CHAPTER ONE

This chapter addresses the aims of the study as well as the research question. A brief overview of the topic is provided, as well as a literature review on the important points regarding this condition. Existing research in the field is also discussed.

1.1 BACKGROUND & LITERATURE REVIEW

Keratoconus (KC) is one of the most common corneal degenerative ectatic disorders. It is a condition characterized by thinning and protrusion of the central or inferior part of the cornea allowing the cornea to assume a conical shape.[1] Recent evidence of overexpression of inflammatory mediators such as cytokines and interleukin 6 (IL-6) in tears of patients with keratoconus, suggests that keratoconus does in fact have an inflammatory component in its pathology.[2,3]

The condition commonly presents within the second decade and early third decade of life and is bilateral with frequent asymmetry.[3] The condition shows preponderance in males with earlier presentation and more rapid progression in this population group. Georgiou et al reported a 2.6 times higher incidence in males than in females.[4] The condition demonstrates stability 8-12 years post diagnosis.

It is found that the true prevalence of keratoconus is often underestimated as studies conducted in hospital clinics review symptomatic patients. Early forms of the disease (forme fruste) are thus often missed.

Risk factors

The aetiology is multifactorial with both genetic and environmental influences. It is believed that environmental factors exacerbate or initiate disease in genetically susceptible individuals.

Genetic factors are apparent with a 14% reported family history in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) study.[5] Consanguinity has more recently been considered a risk factor for disease. Traditional linkage studies have found 19 genetic loci that may contain mutations for keratoconus. This indicates heterogeneity in inheritance. In three studies, chromosome 5 q21.2 has been isolated as a likely locus for keratoconus pathogenesis.[3]

Environmental factors include eye rubbing. Micro trauma as a result of eye rubbing causes surface epithelium to generate elevated levels of matrix metalloproteinase MMP-1 and MMP-13 and inflammatory mediators IL-6 and tumour necrosis factor – alpha (TNF- alpha). Elevated levels of IL-1 are also generated which trigger apoptosis of keratocytes and as a result loss of stromal volume.[3] Corneas with keratoconus display lack of specific enzymes that are essential to the breakdown of reactive oxygen species. These include aldehyde dehydrogenase class 3, catalase or superoxide dismutase.[3] Bawazeer et al reported that only eye rubbing was an associated risk factor for KC however atopy in isolation was not a significant associated feature.[6] Persistent eye rubbing results in progression of disease with continuous elevated levels of protease, inflammatory mediators and protease activity.

Atopy is generally defined as a hypersensitivity reaction. This may include presenting features of asthma, eczema and allergy.[2] Atopy is indirectly related to keratoconus as a high percentage of individuals with atopy have ocular irritation, which predisposes them to eye rubbing.

Sun exposed corneas demonstrate lower levels of aldehyde dehydrogenase class 3 and superoxide dismutase.[3] It is postulated that oxidative stress on the cornea, from ultraviolet (UV) exposure, may predispose the cornea to developing keratoconus.

There exists an association of keratoconus with Down Syndrome, Leber Congenital Amaurosis, Osteogenesis Imperfecta, Ehlers-Danlos Syndrome and other connective tissue disorders including Marfan Syndrome.[7]

Signs and symptoms

Early disease is usually asymptomatic but as progression occurs, visual acuity declines with significant visual distortion and visual loss. Causes of visual loss include irregular astigmatism, myopia, and corneal scarring. Early biomicroscopic findings include Fleischer rings, which are iron deposits in the corneal epithelium. This is usually noted around the base of the cone. Vogt striae are common and are fine vertical lines produced from compression of Descemet's membrane. As disease progression occurs, Munson's sign, Rizutti's sign and hydrops become more prominent. Munson's sign is a v-shaped protrusion of the patient's lower lid on downward gaze as a result of pressure of the ectatic cornea on the lower lid. Rizutti's sign is a bright reflection of the nasal limbus when light is directed to the temporal limbus. Corneal 'hydrops' refers to breaks in Descemet's membrane with associated stromal oedema and pain. This often has an end result of corneal scarring.[8]

These corneas are thinner and have been found to be less sensitive to touch with prominence of corneal nerves.[9] The most common reported optical aberration associated with keratoconus is coma.[10]

Diagnosis

The diagnosis of keratoconus requires clinical suspicion. The clinician is alerted to the likelihood of the diagnosis with a reduction in visual acuity, increasing myopia, increase in irregular astigmatism as evidenced by scissoring reflex on retinoscopy.[7] Diagnosis also involves distorted keratometric measurements and smaller pachymetric corneal thickness.

There is no consensus internationally on the exact criteria regarding diagnosis and staging of keratoconus. The Amsler-Krumeich Classification for Grading Keratoconus (Table to follow on next page and repeated in results for ease of reference) takes into account the patient's refractive error, keratometry and central corneal thickness (CCT).[7] Another commonly used grading system is

the Keratoconus Severity Score (KSS) Ranking Scheme (Appendix B).[11] This takes into account corneal scarring and slit lamp examination features.

Amsler-Krumeich Classification for Keratoconus[7]

Grades	Characteristics
Stage I	Eccentric steepening Myopia and astigmatism < 5.00D Mean central K readings < 48.00D
Stage II	Myopia and astigmatism from 5.00 to 8.00 D Mean central K readings < 53.00 D Absence of scarring Minimum corneal thickness > 400um
Stage III	Myopia and astigmatism from 8.00 to 10.00 D Mean central K readings > 53.00D Absence of scarring Minimum corneal thickness from 300 to 400um
Stage IV	Refraction not measurable Mean central K readings > 55.00D Central corneal scarring Minimum corneal thickness 200um

The gold standard in diagnosing and monitoring keratoconus is corneal topography (based on the principles of Placido disc and Scheimpflug imaging).[3] Scheimpflug imaging is the most sensitive method of assessing corneal shape and allows detection of subclinical cases. It grades severity of disease through graphic representation of a colour coded tomographic map of the corneal surface.

Quantitative methods include KC prediction index (KPI) , KC Index (KCI%) , Keratoconus Percentage Index (KISA%), inferior-superior asymmetry (I-S), asymmetric bow-tie astigmatism (AST) and skewed radial axis (SRAX) values.[3]

It has been reported that measurements of central corneal thickness on optical coherence tomography (OCT) are as specific and sensitive as is the topographic KISA index.[3]

Risk factors for progression of disease

There are many genetic factors that are still being investigated, however certain conditions such as Down Syndrome clearly predispose the individual to progression of disease. It has also been found that a younger age of onset or diagnosis is associated with more progression. Higher corneal curvatures and high corneal cylinders are associated with greater speed of progression.[8]

Treatment

The aim of treatment of keratoconus should be primarily halting the disease progression and visual rehabilitation**.**

The decreased visual acuity accompanying the condition is initially corrected with spectacles. As disease progression occurs with mild to moderate astigmatism, contact lenses prove to be the better alternative.

Mild to moderate astigmatism

- Soft toric lenses
- Rigid gas-permeable lenses (capable of treating irregular astigmatism)
- Hybrid contact lenses
- Piggy-back lenses
- Scleral lenses

As astigmatism increases, rigid gas-permeable lenses have been proven the superior alternative. Specialized rigid gas-permeable lenses have been developed to take into consideration the steep cone of keratoconus and the flatter normal peripheral corneal curvature. Hybrid contact lenses which have a central rigid area and a softer outer skirt provide the benefit of a rigid gas-permeable lens centrally and allow increased comfort to the patient peripherally (from the soft outer skirt). Another alternative is piggy-back lens, which involves a soft contact lens placed on the cornea and a rigid lens placed on top of this.

The last available type of contact lenses are scleral lenses. These are used as a last resort for highly irregular corneas.[8]

Intrastromal corneal ring segments (ICRS) are utilized in patients who are contact lens intolerant. The intrastromal corneal ring adds extra material to the corneal midperiphery, thereby flattening the central cornea and steepening the peripheral cornea. The ICRS are also postulated to provide support to the already thinning cornea. The tunnel created to insert the intrastromal corneal ring segments can be made manually with the assistance of a calibrated diamond knife, or with the assistance of a femtosecond laser. It is postulated that creation of the tunnel with the assistance of femtosecond laser allows for more precision in depth of the tunnel and placement of the ICRS. [8]

Collagen cross-linking (CCL) is now becoming increasingly popular as unlike all other forms of treatment of keratoconus, collagen cross-linking prevents progression of the disease. The procedure involves the use of a photosensitizing agent, riboflavin and UV-A light to create additional covalent bonds between collagen molecules thereby stabilizing the collagen framework of the cornea. The use of riboflavin and UV-A light has also been shown to increase the cornea's resistance to proteolytic enzymes.[12] Inclusion criteria for collagen cross-linking include central corneal thickness above 400 microns, maximum keratometry over 60 diopters and evidence of progression of disease. Patients that are excluded from collagen cross-linking include patients with central corneal scarring, previous eye surgery and ocular surface or tear problems.[13]

In advanced or severe cases, 20% of keratoconus patients will require surgery.[3] Penetrating keratoplasty is the most commonly performed procedure, however deep anterior lamellar keratoplasty (DALK) is gaining popularity as there is decreased endothelial cell loss and a decreased rate of delayed graft failure associated with this procedure.[14]

Extensive research has been conducted analyzing the demographic profile of patients with keratoconus, most of this research pertains to non-African populations.

A study by Gillian et al reviewed 25 patients presenting to the University of Johannesburg Eye Clinic.[15] This study showed a high incidence of eye rubbing (76%) and 48% of patients who had associated atopy. Of note most patients had established disease, with 68% showing Vogt's striae and 68% having Fleischer rings. About half of the patients already had corneal scarring.[15]

Another study by Carmichael et al looked at the keratoconus population at St John Eye Hospital over a period of one year (1997-1998).[16] A total of 45 patients were reviewed and this study found a high incidence of associated vernal keratoconjunctivitis (64%). Eye rubbing was significantly associated with vernal keratoconjunctivitis with an odds ratio of 33.6 (confidence interval 4.74-314). As there were no formal criteria for disease severity in 1998, based on author criteria, most patients were classified as severe keratoconus. During this time period, collagen cross-linking was not known as a management option to halt the progress of the disease.

