist at their practices (Appendix B). The patient records were viewed between October 2011 and January 2012.

This proposed study had received ethical approval from the Human Research Ethics Committee (Medical), University of the Witwatersrand on the 29/07/2011.

A clearance certificate was issued, Reference M110717 (Appendix A).

Each patient record was captured on a data sheet (Appendix C) manually and thereafter captured onto an Excel spread sheet for purposes of statistical review.

Data recorded fell under three periods of time: Pre-CXL, 3 months post-CXL and 6 months post-CXL.

2.2.1 INCLUSION CRITERIA

a) Patients diagnosed with keratoconus in one or both eyes.

b) Patients who had undergone CXL in one or both eyes.

c) All patients were 18 years and older.

2.2.2 EXCLUSION CRITERIA

Inadequate patient record keeping.

Patients who underwent a corneal transplant before the 6 months post-CXL follow up.

2.2.3 STUDY POPULATION

This consisted of 41 eyes of 29 patients that underwent CXL between January 2009 and July 2011.

2.2.4 DATA MANAGEMENT

Records of patients meeting the inclusion criteria were reviewed. Relevant data were extracted from each record by the primary researcher and then captured onto a spread sheet in Microsoft Office Excel 2007.

A master data sheet containing the name of the patient who was linked to the numbered data capture sheet was kept separately. Only the primary researcher had access to the data sheets. This was done to ensure patient anonymity.

For this purpose, each eye of the patient that had undergone CXL was numbered separately.

The following data were extracted from each record:

a) Date of crosslinking
b) Eye that was crosslinked
c) Sex of the patient
d) Age of the patient
e) Medical history
f) Ocular allergy being a risk factor for the development of keratoconus
g) Pre-CXL measures:

    Unaided visual acuity (UnVA)

    Best corrected visual acuity (BCVA)

    Keratometry readings (Pentacam based)

h) Post-CXL follow up at 6 months:

Unaided visual acuity (UnVA)

Best corrected visual acuity (BVCA)

Keratometry readings (Pentacam based) of the CXL eye

i) Keratoconus grouping (based on keratometry readings in dioptres):

Mild (≤47 D)

Moderate (48 - 54 D)

Advanced (≥55 D)

2.3 DATA ANALYSIS

Data was analysed using Stata 12 software.

Descriptive analysis of the data was carried out as follows: Categorical variables were summarised by frequency and percentage, and illustrated by means of bar charts. Continuous variables were described by mean, standard deviation, median, interquartile range and histogram.

A paired t-test was used to compare visual acuity and keratometry readings before crosslinking and 6 months after crosslinking. Where the assumptions of the test were not met, the Wilcoxon matched paired test was used instead.

A 5% significance level was used ($p < 0.05$ was regarded as significant).

2.4 STAFF AND ADMINISTRATION

This study was conducted by Dr Taruna Rowjee (registrar) and supervised by Dr Darshana Soma (consultant) from Ophthalmology (Department of the Neurosciences). Co-supervised by Prof Trevor Carmichael (HOD of Ophthalmology)

Records from four private ophthalmologists were reviewed, namely:

Professor I Mayet (Garden City Hospital)

Dr R Daniel (Morningside Hospital)

Dr A dos Ramos (Optimed in Alberton)

Dr E Jervis (Optimed in Alberton).

Each ophthalmologist gave written consent for the review of their relevant patient records (Appendix B).

2.5 ETHICAL CONSIDERATIONS

An Ethics clearance certificate was issued by the Wits Human Research ethics Committee in July 2011. The ethics protocol number is M110717 (Appendix A).

CHAPTER 3

3.0 RESULTS

3.1 PATIENT BASELINE VARIABLES

Forty-one eyes of 29 patients were reviewed. All 29 patients underwent the classic 'epi-off' CXL. 12 patients had both eyes crosslinked at separate times and the remaining 17 patients had one eye crosslinked.

3.1.1 PATIENT DEMOGRAPHICS

3.1.1.1 GENDER

Of the 29 patients, 20(69%) were males and 9(31%) were females.

