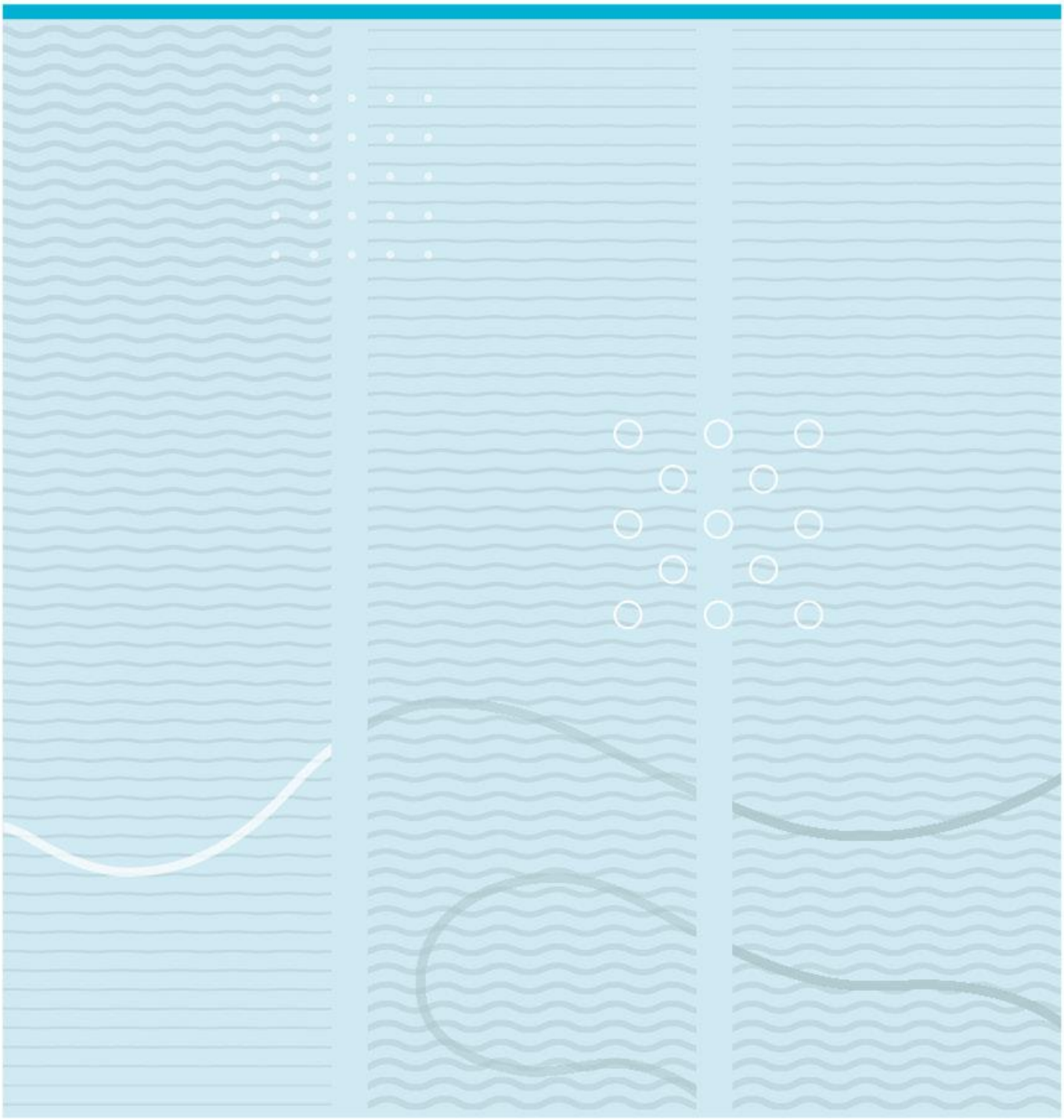
University of South-Eastern Norway
Faculty of Optometry

–

Master's Thesis
Study programme: MPRO5001
Spring 2023

Pia Victoria Haugum Ekker

Clinical outcomes of combined transepithelial phototherapeutic keratectomy and conventional corneal collagen crosslinking (t-PTK+CXL) versus conventional corneal collagen crosslinking (CXL) for progressive keratoconus at St. Olavs Hospital, Trondheim University Hospital: A retrospective comparative study



University of South-Eastern Norway
Faculty of Optometry
Institute of optometry, radiography, and light design
PO Box 235
NO-3603 Kongsberg, Norway

http://www.usn.no

This thesis is worth 30 study points.

1 Abstract

Purpose: To compare the outcomes of corneal collagen cross-linking (CXL) for the treatment of progressive keratoconus using 2 different techniques for epithelial removal: transepithelial phototherapeutic keratectomy (t-PTK) + CXL versus mechanical epithelial debridement.

Design: retrospective comparison study.

Participants: Two hundred and twenty patients (298 eyes) with progressive keratoconus were included.