1.2 Relevance of research

This study looked at a larger sample size with the aim of achieving statistical significance. A minimum of 120 patients was calculated as a statistically significant sample size (p value 0.05). Demographic details included age, gender, ethnicity, whether the patient was in possession of a driver's license and the individual's highest level of education. The patient's current occupation was also enquired about. Another factor this study looked at was the time from onset of symptoms to actual presentation to any facility and the reasons for presentation to the facility. A medical history was also taken enquiring into the family history of keratoconus, history of atopy and ocular allergies as well as a whether previous CCL was done.

File audits were conducted and clinical examination, including keratometry and pachymetry was also done. The clinical examination allowed the researcher to classify the disease severity. The newer treatment modality of collagen cross-linking was looked at and its effect on disease progression.

The grading of severity of the disease affords us the opportunity of assessing the disease burden in our current population. This allowed us to assess and review our current treatment plans. The study may prove useful with regard to allocation of funds to specific treatment modalities. If early disease is prevalent, collagen cross-linking will need to be the forefront of management. If there is a proven high burden of severe disease, measures can be instituted to facilitate more corneal grafts for our population group.

Another consideration was to look at visual outcomes of patients with keratoconus. This however would be difficult in a cross-sectional study as patients presenting will be at various stages of the disease with variable disease duration. Due to the lack of funding and insufficient corneal graft availability, most patients requiring corneal grafts wait long durations and ultimately do not receive these grafts. Their visual outcomes are poor, not as a result of treatment inadequacies but rather a result of inadequate funding and system constraints.

1.3 Objective of the Study

- The primary objective was to assess the staging of disease at presentation to St John Eye Hospital (using the standard Amsler-Krumeich Classification for Keratoconus).
- The secondary objectives were to assess the demographic profile of patients with keratoconus presenting to St John Eye Hospital and to assess the efficacy of collagen cross-linking in altering disease progression.

CHAPTER TWO - METHODOLOGY

2.1 Study Design

This cross-sectional descriptive study was conducted at St John Eye Hospital (a single tertiary eye care facility) over a period of 18 months. The study was conducted over the period November 2016 to April 2018. 105 patients were included in the study of which 102 were examined by the primary researcher and three by a medical officer.

2.2 Approval

The study protocol was approved by the Human Research Ethics Committee (Appendix D) of the University of the Witwatersrand and by the Research Protocol Assessor Group of the University of the Witwatersrand, Department of Neurosciences (protocol reference number: M160922). The study adheres to the principles of the Declaration of Helsinki. The primary researcher has no financial interests. Patient confidentiality was maintained by assigning each patient a case number to which only the primary researcher and statistician were allowed access to. Consent to conduct the study was obtained from CHBAH Research Committee (Appendix E) and the Head of Department at St John Eye Hospital (Appendix F).

2.3 Site of Data Collection

Data collection was obtained from patients attending the Cornea clinic at St John Eye Hospital for management of keratoconus. St John Eye Hospital is a tertiary eye care facility that caters to the low-medium income patients that live in Soweto and surrounding areas. Majority of these individuals are of black ethnicity. The individuals were asked to complete a questionnaire (Appendix F). If the visual acuity precluded the patient being able to write, the necessary data was obtained through an interview by the primary researcher. Demographic data included age, gender, ethnicity, whether the patient possessed a driver's license, highest level of education, current occupation,

age at presentation to any facility and reason for referral. A family history of keratoconus was elicited as well as history of atopy, ocular allergy and previous corneal cross-linking. File audits were conducted for each patient as well as a clinical examination including corneal topography and recorded on a data collection sheet (Appendix G).

2.4 Study Population

Patients presenting to the Cornea clinic at St John Eye Hospital with a confirmed diagnosis of keratoconus were included in the study. Patients are initially screened in the general clinic and then booked for review by the Cornea clinic team and appropriate investigations are then completed. This includes keratometry, pachymetry and where possible Scheimpflug imaging.

2.4.1 Inclusion Criteria

- Patients presenting to the Cornea clinic at St John Eye Hospital with the diagnosis of keratoconus.
- Children who were cooperative enough to have a clinical examination were also included after explicit consent from their parents/legal guardian. The questionnaire was then completed by said parent/legal guardian.
- Patients who had previous CCL
- Patient who had previous keratoplasty

2.4.2 Exclusion Criteria

- Patients with inadequate records
- Patients who had other ocular pathology that could attribute to the poor visual acuity e.g. patient with Marfan Syndrome that has dislocated lenses
- Patients with previous ocular surgery unrelated to the keratoconus

2.5 Statistical Analysis

The data analysis was done with the assistance of a private statistician. Data was analyzed using Microsoft Excel and IBM SPSS Statistics v25. Kruskal-Wallis and Mann-Whitney U tests were utilized for non-parametric data.

CHAPTER THREE - RESULTS

3.1 Demographics

The study comprised 105 participants of which 102 were examined by the principal researcher and 3 by a medical officer.

3.1.1 Age

Table 1 Present ages, age at vision deterioration and at presentation

Age test variables	**Mode**	**Median**	**Mean**	**Standard Deviation**
Age (years)	17	23	24.19	9.434
Age at deterioration of vision (years)	8	13	14.37	6.864
Age presentation (years)	12	15	16.43	7.752

Table 1 presents summary statistics for participants' age profiles. At the time of the study, most often participants were 17 years old (mode = 17) with 50% or more participants being 23 years or older (median = 23). The mean age of the participants was 24.19 ± 9.434 years.

Most often participants' vision started deteriorating at the age of 8 (mode = 8). In addition, 50% or more participants were aged 13 or above when their vision began to deteriorate (median = 13). The mean age for participants' vision deterioration was 14.37 ± 6.864 years.

Most participants presented to a facility for treatment at age 12 (mode = 12). At least 50% of the participants presented at 15 years or older (median = 15) and on average presenting age was 16.43 ± 7.752 years.

As the disease has an early onset and is progressive in nature, there is a large age range in this study population. Ages ranged from 8-60 years.

3.1.2 Gender

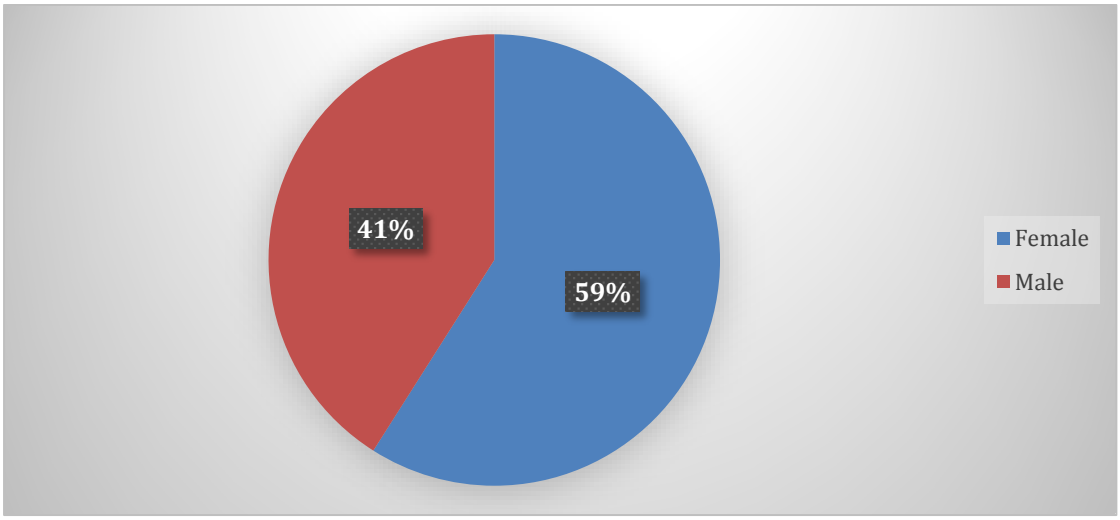


Figure 1 Gender

As evidenced by Figure 1, the majority of the study population were female at 59% (n=62). 41% (n=43) patients were male.

3.1.3 Ethnicity

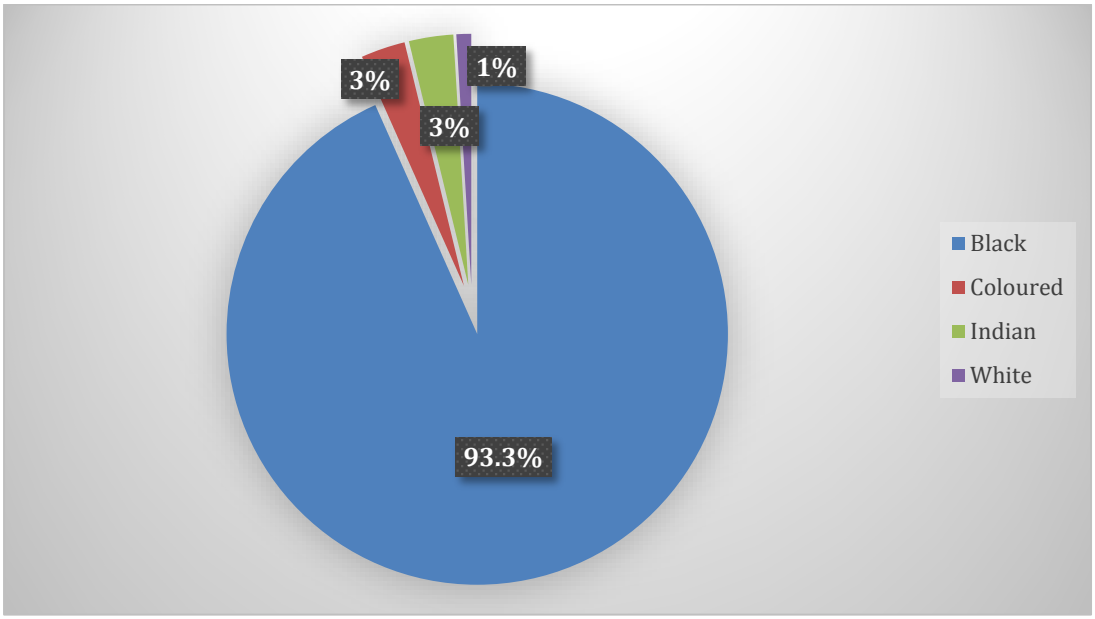


Figure 2 Ethnicity

The most represented ethnic group was Black, with 93.3% (n=98) of the participants belonging to this group. Coloured and Indian participants were equally represented, each with 3% (n=3) of the participant pool. Only one participant was White.