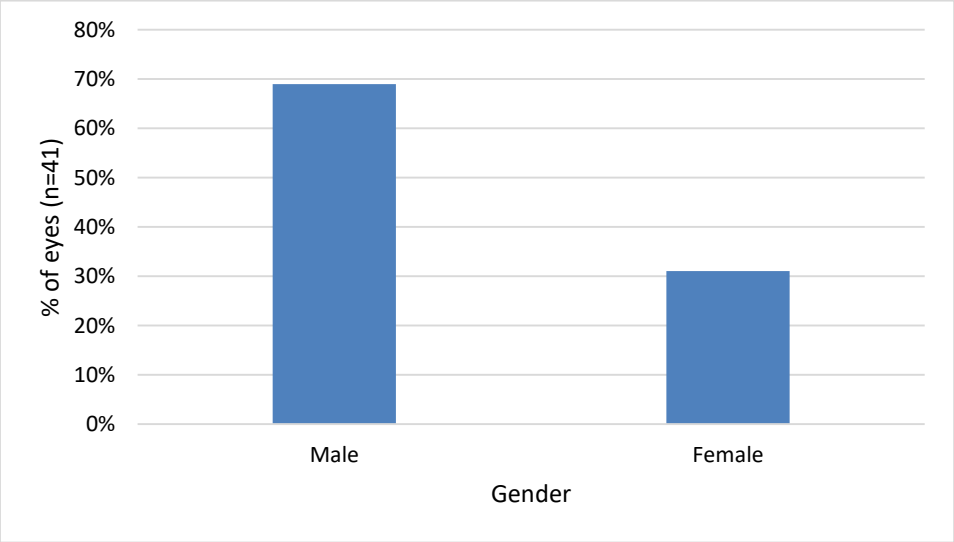

Figure 1. Gender distribution

3.1.1.2 AGE

The median age of the 29 patients is 29 years (interquartile range: 21, 37 years). The ages of the patients ranged from 18 to 55 years.

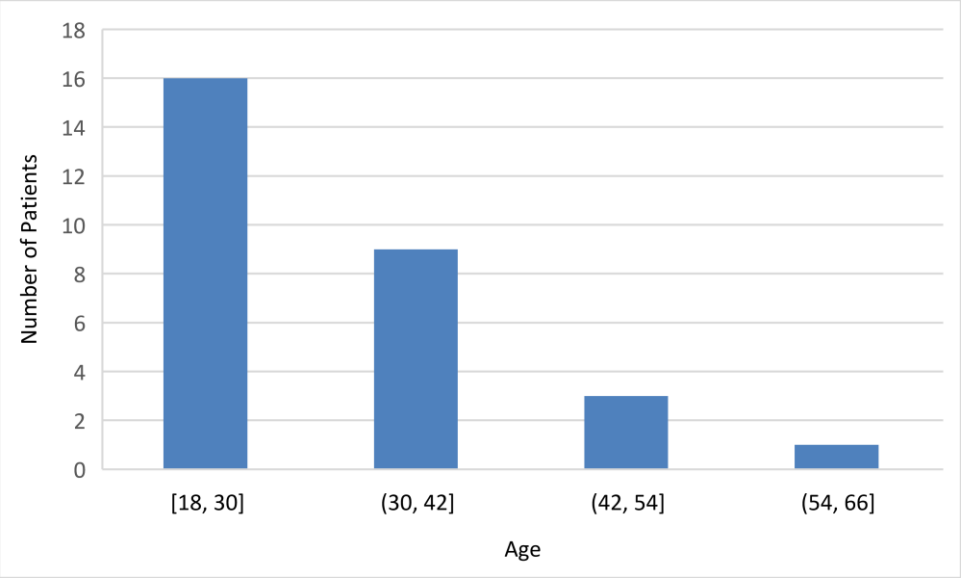

Figure 2. Age distribution of the patients

3.1.2 LATERALITY

Of the 41 eyes that underwent CXL, 24(59%) were right eyes and 17(41%) were left eyes.

3.1.3 MEDICAL HISTORY

Ocular allergy is a common predisposing condition for the development of keratoconus. In this study however, only 3(10%) of the 29 patients had a history of ocular allergy.

3.2 OUTCOME MEASURES

This study looked at the visual acuity and keratometry readings post-CXL. The pre-CXL versus 6 months post-CXL visual acuity and keratometry readings were compared. We wanted to determine if visual acuity improved and keratometry readings flattened at 6 months after CXL.

The study further analysed which group of keratoconus patients benefited most from CXL and this was determined by an improvement or no change in visual acuity and keratometry readings, which implied a halt in progression of keratoconus.

3.2.1 VISUAL ACUITY: PRE-CXL COMPARED TO 6 MONTHS POST-CXL

The LogMar scale of visual acuity was used. The amount of lines gained or lost is showed as Snellen equivalent.

3.2.1.1 UNAIDED VISUAL ACUITY (UnVA)

Before treatment, the median UnVA was 0.3 (interquartile range: 0.1, 0.6). After CXL the median UnVA at 6 months was 0.3 (interquartile range: 0.15, 0.7). The change in UnVA from pre-CXL to 6 months post-CXL was not significant (p = 0.07).

The graph below demonstrates that of the 41 eyes in total, 16(39%) eyes showed an improvement in UnVA at 6 months, 17(41%) eyes showed no change(same), and 8(20%) eyes showed a decrease in UnVA at 6 months, compared to pre-CXL values.