Method: All patients underwent uncomplicated CXL treatment. Hundred and ten patients (155 eyes) underwent epithelial removal using t-PTK (group 1) and ninety-five patients (143 eyes) underwent mechanical epithelial debridement using a Amoils rotating brush (group 2) during CXL treatment. Visual and refractive outcomes were evaluated with keratometric and aberrometric values preoperatively at 12±6 months postoperatively.

Main outcome measures: Uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), manifest refractive spherical equivalent (MRSE), and keratometry readings as steepest radius of anterior curvature (Kmax), and corneal astigmatism (AST.). Additionally, aberometric values root mean square (RMS) and higher order aberrations (HOAs). Secondary outcomes; subjective spherical power, subjective astigmatic power, steepest meridian (K2), flattest meridian (K1) and spherical aberrations (Z40).

Results: In group 1, Snellen decimal mean UDVA and mean CDVA improved from 0.41 ±0.24 and 0.96 ±0.20 preoperatively to 0.67 ±0.32 (p <.001) and 1.03 ±0.19 (p < .005) at 12±6 months postoperatively, respectively. In group 1, mean UDVA improved from 0.50 ±0.35 preoperatively to 0.54 ±0.38 (p <.005) at follow-up, whereas group 2 mean CDVA demonstrated no significant improvement at 12±6 months postoperatively (p >.05). In group 1, Kmax improved from 53.15 ±4.3 dioptres (D) preoperatively to 50.99 ±4.68 D (p <.001), and in group 2 Kmax improved from 53.92 ±8.26 dioptres (D) preoperatively to 53.74 ±8.47 D (p <.001). RMS Total and RMS HOAs both showed significance between baseline and follow-up (p <.001) and between treatments in the same follow-up interval (p <.001).

Conclusions: Epithelial removal using t-PTK during CXL results in better visual and refractive outcomes compared with mechanical epithelial debridement. However, further studies are needed to determine the true differences between treatments.

Abstrakt

Formål: Å sammenligne resultatene av corneal collagen cross-linking (CXL) som behandling av progressiv keratokonus ved hjelp av 2 forskjellige teknikker for epitelfjerning: transepitelial fototerapeutisk keratektomi (t-PTK) + CXL sammenliknet med mekanisk epitel fjerning.

Design: retrospektiv sammenligningsstudie.

Deltakere: To hundre og tjue pasienter (298 øyne) med progressiv keratokonus ble inkludert.

Metode: Alle pasientene gjennomgikk uproblematisk CXL-behandling. Hundre og ti pasienter (155 øyne) gjennomgikk epitelfjerning ved bruk av t-PTK (gruppe 1) og nittifem pasienter (143 øyne) gjennomgikk mekanisk epitel fjerning ved hjelp av en roterende børste (gruppe 2) som et ledd i CXL-behandling. Visuelle og refraktive utfall ble evaluert sammen med keratometriske og aberrometriske verdier preoperativt og 12±6 måneder postoperativt.

Hoved utfall: Ukorrigert avstandssynsstyrke (UDVA), korrigert avstandssynsstyrke (CDVA), manifest brytningssfærisk ekvivalent (MRSE), keratometriavlesninger som krummeste radius av fremre krumning (Kmax) og hornhinne astigmatisme (AST.). I tillegg er aberometriske verdier root mean square (RMS total) og høyere ordens aberrasjoner (HOAs). Sekundære utfall; subjektiv sfærisk styrke, subjektiv astigmatisk styrke, krummeste meridian (K2), flateste meridian (K1) og sfæriske aberrasjoner (Z40).

Resultat: I gruppe 1 ble gjennomsnitt UDVA og gjennomsnittlig CDVA, gjengitt i Snellen desimaler, forbedret fra henholdsvis 0,41 ±0,24 og 0,96 ±0,20 preoperativt til 0,67 ±0,32 (p <,001) og 1,03 ±0,19 (p < .005) ved henholdsvis 12±6 måneder postoperativt. I gruppe 1 økte gjennomsnittlig UDVA fra 0,50 ±0,35 preoperativt til 0,54 ±0,38 (p <,005) ved oppfølging, mens gjennomsnittlig CDVA i gruppe 2 ikke viste signifikant forbedring 12±6 måneder postoperativt (*p* >,05). I gruppe 1 forbedret Kmax seg fra 53,15 ±4,3 dioptrier (D) preoperativt til 50,99 ±4,68 D (*p* <,001), og i gruppe 2 forbedret Kmax seg fra 53,92 ±8,26 dioptrier (D) preoperativt til 53,74 ±8,47 D (*p* <,001). RMS Total og RMS HOAs viste begge signifikans mellom baseline og oppfølging (p <,001) og mellom behandlinger i samme oppfølgingsintervall (p <,001).