3.1.4 Patients with a driver's license

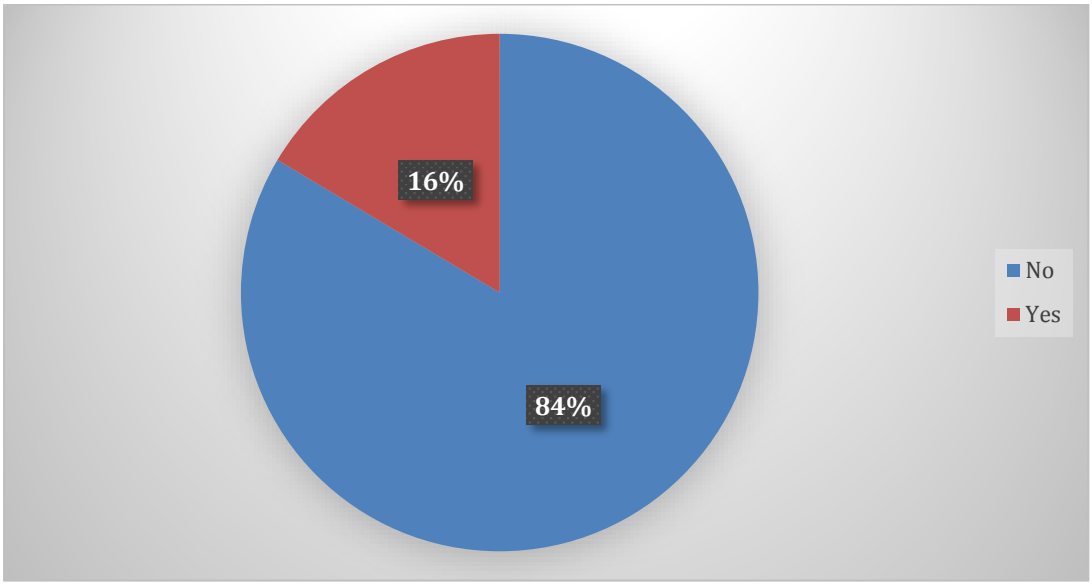


Figure 3 Patients with a driver's license

32 patients (30.5%) were below the age of 18 an did not qualify for a driver's license. Of the remaining 73 patients, only 12 (16%) were in possession of a driver's license. Of the participants that did qualify for a driver's license, 61 (84%) did not have a driver's license.

3.1.5 Level of education

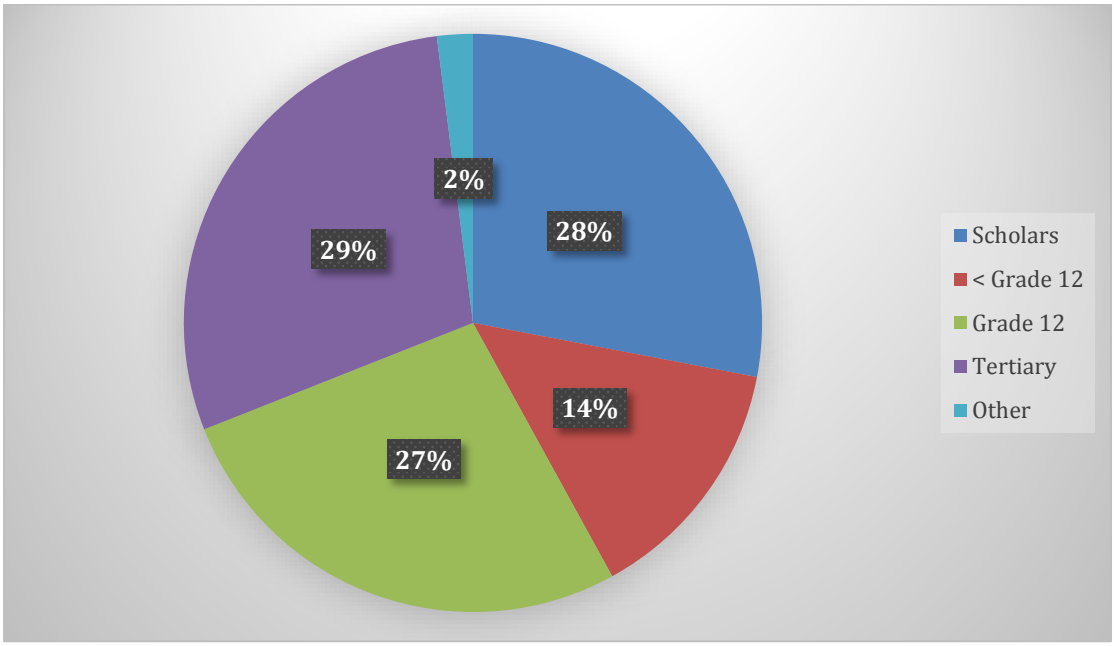


Figure 4 Level of education

As evidenced in Figure 4, all the participants had some form of education. 29% (n=31) of participants had a tertiary level of education. This meant they had completed their grade 12 and had some form of further training or education. 27% (n=28) of the patient population had completed their grade 12 and 14% (n=15) had not completed their secondary schooling. Scholars accounted for 28% (n=29) of the study population. Two participants were classified as other. Of these, one individual had a junior certificate. This indicated that the participant had completed and passed grade 11. The other individual was attending special school.

3.1.6 Occupation

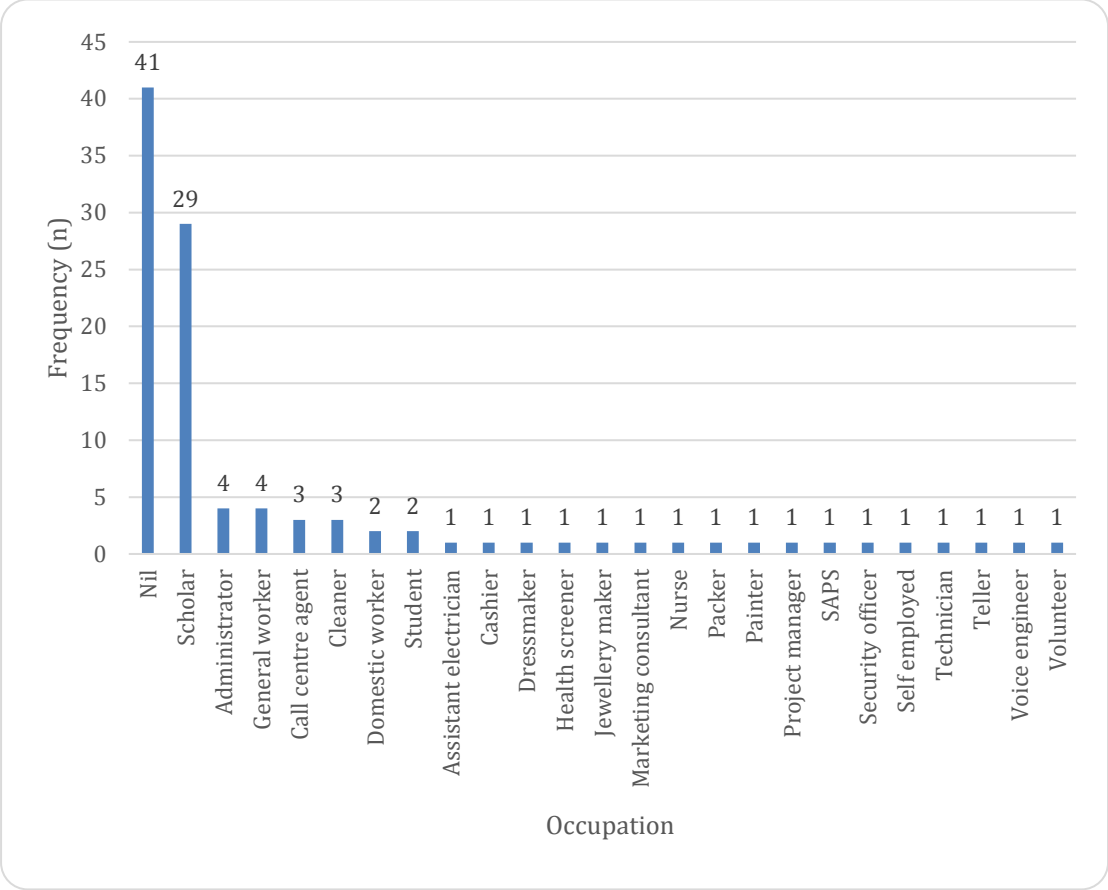


Figure 5 Occupation

Figure 5 shows that most participants were unemployed. This is evidenced in 41 (39%) of them indicating as such. Twenty-nine (27.6%) participants were still scholars and two (1.9%) were students (tertiary education). Of the 33 participants who were employed, 4 (3.8%) were administrators, 4 (3.8%) general workers, 3 (2.9%) call centre agents, 3 (2.9%) cleaners; and 2 (1.9%) domestic workers. The occupations of the remaining 17 participants were very widely dispersed and had one participant each (see above figure).