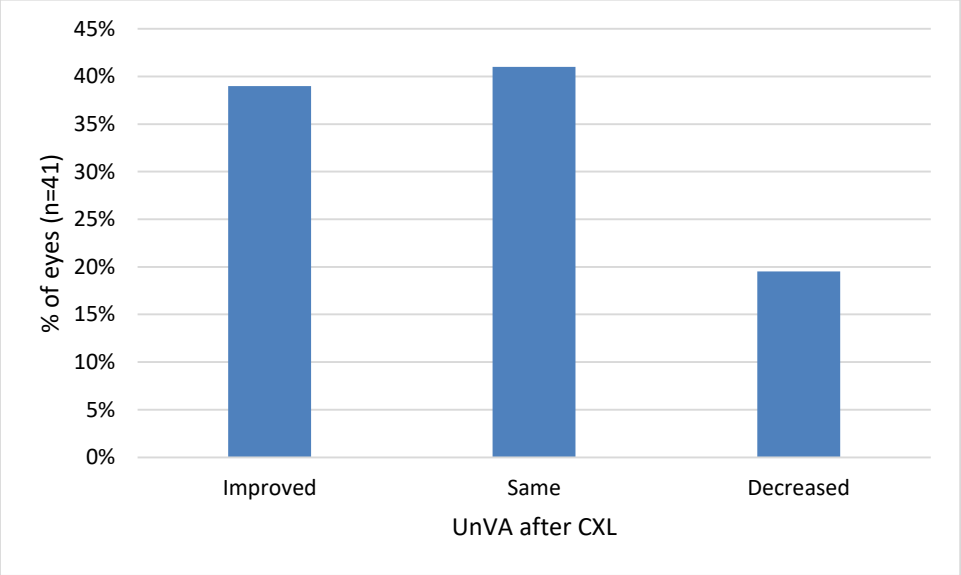

Figure 3. Percentage of eyes showing change in UnVA at 6 months

3.2.1.2 BEST CORRECTED VISUAL ACUITY (BCVA)

Before treatment, the median BCVA was 0.8 (interquartile range: 0.6, 1.0). After CXL the median BCVA after 6 months was 0.9 (interquartile range: 0.6, 1.0). The change in BCVA from pre-CXL to 6 months post-CXL was not significant (p = 0.45).

The graph below demonstrates that 12(29%) eyes showed an improvement in BCVA at 6 months, 18(44%) eyes showed no change(same), and 11(27%) eyes showed a decrease in BCVA at 6 months, compared to pre-CXL values.

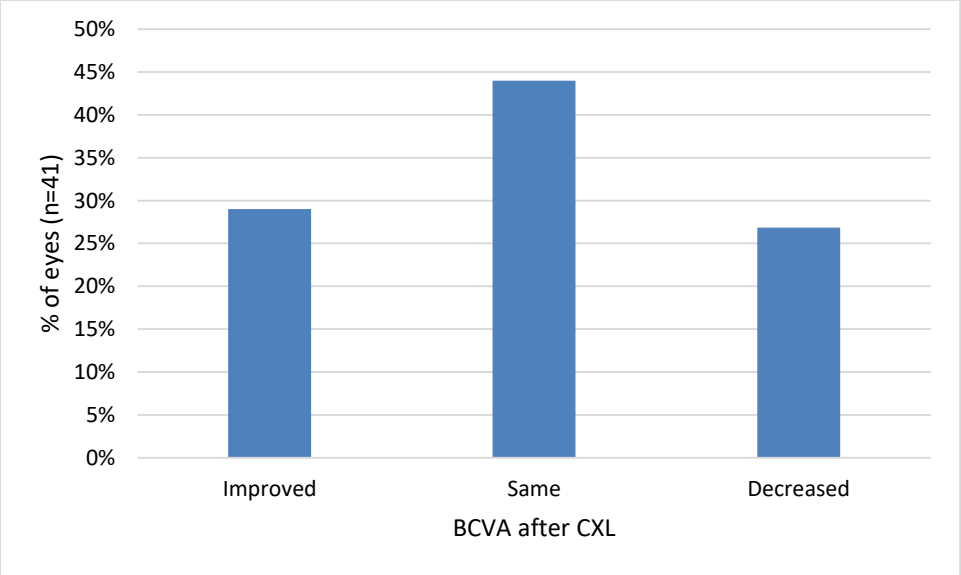

Figure 4. Percentage of eyes showing change in BCVA at 6 months

3.2.2 KERATOMETRY READINGS (CORNEAL CURVATURE)

Before treatment, the median corneal curvature was 45.50 (interquartile range: 44.00, 48.85). After CXL the median corneal curvature after 6 months was 45.50 (interquartile range: 44.00, 48.30). The change in corneal curvature from pre-CXL to 6 months post-CXL was not significant (p = 0.48).