Konklusjon: Epitelfjerning ved bruk av t-PTK under CXL gir bedre visuelle og brytningsutfall sammenliknet med mekanisk epitel debridement. I midlertidig er det behov for ytterligere studier for å avgjøre de sanne forskjellene mellom behandlinger**.**

Table of Contents

2 Acknowledgements

First, I want to thank my self for seeing this through. I always knew I would, but I still think I deserve to tap my own shoulder for finishing this academic grade without compromising my other chores in life like family, work, and activities. One would think there have been some ups and downs. However, they have felt minor thanks to my friend and study partner, Camilla. She has been my SOS-service for both my mental health and school related issues. These three years would not have been nearly as fun without her. I want to thank my kids for trying their absolute best to give me some time to write, and for “waiting a minute” every night. Even if it honestly was long past their bedtime. Thank you to my supervisor, Vibeke, who wanted to do this fun project with me. And thank you to my partner, Peder, who has been waiting for å long time for me to prioritize differently.

3 Introduction

Keratoconus causes visual disturbances that go beyond regular visual ailments like myopia, hypermetropia, and astigmatism. Due to the asymmetrical development of keratoconus between the eyes, individuals often experience anisometropia, astigmatic anisometropia, and visual impairment that cannot be adequately addressed with standard vision aids. As a result, even after treatment, the use of rigid gas permeable contact lenses is often necessary to fully achieve adequate vision. Over the past decade, visual rehabilitation surgery has been explored as an option for these patients (Fernández-Vega-Cueto et al., 2017). This thesis will give supplementary research on transepithelial phototherapeutic keratectomy (t-PTK) combined with collagen corneal cross-linking treatment (CXL).

Keratoconus is most active in early stage of life, teens and early twenties and there is no cure for keratoconus (Flockerzi et al., 2021; Zhang & Li, 2020). The prevalence has been underrated for years, but recent studies suggest that it is approximately 1:400 with this diagnosis (Godefrooij, de Wit, Uiterwaal, Imhof, & Wisse, 2017; Kristianslund, Hagem, Thorsrud, & Drolsum, 2021). In other words, it is more common than previously assumed. Advanced technology and increased knowledge about the characteristics in the pathogenically of keratoconus is probably the reason we have a more precise statistic on this matter. Additionally, and even more important, the same technology ensure early diagnosis. This has led to revolutionary development in treatment with corneal collagen crosslinking (CXL). This treatment is proven to have a process halting effect on keratoconus, meaning it is possible to stabilize the progression of keratoconus at an early stage and potentially prevent it from reaching a severe stage of visual impairment (Wollensak, Spoerl, & Seiler, 2003).

Over the period of 2018-2022, an alternative CXL treatment protocol was performed in 50% of St. Olavs Hospital, Trondheim University Hospitals treatments. The purpose was to improve patients' vision and reduce disturbing aberrations that follows the disease. This study will investigate the pre- and postoperative results of both treatments to determine if the alternative t-PTK+CXL method is successful in regularizing corneal tissue and enhancing vision compared to the conventional CXL approach.

Several studies have observed the effect of t-PTK+CXL regarding refraction, topography, and corneal HOAs. These studies often lack patient volume and describe the conventional photorefractive keratectomy treatment (PRK) combined with CXL, and not the transepithelial phototherapeutic keratectomy (t-PTK) combined CXL treatment. Further, most of them, with some

exceptions (Alessio, L'Abbate, Sborgia, & La Tegola, 2013; Kontadakis et al., 2016) do not use conventional CXL as control group, but rather preoperative measures.

If t-PTK+CXL prove to have a more beneficial restorative effect, it could serve as a foundation for future research aimed at improving the treatment of individuals suffering from keratoconus. It is important to consider the social advantages of restoring visual function, which not only facilitates employment but also allows access to conventional visual aids. Furthermore, this investigation will ensure effective treatment at St. Olavs Hospital, Trondheim University Hospital.

4 Aim/ Research question

The aim of this thesis is to enhance comprehension of the clinical results of two distinct techniques for corneal epithelial removal during the CXL treatment process for progressive keratoconus. The outcomes of both methods will be assessed prior to and following the treatment and compared with each other 12 ±6 months postoperatively.

The overarching research question that guidelines this thesis is as follows:

Will a retrospective study of corneal collagen cross-linking (CXL) for the treatment of progressive keratoconus using two different techniques for epithelial removal: transepithelial phototherapeutic keratectomy (t-PTK) versus mechanical epithelial debridement prove a difference in clinical outcomes?

4.1.1 RQ1

Is there a significant difference of clinical outcomes in each treatment like unaided distance visual acuity (UDVA), corrected distance visual acuity (CDVA), manifest refractive spherical equivalent (MRSE), subjective spherical power (SPH), subjective astigmatism (CYL.), flattest meridian (K_1), steepest meridian (K_2), corneal astigmatism (ASTIG.), steepest radius of anterior curvature (Kmax), root mean square (RMS), higher order aberrations (HOAs), spherical aberrations (Z40) and pachymetry as pre- and postoperatively?