3.1.7 Reason for presentation

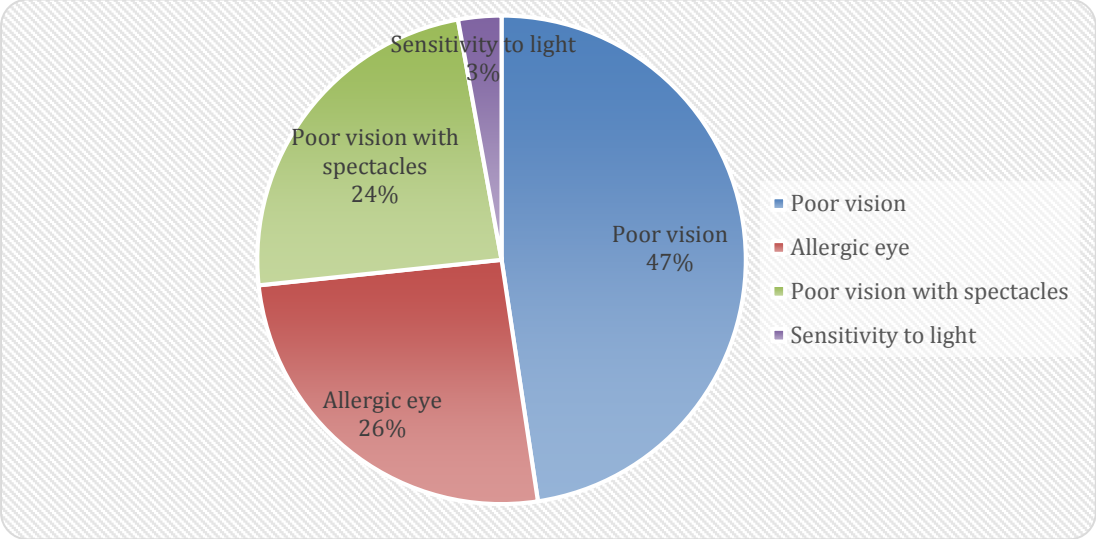


Figure 6 Reason for presentation

The above figure shows that the most frequent reason for presenting was poor vision, with 50 (47%) participants indicating that this was their primary reason for presentation. Ocular allergy (n=27; 26%) and poor vision with spectacles (n=25; 24%) were the second and third highest reasons for presenting. Patients with keratoconus do develop increasing irregular astigmatism that is often not able to be corrected with spectacles. This would explain the individuals presenting with poor vision with spectacles. Sensitivity to light (photophobia) was the least cited reason with only 3 (3%) participants presenting because of it.

3.1.8 Medical history

Table 2 Medical History

Medical History	**%**
Family history of KC	6.7
History of Atopy	3.8
History of VKC	84.8
History of CCL	26.7

As seen above, of the 105 participants only 7 (6.7%) participants had a history of KC in their families. The majority of participants, however, had a history of VKC (n=89; 84.8%). Only 4 (3.8%) participants had a history of atopy. A history of collagen cross-linking (CCL) was observed in 28 (26.7%) participants.

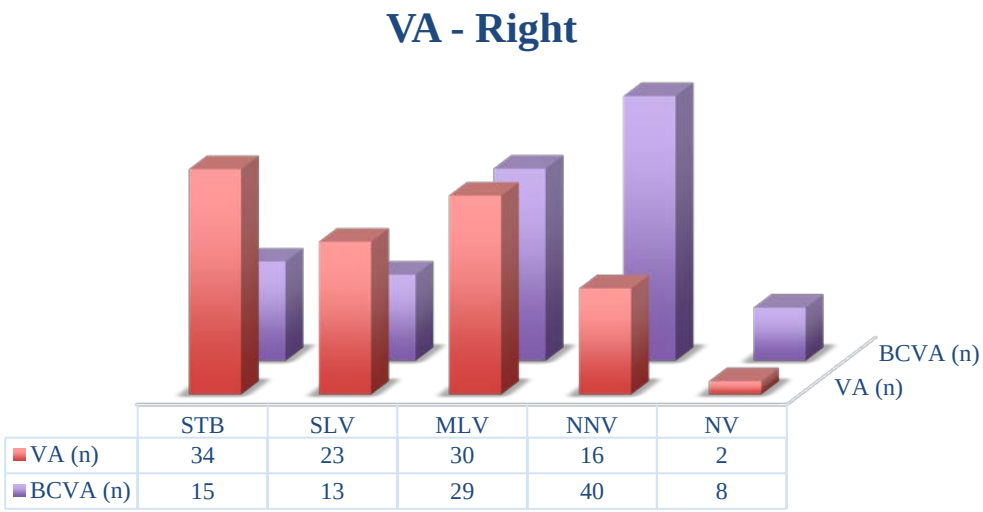
3.2 Visual acuity

To standardize visual acuity (VA) for ease of analysis, Snellen acuities were grouped into the level of vision impairment as per the classification utilized by the World Health Organization (WHO) to classify visual impairment (see Table). The acuities were adjusted in this study for near-normal vision (NNV) to accommodate some readings that fell in the gap between normal vision (NV) and NNV. Instead of starting from 6/9, this study starts from NNV at 6/7. In addition, none of the study participants fell within the moderate blindness (MB) category, as such subsequent analyses did not include this category as part of the scale.

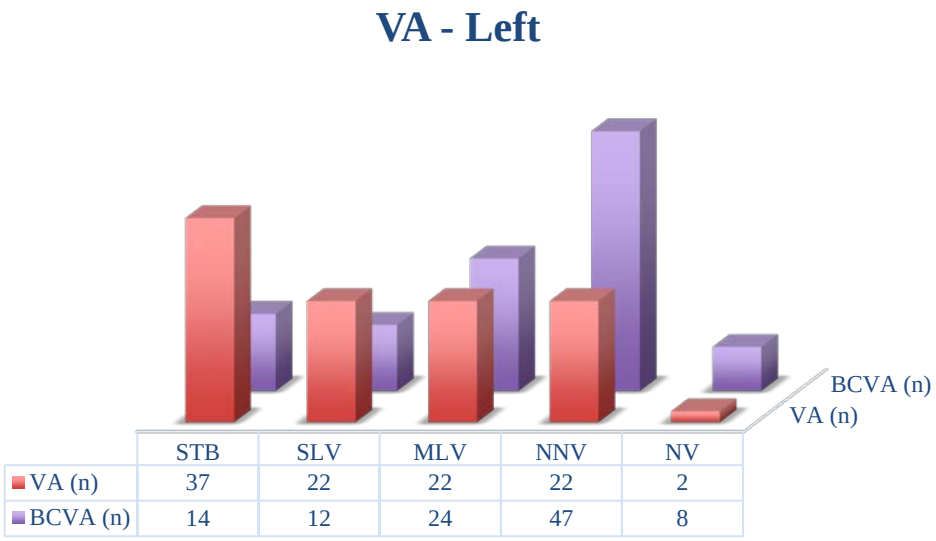
Table 3 Visual acuity classification

Classification of Vision Impairment	Abbreviations	Snellen Acuities	Adjusted Snellen Acuities
Normal Vision	NV	4/6 to 6/6	4/6 to 6/6
Near-Normal Vision	NNV	6/9 to 6/18	6/7 to 6/18
Moderate Low Vision	MLV	6/24 to 6/48	6/24 to 6/48
Severe Low Vision	SLV	6/60 to 6/120	6/60 to 6/120
Moderate Blindness	MB	6/150 to 6/300	none detected
Severe to Total Blindness	STB	HM to NLP	CF to HM

3.2.1 Visual acuity for right and left eyes



	STB	SLV	MLV	NNV	NV
VA (n)	34	23	30	16	2
BCVA (n)	15	13	29	40	8



	STB	SLV	MLV	NNV	NV
VA (n)	37	22	22	22	2
BCVA (n)	14	12	24	47	8

Figure 7 Visual acuities for right and left eyes

The figure above depicts visual acuity (VA) and best-corrected visual acuity (BCVA) for both the right and the left eyes. As can be seen in the figure most participants had severe to total blindness (STB) before BCVA for both the right and the left eyes. Visual acuities for STB in left eyes were slightly more than those of right eyes by 2 participants.

Visual acuities for right eyes indicate that almost 83% of the participants' vision was less than normal (including near normal). Only 2 (1.9%) participants had NV and 16 (15.2%) had NNV. Best corrected visual acuities saw an overall increase in the number of participants having NV by 300% and NNV by 150%. In contrast, STB decreased by 56%, MLV by 3% and SLV by 43% post BCVA.

Visual acuities for left eyes indicate that almost 80% of the participants' vision was less than normal (including near normal). Only 2 (1.9%) participants had NV and 22 (21.2%) had NNV. Best corrected visual acuities saw an overall increase in the in the number of participants having NV by 300%, NNV by 114% and MLV by 9%. In contrast, STB decreased by 64% and SLV by 45% post BCVA.

3.2.2 Impact of best corrective measure on visual acuity

The following table summarizes the change in visual acuity impairment classification groupings (see Table 3 above). The table compares whether participants' vision improved, deteriorated or remained unchanged post BCVA (see following table scale).

Table 4 Scale for measuring degree of improvement of VA post refractive correction

Degree of improvement	**Classification**
Worsened	Deteriorated
Remained the same	Unchanged
Changed within category	Slight improvement
Moved up a category	Moderate improvement
Moved up more than one category	Major improvement