After CXL of the 41 eyes at 6 months, 23(56%) eyes had an average flattening of corneal curvature readings of 0.7 D and the remaining 18(44%) eyes showed more steepening (worsening) of the corneal curvature readings of 0.9 D.

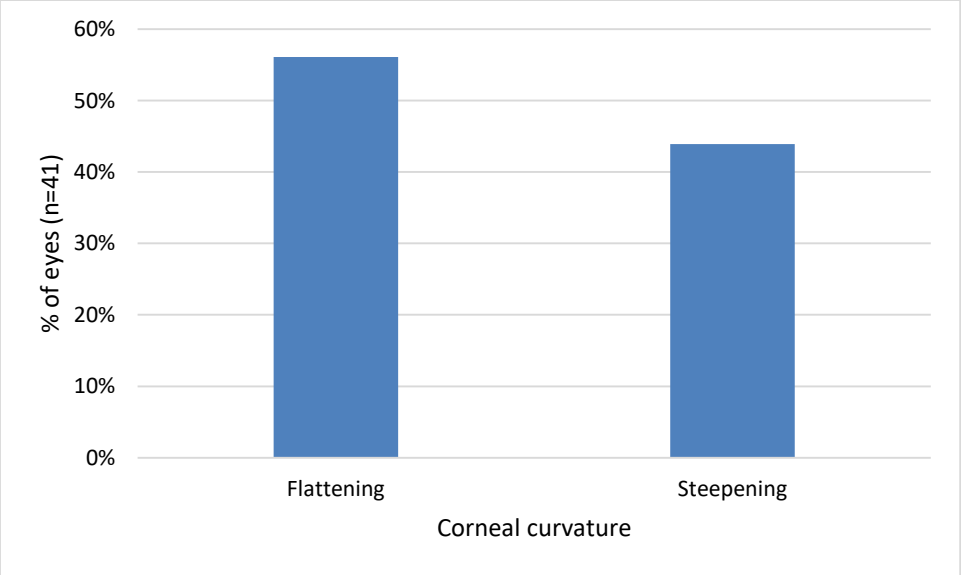

Figure 5. Percentage of eyes showing flattening vs steepening of corneal curvature at 6 months

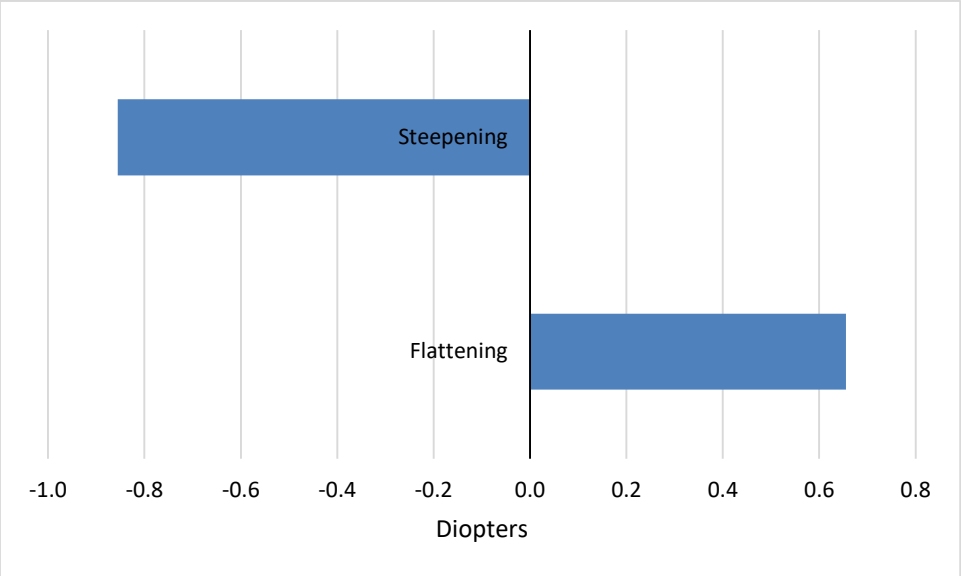

Figure 6. Corneal curvature at 6 months after CXL, measured in diopters

3.2.3 KERATOCONUS GROUPS BASED ON KERATOMETRY READINGS

41 eyes were graded as mild (≤47 D), moderate (48-54 D) or advanced (≥55 D) keratoconus.

The graph below demonstrates that of the 41 eyes, 30(73%) eyes showed mild keratoconus, 7(17%) showed moderate keratoconus and 4(10%) showed advanced keratoconus.