4.1.2 RQ2

Is there a significant difference of clinical outcomes between treatments like unaided distance visual acuity (UDVA), corrected distance visual acuity (CDVA), manifest refractive spherical equivalent (MRSE), subjective spherical power (SPH), subjective astigmatism (Cyl.), flattest meridian (K_1), steepest meridian (K^2), corneal astigmatism (ASTIG.), steepest radius of anterior curvature (K-max), root mean square (RMS), higher order aberrations (HOAs), spherical aberrations (Z40) and pachymetry as pre- and postoperatively?

4.1.3 RQ3

Is it possible to claim that t-PTK + CXL gives better visual quality compared to C-CXL?

5 Background

5.1 What is keratoconus?

Keratoconus is a progressive corneal condition causing thinning of the corneal tissue followed by challenging asymmetric refractive errors with high or progressive astigmatism. It is often associated with loss of best-corrected vision and increased higher order aberrations (HOAs) causing a decrease in the optical quality of the eye and visual performance (McGhee, Kim, & Wilson, 2015). In keratoconic eyes, irregular astigmatism caused by the corneal deformation cannot always be corrected by spectacles, and even with some improvement, ghosting or tails around bright lights often persist (McGhee et al., 2015). The most common differential diagnosis to genetic keratoconus is keratoglobus and Pellucid Marginal Degeneration (PMD). All three conditions are progressive and most often described as non-inflammatory. They are bilateral, but usually asymmetrical (Salmon, 2018).

The ethology of keratoconus is multifactorial, with a general acceptance that the condition is due to underlying genetic predisposition to keratoconus influenced by environment, eye-rubbing, and atopy. There has been an agreement in literature and among practitioners that keratoconus is a non-inflammatory disorder. However, recent clinical evidence and experimental results indicate that inflammatory processes in the corneal epithelium are linked to keratoconus (Santodomingo-Rubido et al., 2022). Corneal inflammation or injury can trigger a complex metabolic process leading to the loss of corneal stromal cells, decreased corneal tensile strength, and the conical expansion of the cornea (Wu et al., 2015).

Clinically, keratoconus usually develops in the second- and third-decade of life and progresses until it stabilises in the fourth decade (Flockerzi et al., 2021). Until now, there has not been a clear definition of progression of keratoconus (Chanbour et al., 2021). The global consensus on Keratoconus and Ectatic Diseases (2015) defined progression by a change in at least two of the following parameters: progressive steepening of the anterior corneal surface, steepening of the posterior corneal surface or thinning or changes in the pachymetric rate of change (Gomes et al., 2015).

5.2 Prevalence of keratoconus

Epidemiological research has shown significant variability in the prevalence and incidence of keratoconus, making it challenging to compare studies due to differences in ethnicity, geography, and the definition of the condition (Santodomingo-Rubido et al., 2022). Nevertheless, recent studies from Norway and the Netherlands have reported a prevalence of 1: 521 and 1: 375, respectively, have demonstrated that the prevalence of keratoconus might be higher than previously assumed (Godefrooij et al., 2017; Kristianslund et al., 2021).

In a study conducted in Denmark and covering hospital patients of all ages, a prevalence of 1:2272 was reported. However, the accuracy of this estimate may have been compromised by the data collection period, which extended from 2015 back to 1977. This time frame likely led to an underestimation of the prevalence of keratoconus, particularly given that the development of collagen corneal crosslinking (CXL) treatment in 2010 has led to a growing incidence of diagnosed cases (Bak-Nielsen, Ramlau-Hansen, Ivarsen, Plana-Ripoll, & Hjortdal, 2019).

5.3 Pathological signs

Pachymetry is a diagnostic tool used to measure the thickness of the cornea. This measurement is particularly important in the detection and monitoring of keratoconus, a condition characterized by corneal thinning. Multiple studies have explored the link between keratoconus and corneal thickness as determined by pachymetry. Gherghel et al. (2004) found that individuals with keratoconus had significantly thinner corneas than healthy individuals when assessed through pachymetry. Meiri et al. (2016) discovered that pachymetry-derived corneal thickness measurements could help identify early stages of keratoconus. In a study conducted by Savini, Carbonelli, Barboni, and Hoffer (2011), normal, healthy eyes had a mean (SD) minimum corneal pachymetry of 549.51 (±29.29) µm, while keratoconic eyes had a mean (SD) minimum corneal pachymetry of 467.11 (±38.30) µm.

5.4 How does keratoconus affect vision?

Astigmatism is a common visual problem that impacts several visual functions including visual sharpness, perception of light, and contrast sensitivity. Patients may experience symptoms like reduced vision, watery eyes, double vision, eyestrain, and visual distortion. Astigmatism is a

challenging problem to treat as it may cause distortions after correction compared to other refractive errors. The occurrence of astigmatism is caused by the uneven power across different meridians of the cornea, resulting in a distorted interpretation of a single point from a source within our visual system (Mohammadi, Khorrami-Nejad, & Hamidirad, 2019). There is found to be a direct connection between HOAs and contrast sensitivity, with reduced contrast sensitivity in keratoconic patients (Hefner-Shahar, Erdinest, & Barbara, 2016).