3.2.2 continued

Impact of best corrective measure on visual acuity

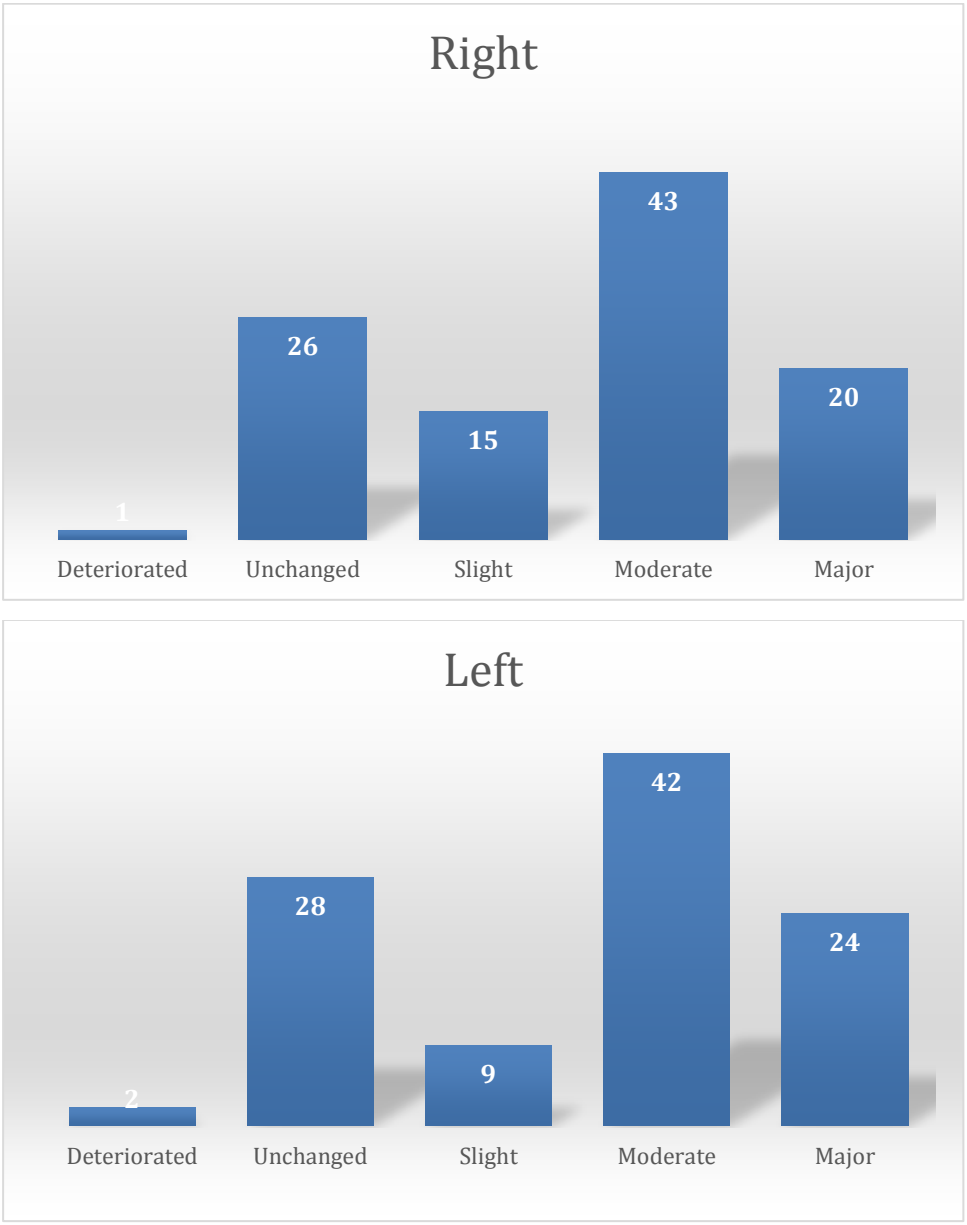


Figure 8 Impact of best corrective measure on visual acuity

As can be seen in Figure 8, one participant's right eye deteriorated despite BCVA. In addition, two participants' left eyes also deteriorated despite BCVA. Most frequently participants showed a moderate increase (i.e. moved up a visual classification category) in VA after corrective measures were used on them. This held true for both the right eyes (41% improvement, n=43) and left eyes (40,4% improvement n=42). There were 20 (19%) participants who

showed major improvements (i.e. moved up 2 or more visual classification categories) in their right eyes, while 24 (23.1%) showed similar improvement in their left eyes. A slight improvement in visual acuity was demonstrated in 15 (14.3%) and 9 (8.7%) of right and left eyes respectively. However, 26 (24.8%) and 28 (26%) experienced no change in VA in right and left eyes respectively, post attempted refractive correction.

3.3 Keratoconus grading

3.3.1 Keratometry reading

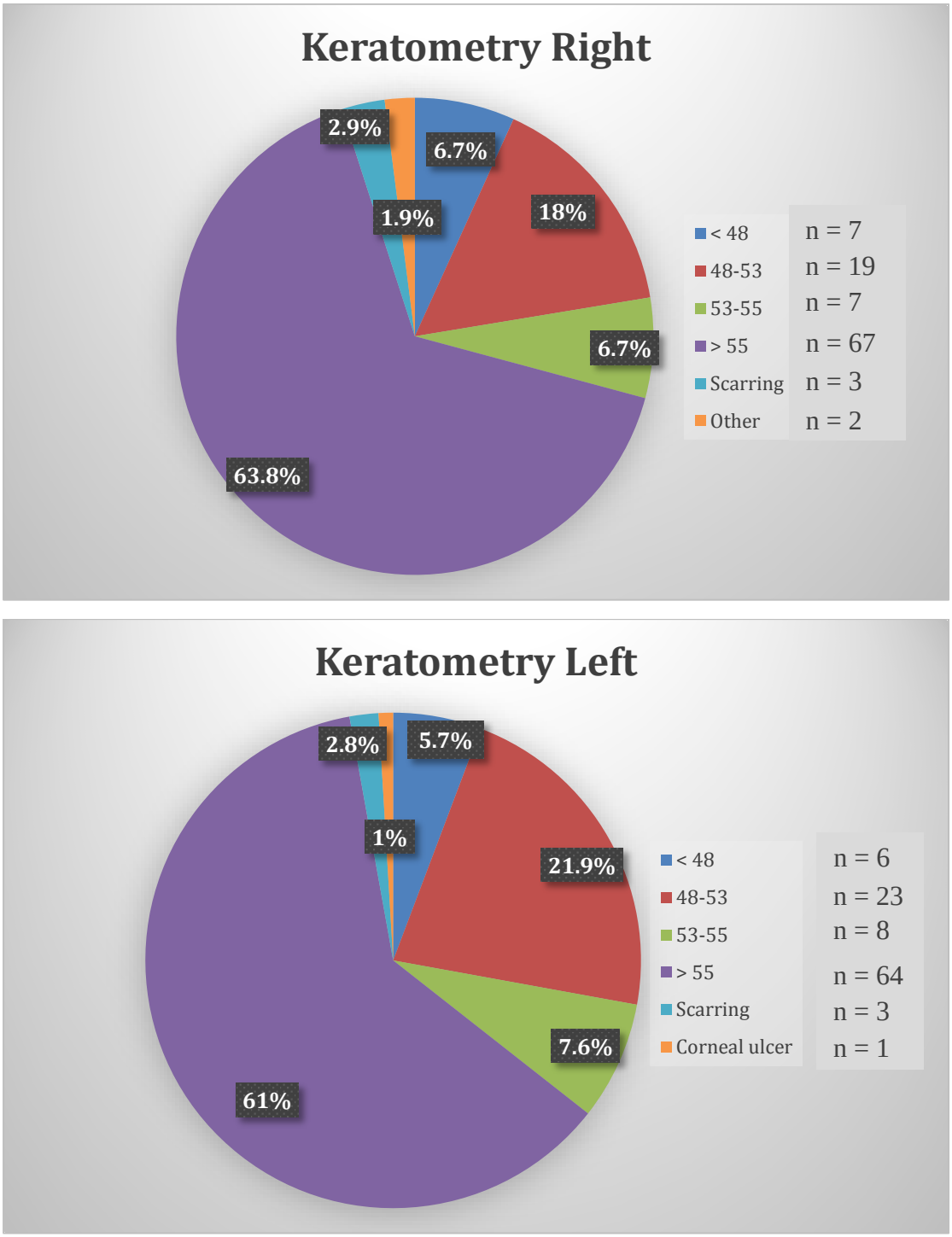


Figure 9 Keratometry reading

As seen in this figure, the majority of participants had keratometry readings >55D. This held true for both right eyes and left eyes with 67 (63.8%) and 64 (61%) participants falling within this range respectively. The second highest range was between 48 - 53D, with 19 (18%) and 23 (21.9%) participants falling within this range for right and left eyes respectively. The same number of participants fell within the below 48D and the 53D - 55D ranges for right eyes, each having 7 (6.7%) participants. Left eyes had 6 (5.7%) and 8 (7.6%) for the same ranges respectively. 3 (2.9%) participants had scarring in their right eyes and 3 (2.8%) had scarring in their left eyes. One more participant had a corneal ulcer in her left eye. This was a bacterial keratitis secondary to contact lens usage.