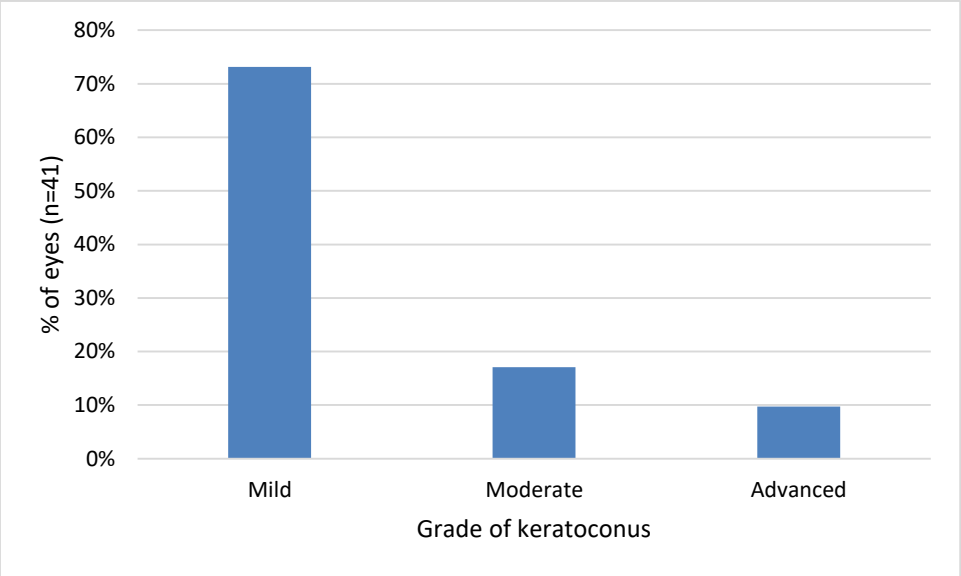

Figure 7. Keratoconus grades based on keratometry readings

19 of the 30 eyes in the mild keratoconus group (73%) showed an average flattening of corneal curvature of 0.6 D. The remaining showed no change.

4 of the 7 eyes in the moderate keratoconus group (17%) showed an average flattening of corneal curvature of 0.7 D. The remaing 3 eyes showed no change.

All 4 patients in the advanced group (10%) had steepening of their corneal curvatures with an average of 1.2 D of steepning. The maximum amount of steepening of corneal curvature was 3.0 D in 1 patient.

CHAPTER 4

4.0 DISCUSSION

Keratoconus is a progressive ectasia, with an incidence of 1 in 2000, typically beginning during puberty and naturally regressing by the 3rd to 4th decade.[4,6,7,8,9,10,15,17] Progression of the disease, both hereditary and acquired forms, needs to be controlled to avoid having to resort to performing a corneal transplant.[7,18] For this purpose corneal collagen crosslinking has shown to slow down the progression of keratoconus.[7,8,12,13] CXL has also been used for the treatment of pellucid marginal degeneration, prophylactically for the treatment of iatrogenic keratectasia and for the treatment of infectious corneal ulcers.[14]

Keratoconus progression is said to halt or slow down when visual acuity increases or remains the same, and if corneal curvature readings (keratometry) flatten or remain the same, after collagen crosslinking.

The classic or ‘epi-off’ crosslinking has been trialled by the likes of Gregor Wollensak, Theo Seiler and Eberhard Spoerl, the pioneers in this procedure.[9,10,11,13] More recently transepithelial or epithelium-on CXL has been favoured for the paediatric population.[17,18,19] Our study focuses on the outcomes after epithelium-off or classic CXL in keratoconic patients and its effects on vision and corneal curvature. The classic CXL technique has proven to be safe, as riboflavin acts as a protective barrier for other intraocular structures (endothelium,

lens and retina), absorbing the UVA light exposed to the cornea in order for CXL to take place.[23]

Our keratoconic population showed a male predominance of 69% which has been found in similar studies.[6,7,18,19,22] Ocular allergy with chronic eye rubbing has been found to play a role in the etiology of keratoconus,[4,8] however in our study, there were few patients (3%) with ocular allergy.

The median age of the patients was 29 years. Our inclusion criteria included patients 18 years and older, with the youngest being 18 years and the oldest 55 years. Even though keratoconus is known to start at puberty, for consent purposes we chose to only include those patients 18 years and above. It was found that diagnosing keratoconus in the paediatric age group, had a poorer prognosis due to rapid disease progression and ultimate corneal transplant.[18] None of our patients had undergone or needed to be scheduled to have a corneal transplant at their 6 months of follow up.