5.5 Wavefront

The full refraction of the eyes is primarily influenced by the anterior cornea due to the significant contrast between the refractive index of air and the cornea. Hence, in the case of abnormal corneas such as in keratoconus, the anterior surface accounts for the primary source of optical impairment (Hefner-Shahar et al., 2016). Total root-mean square is a measurement of the overall wavefront aberration of the eye. It is calculated by measuring the deviation of the wavefront from the ideal wavefront of a perfect eye. The calculation of total root-mean square includes both the lower-order aberrations (such as defocus and astigmatism) and higher-order aberrations (such as spherical aberration, coma, and trefoil).

Keratoconic eyes have five to six times more HOAs, especially coma-like aberrations, than in healthy eyes (Hefner-Shahar et al., 2016). The disturbances of HOAs in keratoconic eyes increases secondary astigmatism that further affect spherical aberrations. As the understanding of HOAs has advanced through wavefront imaging, we also understand the impact HOAs has on the visual quality, especially on the irregular cornea. HOAs represent the resultant imperfections which cannot be corrected with conventional optics and explains why patient with perfectly fitted optical aids still seemingly report unexplainable blur or night-vision disturbances (Lundquist & Yoon, 2021). Because the ectasis area of keratoconus often is located inferior on the cornea, these patients frequently describe vertical monocular ghosting.

With wavefront imaging, our comprehension of the optics associated with ocular function has increased. Light rays move through a vacuum in a linear fashion and subsequently reflect within the optical interfaces situated within the eye, such as the cornea or crystalline lens, prior to ultimately reaching the macula. If the light is disturbed with a change in direction the path obeys the “law of refraction” also known as “Snell’s law”, also described as “The proportion between sine values of angle of incidence and angle of refraction is a constant value” (Schechter, 1977). Most natural light

sources are polychromatic, meaning that the radiation is composed of more than one wavelength. In contrary, laser light is almost entirely (although not completely) monochromatic, meaning that it consists of a single wavelength or frequency. Wavefront analysis is performed using infrared light and can travel through ocular media and reflect on the retina. An optical wavefront aberration is defined as “a deviation from the predicted behaviour of a wavefront compared to the reference wave created in an optically perfect eye”. This distortion leads to imperfections or blur in the image viewed (Gatinel, 2007). Higher order aberration can be explained as imperfections in the wavefront optics, even with the best spectacle power selected.

5.6 Zernike Polynomials

Zernike polynomials are used in optometry and ophthalmology to portray wavefront aberrations in either the cornea or lens caused by deviating from a perfectly spherical shape, leading to refraction inaccuracies. These unique mathematical formulas have good corresponding relationships with classical aberrations, such as astigmatism, coma, and spherical aberration (Niu & Tian, 2022). The Zernike polynomials are ranged by order. First order (n=1) is not clinically significant. Second order (n=2) are the lower aberrations of defocus, or as we know them, myopia or hypermetropia and astigmatism. All other orders beyond n=2 is Higher Order Aberrations. The third order (n=3) is what we know as Coma like aberrations (Z3/3= vertical trefoil, vertical coma, horizontal coma), and is often described as an important measure due to its demonstrably large deviations when it comes to keratoconus (Koh et al., 2022). The name “coma” reflects the visual distortion of a comet like aberration when there is an irregularity in optical system. Trefoil and coma are both classified as a form of irregular astigmatism which results in an irregular or distorted wavefront (Unterhorst & Rubin, 2015). The fourth order (n=4) is the spherical aberration and by far the most visually significant of all the HOA. The higher order aberrations that are described to have the most deleterious effect of vision in the human vision is spherical aberrations (n=4), Coma (n=3), and trefoil (n=3) Figure 1.