3.3.2 Keratometry mean (Kmean) reading

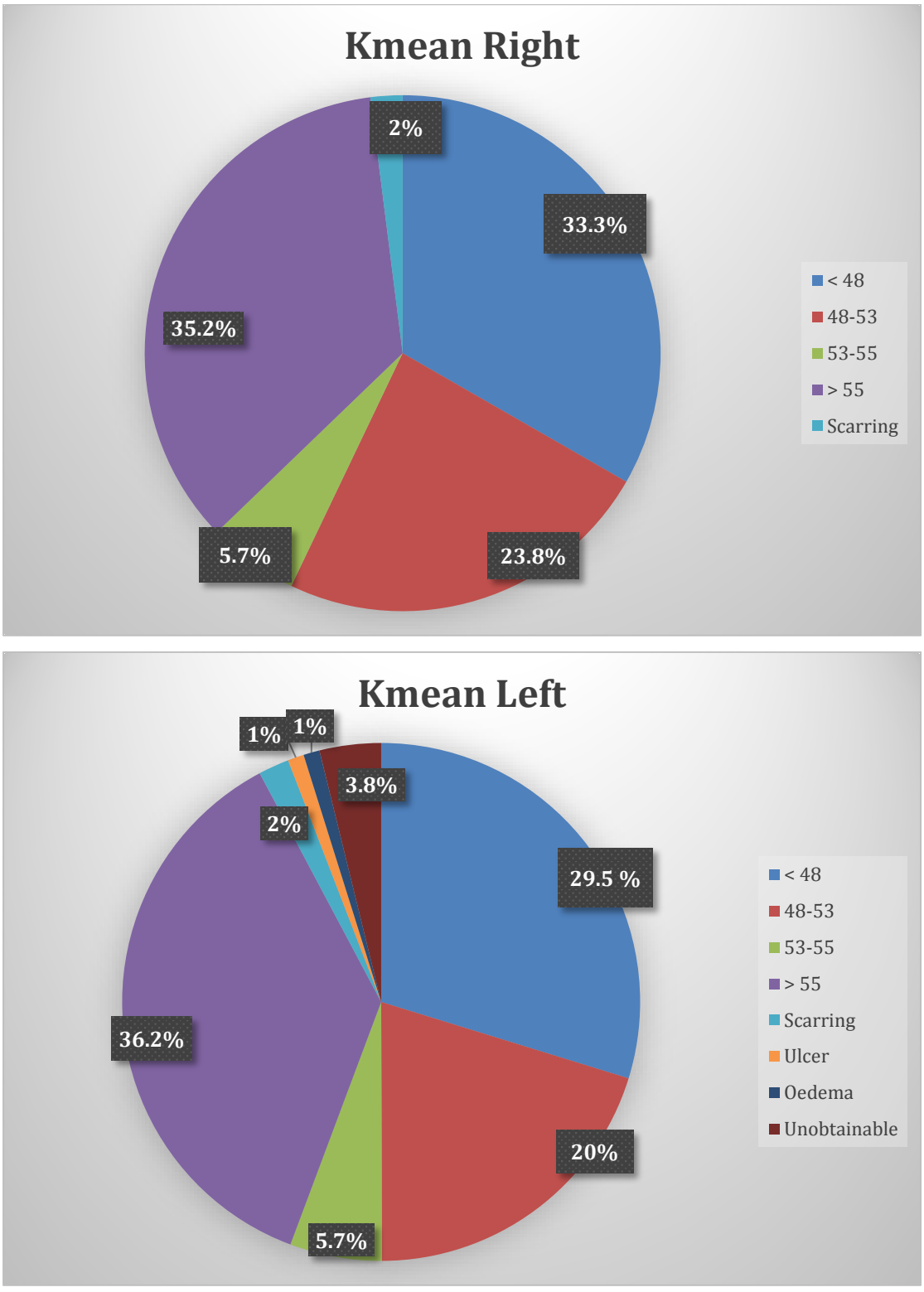


Figure 10 Keratometry mean reading

As seen in the above figure, a similar trend was observed in the Kmean readings for both the right and left eyes. The majority of participants had Kmean

readings >55D for right eyes (n=37; 35.2%) and left eyes (n=38; 36.2%). This was followed by Kmean readings < 48D (n=35; 33.3%), between 48-53D (n=25; 23,8%), between 53-55D (n=6; 5.7%) for right eyes; and < 48D (n=31; 29.5%), between 48-53D (n=21; 20%), between 53-55D (n=6; 5.7%) for left eyes. One participant had scarring in his right eye, while 2 (2%) had scarring in their left eyes. Moreover, one participant had a corneal ulcer in her left eye and another corneal oedema. 4 patients (3.8%) had unobtainable values on the left eye. This was related to suboptimal patient co-operation and data gaps on Scheimpflug imaging precluding the use of this data.

3.3.3 Central corneal thickness

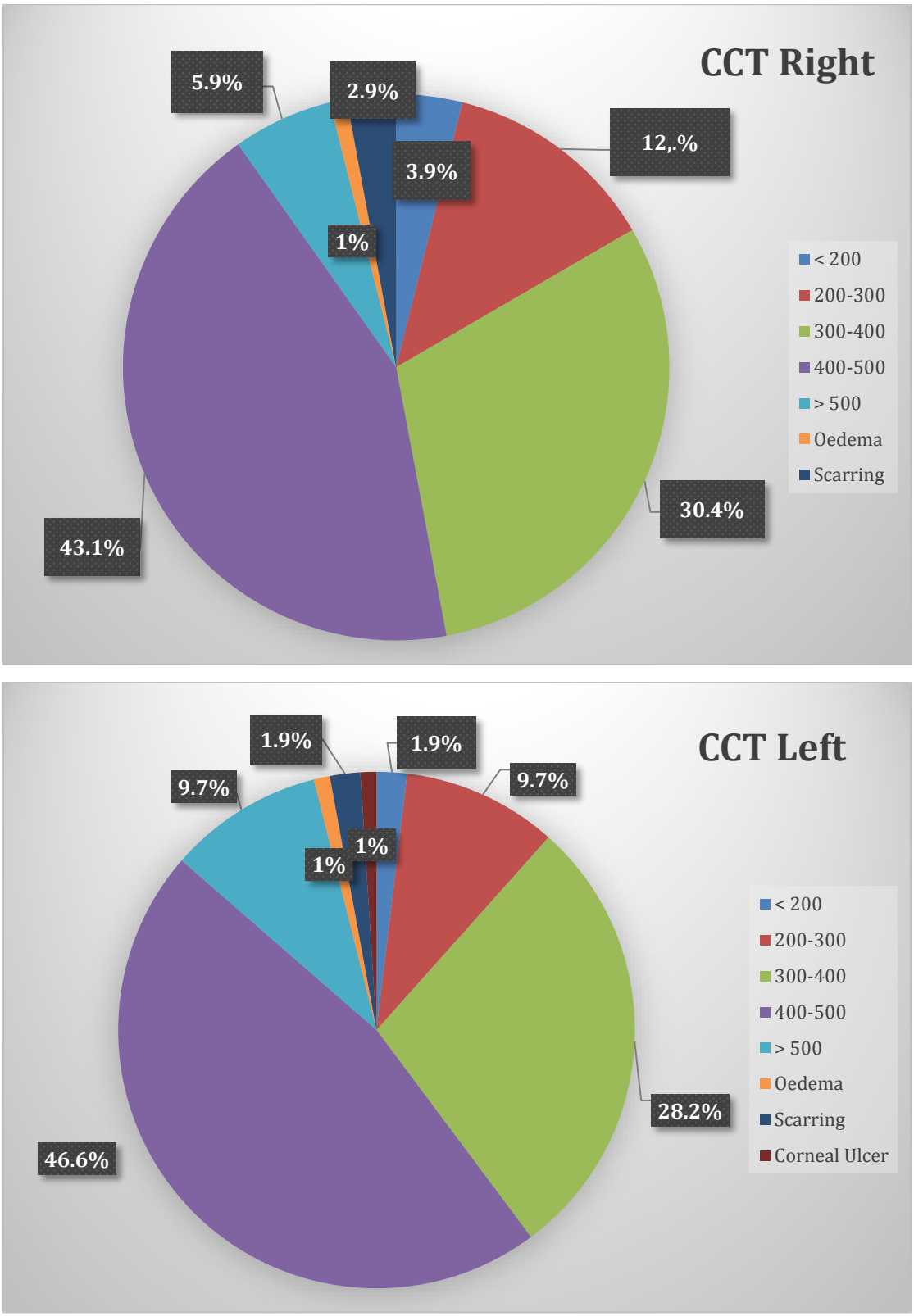


Figure 11 Central corneal thickness

In Figure 11, only 5.9% of participants had a CCT >500um on the right eye. Majority of the participants fell into the 400 – 500um (n=44; 43.1%) followed by the 300-400um group with 30.4% (n=31) in the right eye. One participant had oedema in both his right eye and left eye (data shows that it is the same patient).

Only 9.7% of individuals had a CCT >500um in the left eye (n=10). A sizeable number of patients fell into the 400-500um category (n=48; 46.6%) followed by the 300-400um group with 28.2 % (n=29).

3 patients (2.9%) and 2 (1.9%) had scarring in their right and left eyes respectively. One participant also had a corneal ulcer in her left eye.

3.3.4 Keratoconus staging

Keratoconus staging (Amsler-Krumeich Classification of Keratoconus repeated below for ease of reference)

Grades	Characteristics
Stage I	Eccentric steepening Myopia and astigmatism < 5.00D Mean central K readings < 48.00D
Stage II	Myopia and astigmatism from 5.00 to 8.00 D Mean central K readings < 53.00 D Absence of scarring Minimum corneal thickness > 400um
Stage III	Myopia and astigmatism from 8.00 to 10.00 D Mean central K readings > 53.00D Absence of scarring Minimum corneal thickness from 300 to 400um
Stage IV	Refraction not measurable Mean central K readings > 55.00D Central corneal scarring Minimum corneal thickness 200um

Table 5 Keratoconus staging

Stage	n = 105	%
I	9	8.6
II	18	17.1
III	19	18.1
IV	59	56.2

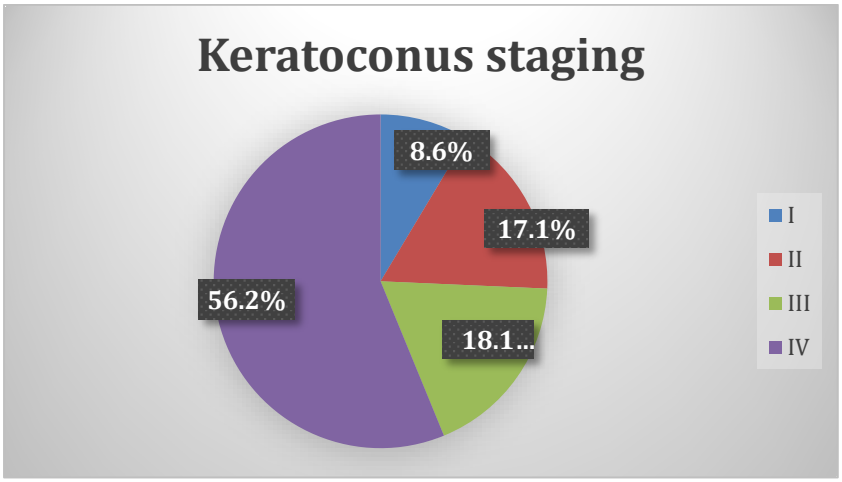


Figure 12 Keratoconus Staging

The table and figure (previous page) show that the majority of participants fell into the stage IV category (n=59; 56.2%). An almost equal number of participants fell into the stage III and stage II category with 19 (18.1%) and 18 (17.1%) respectively. Only 9 (8.6%) participants fell into the stage I category.

3.4 Clinical findings

Table 6 Clinical findings

Clinical Findings	**n = 105**	**%**
Munson's sign	96	91.4
Corneal scarring	56	53.3
VKC	54	51.4
Vogt's striae	28	26.7
Flesicher ring	11	10.5
Corneal neovascularization	8	7.6
Prominent corneal nerves	5	4.8
Corneal staining	4	3.8

As seen in Table 6, the majority of the participants had Munson's sign (n=96; 91.4%). This was followed by corneal scarring (n=56; 53.3%), VKC (n=54; 51.4%) and Vogt's striae (n=28, 26.7%). Fleischer rings were observed in 11 (10.5%) participants, corneal neovascularization in 8 (7.6%) and prominent corneal nerves in 5 (4.8%). The least observed clinical finding was corneal staining that was present in 4 (3.8%) participants.