Considering the outcomes of CXL, which includes vision and corneal curvature, our study focused on these at 6 months after crosslinking. Both the change in UnVA and BCVA after CXL from pre-CXL to 6 months post-CXL were not statistically significant. This could be due to the small population size and/or the short follow up duration. Similar studies in the literature had significant

improvement in visual outcomes. The follow up periods differed in each study.[7,9,10,24,25,26,27,28] One of the first studies that followed patients up for 4 years, treated 23 eyes with crosslinking showed a 2.01 D flattening of corneal curvature and 65% of the eyes had a slight improvement in vision at the end of the 4 years.[9]

Our study however showed that approximately 20% of eyes had a decrease in visual acuity (UnVA and BCVA) after 6 months, which meant the remaining 80% had either an improvement or no change in vision when comparing before and after CXL at 6 months.

UnVA improved in 39% of eyes with a 1.3 Snellen line improvement while 41% of eyes showed no change in their unaided visual acuity at 6 months. BCVA improved by 1.2 snellen lines in 29% of eyes and 44% of eyes had no change at the end of 6 months follow up. With these results after 6 months we have been able to determine that keratoconus progression can at least be halted by either improving vision slightly or keeping the vision unchanged after the crosslinking.

Corneal curvature flattening occurred in 56% of patients with an average flattening of 0.7 D. The largest flattening of corneal curvature was 2.85 D in 1 patient, very similar to Wollensak et al with 2.01 D average.[9] When looking at other similar studies, their mean corneal curvature flattening values were around 2.0 D, which was significant.[7,9,10,24,25,26,27,28] Even though corneal curvature flattening was not significant in our study, just more than half the eyes (56%) in this study had corneal curvature flattening.

The table below summarises similar studies. It is apparent that the above studies had similar corneal curvature flattening values. The visual acuity values were also similar. They all however had more than a 6 month follow up period. The study that is probably the most similar to this study is the Turkish study by Coskunseven et al.[7]

	Number of eyes	Follow-up period	Average corneal curvature flattening	Visual acuity improvement
Wollensak 2003[9] (Germany)	23	4 years	2.01D	1.26 lines
Coskunseven 2008[7] (Turkey)	38	9 months	2.01D	1 line
Hersh 2011[28] (USA)	49	1 year	≥2.0 D	≥2 lines

Table 1. Similar studies showing their outcomes after CXL

Our study looked at another aspect of keratometry readings by separating the 41 eyes into keratoconus severity groups. This enabled us to determine which group, based on the keratometry readings showed promising results at 6 months.

Of the 23 eyes that had the 0.7 D flattening in keratometry readings, 19 eyes were in the mild keratoconus group and 4 eyes were in the moderate keratoconus group. In the mild keratoconus group of 19 eyes, 4 eyes had a 1.3 snellen line improvement in vision. The advanced keratoconus group (4 eyes) had steepening of corneal curvature with an average of 1.2 D and a maximum of 3.0 D in 1 patient.

Even though corneal curvature did not flatten significantly (p= 0.48), in this study, the groups that at least had some improvement or no change at all in both visual acuity and corneal curvature flattening were the mild and moderate keratoconus groups. Performing CXL on these groups may be beneficial in halting the process earlier rather than later. The advanced keratoconus group did not show any benefit from performing CXL.

By treating keratoconus in its mild to moderate form, the disease may at least be halted and the need for later corneal transplants (penetrating keratoplasty) can be minimised. Makgotloe and Carmichael (South African study) showed that the availability of corneal tissue for keratoplasty favours that of private healthcare.[21] The need for corneal tissue can be minimised if keratoconus is treated earlier.

Agrawal also raised a similar finding in an Indian study that also revealed the lack of tissue availability for transplants.[24]

Our study proves that corneal collagen crosslinking offers a non-invasive treatment option for patients suffering with keratoconus. With improvement in visual acuity and minimal corneal curvature flattening, keratoconus can at least be halted and the need for keratoplasty can be decreased. The mild and moderate group of keratoconus patients benefit most from CXL.

Limitations in this study were, the small population size and the short follow up period. A larger, long-term prospective study would probably be a good follow on from this. A comparative study, looking at transepithelial versus classic CXL would also assist with deciding which of the 3 groups of keratoconus patients improve most in visual outcome post-CXL.

CHAPTER 5

5.0 CONCLUSION

Corneal collagen crosslinking is a good treatment option for patients with keratoconus. It is safe, non-invasive and it halts keratoconus by flattening corneal curvature and in improving visual acuity even at the slightest. The patients benefit most when keratoconus is treated earlier during the mild to moderate stages of keratoconus, rather than in the advanced form. If earlier treatment is carried out, the need for future corneal transplants can be decreased and this can assist with eliminating tissue availability issues that may arise especially for the public sector.