Zernike polynomials pyramid

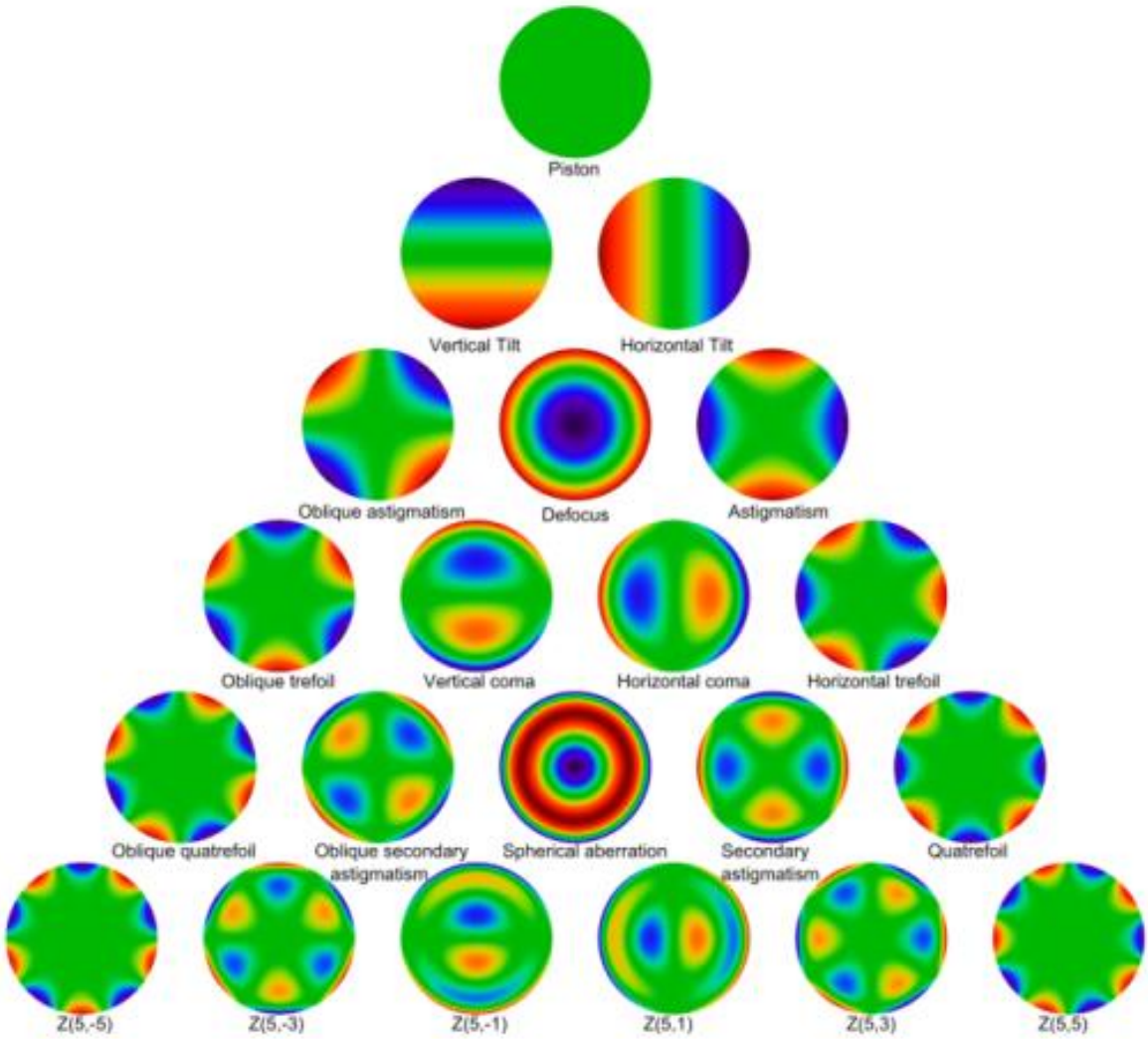


Figure 1 Zernike polynomials up to the fifth order, plotted on a unit circle. Picture credit: Comsol Multiphysics 5.2a Release highlights.

5.7 Quality of life

Progression of keratoconus is associated with changes that are not only limited to anatomical and morphological alterations. Development of keratoconus is also associated with decrease in optical quality and may sometimes result in reduced quality of life (Aydin Kurna, Altun, Gencaga, Akkaya, & Sengor, 2014; Kandel, Pesudovs, & Watson, 2020). There are several classifications system that consider optical and visual function (Alió et al., 2011; Jorge L Alió & Mohamed H Shabayek, 2006; T. T. McMahon et al., 2006), but the most proximate in this case was considered to be the Belin ABCD grading system (Belin & Duncan, 2016). Belin Ambrosio Enhanced Ectasia Display (BAD) is a grading system used to assess optical function in patients with keratoconus. BAD is a

sophisticated algorithm that uses corneal tomography data to provide a quantitative analysis of corneal shape and thickness. The BAD grading system uses the ABCD classification to evaluate the severity of keratoconus. Keratoconus severity is graded based on four variables: A stands for asymmetry, which measures the difference between the steepest and flattest curvature of the cornea (anterior and posterior corneal radius). B represents the best fit sphere (BFS) and measures the difference between the actual corneal shape and a hypothetical perfect sphere (curvature of the 3.0 mm central zone of the thinnest corneal location). C measures the corneal thickness at the thinnest point (thinnest pachymetry), and D is the deviation map, which measures the irregularity of the corneal surface (distance best corrected visual acuity). This grading system is integrated in the Oculus Pentacam Scheimpflug-based system (Pentacam HR, Oculus Optikgeräte GmbH, Münchholzhäuser).