3.5 Keratoplasty type

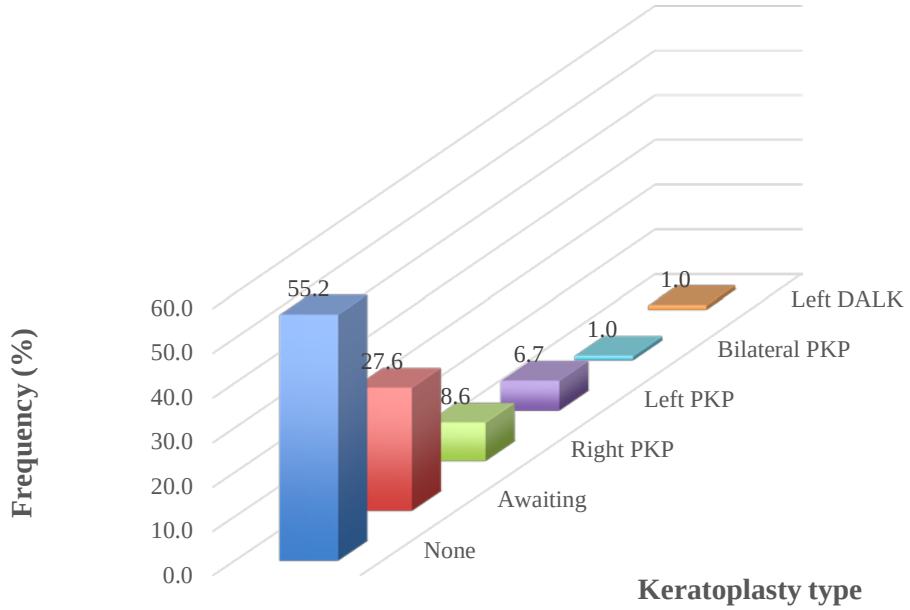


Figure 13 Keratoplasty types

The above figure indicates that most participants did not have any form of keratoplasty done (n=58; 55.2%). Furthermore 29 (27.6%) participants were still waiting to have keratoplasty. 9 (8.6%) participants had right PKP while 7 (6.7%) had left PKP. Only one participant had bilateral PKP. Similarly, only one participant had left DALK. DALK can only be performed in individuals who have not had hydrops or full-thickness corneal scars.

3.6.1 Collagen cross-linking

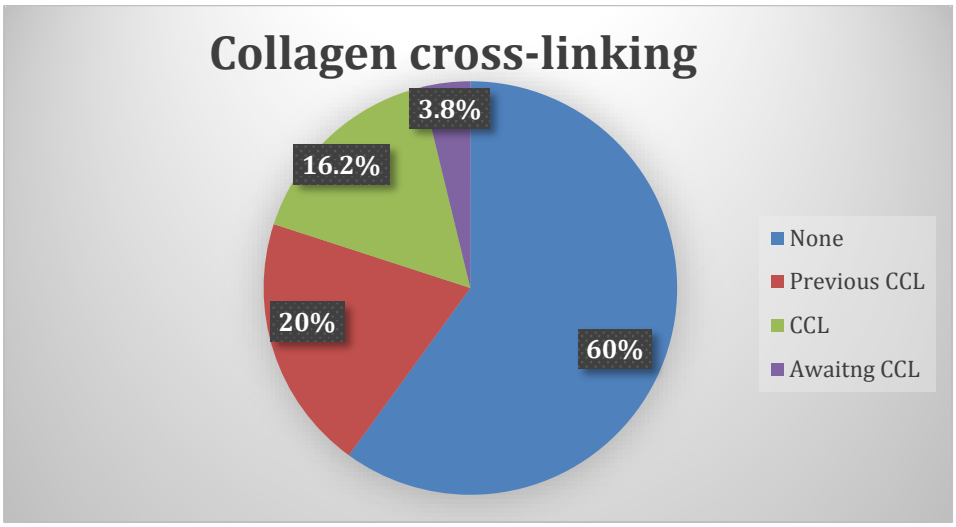


Figure 14 Collagen cross-linking

As seen in the above table, the majority (n=63; 60%) of participants did not have any collagen cross-linking (CCL). Twenty-one (20%) had CCL done prior research investigation. During the study, 16.2 % (n=17) of patients had CCL. 9 (8.6%) participants had bilateral CCL performed, 7 (6.7%) had unilateral CCL done and 1 participant had repeat CCL done. 4 (3.8%) participants were still awaiting CCL to be performed on them.

3.6.2 Staging of KC severity in patients with previous CCL

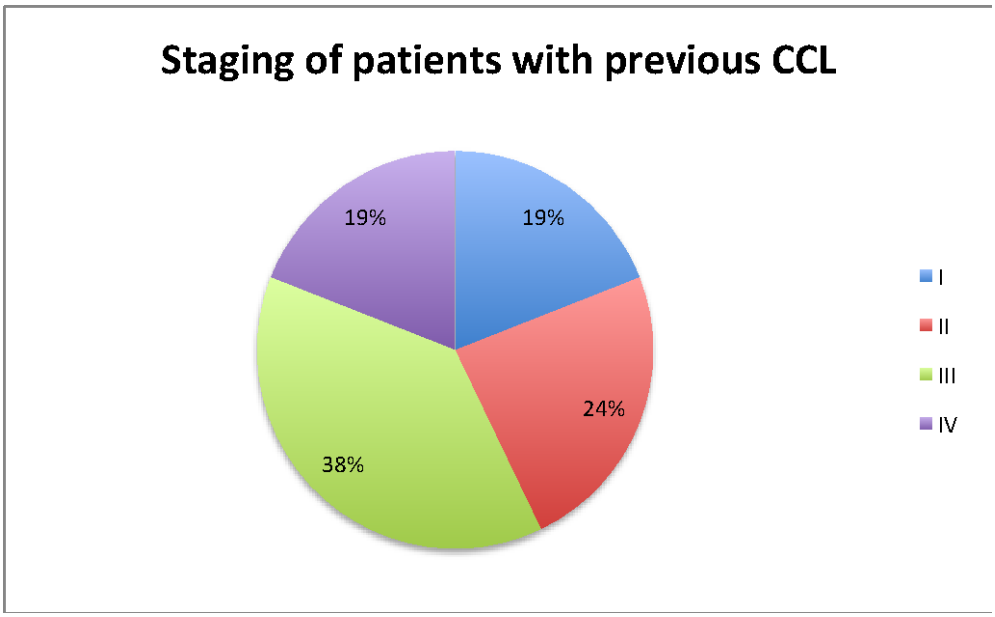


Figure 15 Staging of keratoconus in patients with previous CCL

Data of the 21 patients who had collagen cross-linking prior to the study was looked at. The eye that had cross-linking was staged. 19% (n=4) patients were classified as stage I and similarly 19% (n=4) of patients were classified as stage IV. 24% (n=5) patients were classified as stage II and the remaining 38% (n=8) was categorized as stage III.

CHAPTER FOUR - DISCUSSION

This study reports demographic data, clinical findings and disease severity in patients presenting to a single tertiary eye care centre in Soweto, Johannesburg, South Africa. There was a higher percentage of female patients in our study group which contradicts other studies that report a higher prevalence of disease in males (72%).[17] Possible reasons for having a higher female preponderance could be related to the larger number of males being of the working population. Employment and limitations with regard to sick leave make it more likely for this population group to present when essentially necessary rather than for routine follow-up. St John Eye Hospital is located in Soweto and caters to the Diepkloof and surrounding areas, where the majority of the population is black in ethnicity. As expected, the majority of the study population was black in ethnicity. The majority of the study population that qualified for a driver's license (age over 18 years) was not in possession of one. Factors explaining this could be related to poor visual acuity or related to the socio-economic status of the population. Despite the high rate of unemployment at 39%, one cannot entirely attribute this to patient's poor visual acuity. In this study population, there does exist a high rate of unemployment related to socioeconomic factors.

This study showed that 28% of individuals were still of the school going age with ages below 18 years old. This could suggest that the disease presentation occurs quite early in this population.

Mean age of diagnosis of keratoconus is typically in the second decade of life.[3] In our study the mean age of presentation was at 16.43 years. Early presentation of disease could correlate with earlier onset of disease and faster progression when compared to other population groups.[8] As keratoconus is an evolving disease, we expected to have a large range in age. The youngest patient was 8 and the oldest patient was 60.

The majority of our study group had a history of ocular allergy (85%) with only a minority having a history of atopy (3.8%). Allergic eye disease and ocular

rubbing is postulated to cause release of inflammatory mediators and an increase in protease activity predisposing genetically susceptible individuals to the development of keratoconus.[3] 51.4 % of the study population had signs of VKC on clinical examination. As the association between VKC and KC has already been proven in this population, recommendations to treat VKC aggressively can be advocated for. Screening of patients with VKC might allow early detection of forme fruste disease in this population. Only 6.7% of study participants had a family history of keratoconus. This is lower than the CLEK study which reported a family history of 14%.[5] The CLEK study was an 8-year, multi-centre, natural history study observing 1209 patients with KC. The large size and long follow-up could be a possible reason such a high prevalence of family history was observed. Lack of awareness and access to medical care is another possibility that could explain this study's lower history of keratoconus.

A significant percentage of our study group still had moderate visual impairment despite refractive correction i.e. spectacles and contact lenses. This could be related to the high cost of rigid gas permeable contact lenses and scleral lenses and financial constraints in our population group. Another factor that could account for this is the high percentage (53.3%) of patients who already had corneal scarring and advanced disease where penetrating keratoplasty is the only remaining treatment option. Intracorneal ring segments are not available to this population group due to the high cost. There is also no access to femtosecond laser.

The majority of our study group had severe keratoconus. This could be due to delayed presentation, lack of awareness regarding the association between keratoconus and VKC, suboptimal access to medical care, and the progressive nature of the disease. The primary objective of staging the disease severity of patients presenting to the Cornea clinic at St John Eye Hospital was achieved. With the high burden of severe disease in this study population, measures to facilitate more corneal grafts is a possible suggestion to enhance patient care.

There does exist a notable back log of patients awaiting keratoplasty (27.6% n=29). Likely attributing factors impeding access to keratoplasty include availability of tissue, inadequate funding and financial and system constraints.