APPENDIX A

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Taruna Rowjee

CLEARANCE CERTIFICATE	**M110717**
PROJECT	A Retrospective Analysis of the Outcomes in Visual Acuity and Keratometry Readings After Collagen Crosslinking in Keratoconus
Corneal	
INVESTIGATORS	Dr Taruna Rowjee.
DEPARTMENT	Division of Opthalmology
DATE CONSIDERED	29/07/2011
DECISION OF THE COMMITTEE*	Approved unconditionlly

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 29/07/2011 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Dr D Soma

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

APPENDIX B

APPENDIX B

Informed consent form

I hereby confirm that Dr Taruna Rowjee has clearly informed me, and pointed out the purposes of the research she will be conducting. I have read and understood the information sheet provided.

- I am aware that my private practice can be withdrawn from the study at any given point, should I be unsatisfied
- Patient confidentiality will be maintained at all times. No patient shall be named or contacted for the purposes of the study
- The patient record file is the only documentation required for data collection.
- The data collection will be taken for the duration of 3 years as stated on the information sheet.
- If I have any questions or queries, they will be directed accordingly.

PARTICIPATING OPHTHALMOLOGIST:

L. MAYET		20/11/2011
Full Name & Surname	**Signature**	**Date & Time**

I, Dr Taruna Rowjee hereby confirm that I have fully informed the participating ophthalmologist of the nature and purposes of my study.

STUDY DOCTOR:

TARUNA ROWJEE		20/11/2011 14h35
Full Name & Surname	**Signature**	**Date & Time**

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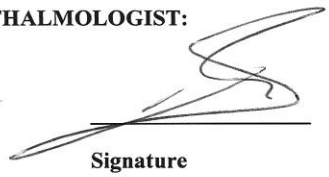
- The patient record file is the only documentation required for data collection.
- The data collection will be taken from January 2007 onwards, as stated on the information sheet.
- If I have any questions or queries, they will be directed accordingly.

PARTICIPATING OPHTHALMOLOGIST:

Robert Lawson		05 Nov 2011
Full Name & Surname	**Signature**	**Date & Time**

I, Dr Taruna Rowjee hereby confirm that I have fully informed the participating ophthalmologist of the nature and purposes of my study.

STUDY DOCTOR:

TARUNA ROWJEE		05/11/2011 11h15
Full Name & Surname	**Signature**	**Date & Time**

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PARTICIPATING OPHTHALMOLOGIST:

Antonio dos Ramos		13/1/2012.
Full Name & Surname	**Signature**	**Date & Time**

I, Dr Taruna Rowjee hereby confirm that I have fully informed the participating ophthalmologist of the nature and purposes of my study.

STUDY DOCTOR:

TARUNA ROWJEE		13/1/2012 10h05
Full Name & Surname	**Signature**	**Date & Time**

APPENDIX B

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- The data collection will be taken from January 2007 onwards, as stated on the information sheet.
- If I have any questions or queries, they will be directed accordingly.

PARTICIPATING OPHTHALMOLOGIST:

E. Hodgson Jones		13/1/12 10h00
Full Name & Surname	**Signature**	**Date & Time**

I, Dr Taruna Rowjee hereby confirm that I have fully informed the participating ophthalmologist of the nature and purposes of my study.

STUDY DOCTOR:

TARUNA ROWJEE		13/2012 12h35
Full Name & Surname	**Signature**	**Date & Time**

APPENDIX C

Data capture sheet

Eye number: _____ Involved eye: _____ Date of CXL: _____ Age: ___

Sex: M ___ or F ___ Medical History: _____

Examination *before* CXL (pre-CXL): **Post-CXL at 6 months:**

(Right) Eye (Left)

UnVA UnVA

BCVA BCVA

K1 Keratometry K1 K1 Keratometry K1

K2 K2 K2 K2

Cornea

AC

IOP

Lens

Fundoscopy

1 month post-CXL

UnVA

BCVA

K1 Keratometry K1

K2 K2

Future management plan: _____

UnVA: Unaided visual acuity BCVA: Best corrected visual acuity

REFERENCES

1. Daxer A, Fratzl P. Collagen Fibril Orientation in the Human Corneal Stroma and Its Implication In Keratoconus. *Invest Ophthalmol Vis Sci* 1997; **38**: 121-129.
2. Meek KM, Tuft SJ, Huang Y, et al. Changes in collagen Orientation and Distribution in Keratoconus Corneas. *Invest Ophthalmol Vis Sci* 2005; **46**: 1948-1956.
3. American Academy of Ophthalmology: External Disease and Cornea. Ectatic Disorders. Section 8. 2010-2011: 296-300.
4. Rabinowitz YS. Keratoconus. *Surv Ophthalmol* January-February 1998; **42**(4): 297-319.
5. Kanski JJ. Clinical Ophthalmology: A Systematic Approach. Elsevier Butterworth-Heinemann. 6th Edition. 2007: 288-289.
6. Abalain JH, Dossou H, Colin J, et al. Levels of Collagen Degradation Products (Telopeptides) in the Tear Film of Patients with Keratoconus. *Cornea* 2000; **19**(4): 474-476.
7. Coskunseven E, Jankov II MR, Hafezi F. Comparative Study of Corneal Collagen Cross-linking With Riboflavin and UVA Irradiation in Patients With Keratoconus. *J Refract Surg* 2008: 1-6.
8. Samaras KE, Lake DB. Corneal Collagen Cross Linking (CXL): A Review. *Int Ophthalmol Clin* 2010; **50**(3): 89-100.