Research questionnaires such as Pinto et al. (2021), stated that that BCVA in the better eye and history of crosslinking are factors associated with higher quality of life. Additionally, studies have examined the impact of rigid gas-permeable contact lenses (RGP) on quality of life for keratoconus patients (Aydin Kurna et al., 2014; Sara Ortiz-Toquero et al., 2016). It is possible that higher corrected distance visual acuity (CDVA) with RGP contact lenses, and independence from spectacles may account for these findings. However, recent studies suggest that wearing contact lenses may elicit an inflammatory response in the tears of keratoconus patients (Aydin Kurna et al., 2014; Efron, 2017; Walker, Lema, & Redfern, 2020). Therefore, the question remains of whether it is possible to improve the quality of life for these patients without using contact lenses or spectacles (Efron, 2017; Walker, Lema, & Redfern, 2020).

Further, visual quality depends on the perfection of the whole optical system to create a stigmatic image. High values of Kmax, MRSE and low visual acuity is an expression of disease severity, and these eyes is more likely to be associated with improved visual and tomographic outcomes (Wajnsztajn, Shmueli, Zur, Frucht-Pery, & Solomon, 2022).

5.8 Treatment

There is currently no cure for keratoconus. Improving the visual acuity and delaying the development of the disease are the main clinical intervention purposes (Zhang & Li, 2020). Empirically, the treatment of keratoconus consisted of optimalisation with optical aids such as glasses and/RGP contact lenses (Colin & Velou, 2002).

In the era prior to CXL, the only options available for management of keratoconus were RGP lenses or surgery. If a patient was unable or intolerant to wear contact lenses, the next resort was typically surgical intervention, such as full penetrating corneal graft (PK) or endothelial keratoplasty (DALK) (Colin & Velou, 2002). In Europe, keratoconus is the main reason for corneal transplantation (Matthaei et al., 2017). It is often a successful surgery; graft survival rates are over 90% after 10 years and the average life of a transplant is around 15-20 years (Henein & Nanavaty, 2017). However, corneal transplantation should only be performed if it is necessary (Gediz, Yüksel, Küsbeci, Akmaz, & Kartı, 2019). For the past two decades there have been remarkable advancements in the treatment and management of keratoconus, especially with the introduction of CXL which stops the progression of the disease.

The severity of keratoconus is reflected by classified based morphological features, ocular signs, and index-based systems (Santodomingo-Rubido et al., 2022). At the same time there are some limitations when it comes to high severity of the disease and performance of CXL. For example, pachymetry is an important factor when deciding whether it is safe to proceed with the CXL treatment, to thin corneas should not be treated. Guidelines seem to vary, but the Norwegian study by Chen, Stojanovic, Eidet, and Utheim (2015) recommended $\geq$400 µm as threshold. This is also confirmed in other studies (Kankariya, Kymionis, Diakonis, & Yoo, 2013; Kapasi, Baath, Mintsioulis, Jackson, & Baig, 2012).

CXL offers a conservative and minimally invasive approach to tackling progressive keratoconus, allowing us to combine different methods of treatment. Though contact lenses may still be necessary in most cases, CXL provides stabilization that allows for additional time to identify the most effective visual correction options. It is important to individualize the treatment and it is likely that surgical treatment to better vision in addition to the CXL treatment will be more common (Morgenstern, Chang, & Eiden, 2020). Although refractive surgery is not recommended for those with progressive keratoconus, there are several surgical interventions described in the literature that can lead to improved visual outcomes for those with stabilized keratoconus (Kankariya et al., 2020).

5.9 CXL

The concept of CXL was introduced by Theo Seiler and Eberhard Spoerl in 1998, who discovered that the corneal collagen fibres could be crosslinked using riboflavin and UV-A radiation (Spoerl, Huhle, & Seiler, 1998). The presence of riboflavin combined with ultraviolet-A light induces a

photochemical reaction in the corneal stroma leading to a more covalent connection between collagen fibres and hence, stabilizing the cornea and improving collagen structure (Raiskup, Theuring, Pillunat, & Spoerl, 2015). The first clinical trials of CXL were conducted in 2003 and became revolutionary with long-term stabilization topographically. Since then, numerous studies have been published evaluating its efficacy and safety. According to Wollensak et al. (2003), this method of treatment has been used in a range of corneal afflictions, such as keratoconus and corneal ectasia. Furthermore, it is the primary, first-line treatment with the objective of preventing the advancement of keratoconus. As McGhee et al. (2015) have noted, the focus of keratoconus treatment has shifted to preventing its progression and enhancing visual acuity.

There are two main techniques for performing CXL: epithelium-off (epi-off) and epithelium-on (epi-on). Epi-off CXL involves removing the corneal epithelium prior to the application of riboflavin and UV-A radiation, while epi-on CXL involves leaving the epithelium intact. Epi-off CXL is the more common technique and has been the gold standard for many years due to its efficacy in stopping the progression of keratoconus. However, it has some disadvantages, including pain, delayed visual recovery, and an increased risk of infection. Epi-on CXL was introduced as an alternative to epi-off CXL to address these issues and have gained popularity in recent years (Cifariello et al., 2018). Cifariello et al. (2018) found that both treatment modalities are equivalent in terms of results and related complications, and therefor concluded that the CXL epi-on technique was preferable to CXL epi-off. However, Epi-off CXL has been shown to provide better regularisation of the corneal surface and an improvement of HOAs compared to epi-on CXL (Arance-Gil, Villa-Collar, Pérez-Sanchez, Carracedo, & Gutiérrez-Ortega, 2021)