Though we were able to effectively describe the demographic profile of our KC population, the efficacy of collagen cross-linking could not be adequately reviewed. Access to records prior to collagen cross-linking was limited. This made confirming the efficacy of the procedure in halting disease progression difficult. The small sample of patients who had prior CCL, the lack of records prior to the procedure and of the CCL itself and the evolving methods of CCL preclude any conclusions to be drawn from this data.

Limitations to this study include being of a cross-sectional nature with many individuals being seen at various stages of the disease. In order to obtain a confidence interval of 95% and a p-value of 0.05 as significant, sample sizes required would be above 120 patients. This was difficult in our setting, due to poor record keeping and patient files being given to the patients and being lost at home, as well as no recorded data stored at the hospital/clinic. Further studies of a prospective nature with a larger sample size are needed to verify and better understand our results.

CHAPTER FIVE - CONCLUSION

Opportunistic health promotion, through screening of patients with ocular allergies may assist in detecting early asymptomatic stages of the disease in predisposed individuals. Despite advances made in refractive correction of patients with keratoconus, increased availability of keratoplasty and attempts to halt the progression of the disease, there remains a large burden of morbidity in terms of visual disability with impairment of quality of life. Despite the high level of unemployment and patients without drivers' licenses, we cannot infer that this is related to their visual acuity in isolation. Various socioeconomic factors could also account for this finding. With a high burden of severe keratoconus in our population, and a significant backlog in patients requiring keratoplasty, measures to facilitate keratoplasty need to be implemented. The

likely factors hampering keratoplasty access include availability of tissue and financial and system constraints.

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APPENDIX A – PLAGIARISM FORM

DEPARTMENT OF NEUROSCIENCES

Neurology, Neurosurgery, Ophthalmology,
Otorhinolaryngology, Psychiatry
School of Clinical Medicine, Faculty of Health Sciences,
7 York Road, Johannesburg 2193, South Africa
Tel: +27 11 717-2774 · Fax: +27 11 717 2775

Plagiarism declaration for written work

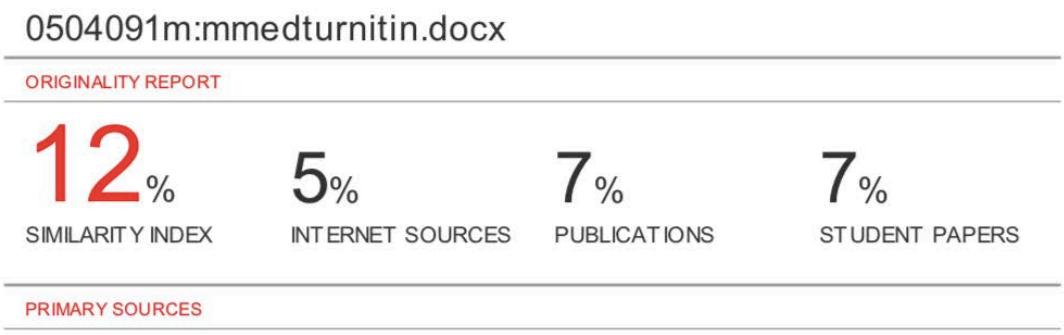
I ……Fathima Mitha……. as a postgraduate student registered for a MMed at the
University of the Witwatersrand declare the following:

I am aware that plagiarism is the use of someone else's work without their permission and or without acknowledging the original source.
I am aware plagiarism is wrong.
I confirm that this written work is my own work except where I have stated otherwise.
I have followed the required conventions in referencing the thoughts and ideas of others.
I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or if I have failed to acknowledge the ideas or writing of others.

Signature ……..

Date ……

APPENDIX B – TURNITIN REPORT



APPENDIX C – Keratoconus Severity Score (KSS) Ranking Scheme

Grade	Stage	Corneal Scarring	Slit lamp Signs	Axial Pattern	Other Features
0	Normal topography	None	None	Typical	Average corneal power (ACP)≤47.75D. Higher –order RMS error≤ 0.65
1	Atypical topography	None	None	Atypical - Irregular - Sup. bowie - Inf. Bowie - Inf. Or Sup. Area of steepening no more than 3.00D steeper than ACP	ACP ≤48.00D, Higher-order RMS error ≤1.00D
2	Suspect topography	None	None	Isolated area of steepening - Inferior - Superior - Central steep	Additional features: ACP ≤49.00Dor Higher-order RMS error > 1.00, ≤1.50
3	Mild disease	None	Possible	Consistent with KCN	Additional features:ACP ≤52.00Dor Higher-order RMS error>1.50,≤ 3.50
4	Moderate disease	Add Features: Corneal scarring and overall CLEK grade up to 3.0	Possible	Consistent with KCN	Additional features: ACP>52.00, ≤56.00 or Higher-order RMS error >3.50, ≤5.75
5	Severe disease	Add features: Corneal scarring CLEK grade 3.5 or greater overall	Must have	Consistent with KCN	Additional features: ACP >56.00D or Higher-order RMS error>5.75

APPENDIX D – ETHICS CLEARANCE CERTIFICATE

Human Research Ethics Committee (Medical)

Research Office Secretariat: Senate House Room SH 10005, 10th floor.
Medical School Secretariat: PV Tobias Building 3rd Floor.
Private Bag 3, Wits 2050. www.wits.ac.za
Email: HREC-Medical.ResearchOffice@wits.ac.za

Tel +27 (0)11-717-1252
Tel +27 (0)11-717-2700
Fax +27 (0)11-717-1265

21 October 2016

To Whom It May Concern

SUBJECT: **CONFIRMATION OF STUDY APPROVAL**

Protocol Ref No: M160922

Protocol Title: Keratoconus: A Cross Sectional Descriptive Study Looking at Disease Severity of Patients Presenting to the Corneal Clinic at St John Eye Hospital in Soweto (as Part of the University of the Witwatersrand Academic Circuit), Johannesburg, South Africa

Principal Investigator: Dr Fathima Mitha

Department: Ophthalmology

This letter serves to confirm that the Human Research Ethics Committee (Medical) has received an ethics application for the abovementioned study. In order for a clearance certificate to be issued, the researcher is required to submit written approval to conduct the study in your district/institution.

The researcher has been informed that this study cannot commence without your approval and receipt of the Clearance certificate from the HREC (Medical).

Should you have any queries, you may contact me at tel: 011 717 1234/2700/2656 or by email Rhulani.Mkansi@wits.ac.za

Yours Faithfully,

Mr Rhulani Mkansi
Administrative Officer
Human Research Ethics Committee (Medical)

UNIVERSITY OF THE WITWATERSRAND
OFFICE OF THE DEPUTY VICE CHANCELLOR RESEARCH
21 OCT 2016
RESEARCH OFFICE HREC (Medical)
JOHANNESBURG

APPENDIX E – MEDICAL ADVISORY COMMITTEE CHBAH PERMISSION TO CONDUCT RESEARCH

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE
CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 10 June 2016

TITLE OF PROJECT: Keratoconus: a descriptive study into the demographic profile of patients presenting to St John Eye Hospital in Soweto, Johannesburg, South Africa

UNIVERSITY: Witwatersrand

Principal Investigator: F Mitha

Department: Ophthalmology

Supervisor (If relevant): N Welsh

Permission Head Department (where research conducted): Yes

Date of start of proposed study: June 2016
Date of completion of data collection: Dec 2018

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Hospital. The CEO /management of Chris Hani Baragwanath Hospital is accordingly informed and the study is subject to:-

- Permission having been granted by the Human Research Ethics Committee of the University of the Witwatersrand.
- the Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- the MAC will be informed of any serious adverse events as soon as they occur
- permission is granted for the duration of the Ethics Committee approval.

.....
Recommended
(On behalf of the MAC)
Date: 10 June 2016

.....
Approved/Not Approved
Hospital Management
Date: 13/06/16

APPENDIX F – APPROVAL FROM HEAD OF DEPARTMENT

File audits will then be conducted for each of these patients to obtain the following data

- Patients current uncorrected and corrected visual acuity
- Current method of refractive correction: this includes spectacles, contact lenses (type of lens: soft, rigid gas-permeable, toric, piggy-back, scleral) and/or keratoplasty
- Current eye examination findings: these include Fleischer rings, corneal scarring, corneal staining, prominent corneal nerves and/or Vogt's striae
- Stage of disease: this includes measurements of central corneal thickness and keratometry

All data will be collected in a retrospective manner as per the submitted protocol, and will remain strictly confidential to the author. All data collection will be performed after approval by the Human Research Ethics Committee of the University of the Witwatersrand.

The intended research will be fully funded by the applicant and will not interfere with the daily running of the hospital or hospital equipment.

Head of Department Ophthalmology St John Eye Hospital

Name G D McLAREN Date 6/06/2016

Signature

APPENDIX G - QUESTIONNAIRE

Questionnaire

Patient Study Number:

Initials:

Age:

Gender:

Ethnicity:

Highest level of education:

Current Occupation:

Current Driver's License YES NO

Age of deteriorating vision:

Age of presentation to any facility:

Reason for presentation

- blurred vision
- frequent change of spectacles
- poor visual acuity with spectacles
- sensitivity to light

Family history of keratoconus YES NO

History of atopy: HAY FEVER ASTHMA ECZEMA

History of allergic eye disease/frequent eye rubbing YES NO

History of collagen cross-linking: YES NO

APPENDIX H – DATA COLLECTION SHEET

Examination and File Audit

	RIGHT	LEFT
VISUAL ACUITY - uncorrected - corrected		
Refractive Correction - spectacles - contact lenses (type)		
Keratometry reading		
Central Corneal Thickness		
Staging of KC		
Munson's Sign		
Fleischer Ring		
Corneal Scarring		
Corneal Neovascularization		
Corneal Staining		
Prominent corneal nerves		
Vogt's Striae		
Vernal Keratoconjunctivitis		
Keratoplasty (date)		
Collagen cross-linking (date)		

Continued on next page

Continued from previous page

Collagen cross-linking

	Right	Left
Pre cross-linking keratometry		
Post cross-linking keratometry		
Pre best corrected visual acuity		
Post best corrected visual acuity		