9. Wollensak G, Spoerl E, Seiler T. Riboflavin/Ultraviolet-A-induced Collagen Crosslinking for the Treatment of Keratoconus. *Am J Ophthalmol* 2003; **135**(5): 620-627.
10. Wollensak G. Crosslinking treatment of progressive keratoconus: new hope. *Curr Opin Ophthalmol* 2006; **17**: 356-360.
11. Spoerl E, Huhle M, Seiler T. Induction of Crosslinks in Corneal Tissue. *Exp Eye Res* 1998; **66**: 97-103.
12. Dahl BJ, Spotts E, Truong JQ. Corneal collagen cross-linking: An introduction and literature review. *Optometry* 2012: **83**: 33-42.
13. Wollensak G, Wilsch M, Spoerl E, et al. Collagen Fiber Diameter in the Rabbit Cornea After Collagen Crosslinking by Riboflavin/UVA. *Cornea* 2004; **23**(5): 503-507.
14. Jankov II MR, Jovanovic V, Nikolic L, et al. Corneal Collagen Cross-Linking. *Middle East Afr J Ophthalmol* 2010; **17**(1): 21-27.
15. Mazzotta C, Balestrazzi A, Traversi C, et al. Treatment of Progressive Keratoconus by Riboflavin-UVA-Induced Cross-Linking of Corneal Collagen. *Cornea* 2007; **26**(4): 390-397.
16. Franzco GRS. Collagen cross-linking: a new treatment paradigm in corneal disease – a review. *Clin and Experim Ophthalmol* 2010; **38**: 141-153.
17. Buzzonetti L, Petrocelli G. Transepithelial Corneal Cross-linking in Pediatric Patients: Early results. *J Refract Surg* 2012; **28**(11): 763-767.
18. Magli A, Forte R, Tortori A, et al. Epithelium-Off Corneal Collagen Cross-linking Versus Transepithelial Cross-linking for Pediatric Keratoconus. *Cornea* 2013; **32**: 597-601.

19. Leccisotti A, Islam T. Transepithelial Corneal Collagen Cross-linking in Keratoconus. *J Refract Surg* 2010; **26**(12): 942-948.
20. Caporossi A, Mazzotta C, Baiocchi S, et al. Long-term Results of Riboflavin Ultraviolet A Corneal Collagen Cross-linking for Keratoconus in Italy: The Siena Eye Cross Study. *Am J Ophthalmol* 2010; **149**: 585-593.
21. Makgotloe AM, Carmichael TR. Plummeting corneal donations at the Gauteng Cornea and Eye Bank. *S Afr Med J* 2009; **99**(11): 797.
22. Chopamba-Kamba A. Factors Associated with Keratoconus at St John Eye Hospital. Mmed [Research Report]. University of the Witwatersrand; 2003.
23. Spoerl E, Mrochen M, Sliney D, et al. Safety of UVA-Riboflavin Cross-linking of the Cornea. *Cornea* 2007; **26**: 385-389.
24. Agrawal VB. Corneal collagen cross-linking with riboflavin and ultraviolet-A light for keratoconus: Results in Indian eyes. *Indian J Ophthalmol* 2009; **57**: 111-114.
25. Wittig-Silva C, Whiting M, Lamoureux E, et al. A Randomized Controlled Trial of Corneal Collagen Cross-linking in Progressive Keratoconus: Preliminary Results. *J Refract Surg* 2008; **24**: S720-S725.
26. Vinciguerra P, Albe E, Trazza S, et al. Refractive, Topographic, Tomographic, and Aberrometric Analysis of Keratoconic Eyes Undergoing Corneal Cross-linking. *Ophthalmology* 2009; **116**: 369-378.
27. Vinciguerra P, Albe E, Trazza S, et al. Intraoperative and Postoperative Effects of Corneal Cross-linking on Progressive Keratoconus. *Arch Ophthalmol* 2009; **127**(10): 1258-1265.

28. Hersh PS, Greenstein SA, Fry KL. Corneal collagen crosslinking for keratoconus and corneal ectasia: One-year results. *J Cataract Refract Surg* 2011; **37**: 149-160.