The conventional Dresden Protocol (C-CXL) is performed by removing the epithelial layer evenly with Amoils brush to let the riboflavin penetrate the stromal tissue prior to ultraviolet-A (UVA) light to increase the biomechanical corneal stability (Kankariya et al., 2020; Subasinghe, Ogbuehi, & Dias, 2018). However, the C-CXL procedure does not rehabilitate the visual function. Patients with complex visual challenges or issues with contact lenses will still face the same visual struggles as pre-surgery (Kankariya et al., 2020). Therefore, the concept of additional refractive procedures was introduced to improve the optical insufficiency by decreasing the irregular astigmatism, correct the residual refractive error and improve visual function for patient with keratoconus.

In 2011 Kymionis introduced the term “CXL plus”. This was a concept designed to ensure visual recovery by incorporate adjunctive use of refractive surgery in addition to CXL to improve

functional visual outcome in keratoconus patients. Among known refractive procedures is conductive keratoplasty (CK), intrastromal corneal ring segments implantation (ICRS), phakic intraocular lens (PIOL), photorefractive keratectomy (PRK) and transepithelial phototherapeutic keratectomy (t-PTK) (Kankariya et al., 2020). Of these, phakic intraocular lens (PIOL) and photorefractive keratectomy (PRK) have been the most widely studied (Fernández-Vega-Cueto et al., 2017; Kim & Mian, 2020). Of the authors knowledge, none of these alternative treatments have challenged the C-CXL method as gold standard treatment for keratoconus.

5.10 PTK

The phototherapeutic keratectomy (PTK) procedure involves removing a small amount of corneal tissue with an excimer laser. PTK treatment is commonly used for conditions as recurrent epithelial erosions, corneal dystrophies, spheroidal dystrophies, corneal scars, superficial corneal opacities, and keratoconus. In general, PTK is considered to be a superficial treatment and a minimal invasive procedure and often successful in preventing or delaying more invasive corneal surgery (Rapuano, 2010). The term and concept for treatment of corneal pathologies, *Phototherapeutic* keratectomy (PTK), was introduced secondly to the excimer laser treatment for refractive errors, *Photorefractive* keratectomy (PRK). The primary clinical interest and outcomes of PTK treatment is precisely and accurately removal of the superficial corneal layers, the epithelial and bowman's membrane, leaving the underlying stroma clear and untouched (Deshmukh, Reddy, Rapuano, & Vaddavalli, 2020). The procedure is typically performed under local anaesthesia, and the patient may experience some discomfort and sensitivity to light in the days following the procedure (Gaster, Ben Margines, Gaster, Li, & Rabinowitz, 2016)

PTK treatment was approved by the United States Food and Drug Administration (FDA) in 1995 with requirement of postoperative residual stroma thickness of 250 µm (Deshmukh et al., 2020). However, recent research suggests a residual corneal thickness of 350-400 µm to prevent development of ectasia (Wilson, Marino, Medeiros, & Santhiago, 2017).

Although complications associated with PTK are infrequent, postoperative infection is the most feared. Generally, haze is not a major concern, but there may be instances of scar tissue forming in the cornea following previous surgery (Fagerholm, 2003). Contraindications for treatment is history of postoperative healing process, severe dry eye, ocular surface disease and eyelid malfunction, as well as systemic diseases such as diabetes mellitus and vascular diseases (Nagpal et al., 2020).

The Cretan PTK CXL protocol combines two techniques: transepithelial phototherapeutic keratectomy (t-PTK) and CXL. And while the Dresden protocol procedure consists of brushing off only a thin layer of the epithelium (central 6–7 mm of corneal epithelium), the Cretan protocol procedure involves an even, and smooth removal of 65 µm tissue, regardless of tissue layer. Previous research has indicated that in order to perform phototherapeutic and photorefractive keratectomy a corneal thickness of 400 µm or more is required, even after epithelial removal (Kankariya et al., 2020; Kapasi et al., 2012; Kapasi, Dhaliwal, Mintsioulis, Jackson, & Baig, 2016).

5.11 Previous studies

There are few studies combining t-PTK and CXL. Studies and case reports by Kapasi et al. (2012) and G. D. Kymionis et al. (2012) conclude that epithelial removal using t-PTK during CXL resulted in better visual and refractive outcomes compared to mechanical epithelial debridement. In contrary, Gaster et al. (2016) reported no statistically significant difference in visual, refractive, or keratometric outcomes when comparing the two methods in a retrospective comparison study. None of these studies included aberrations as a predictor- or outcome variable. Hypothetically because detections of HOAs only can be detected with wavefront aberrometers (Lin, Chen, & Lee, 2013). However, one study that did include aberrometric values and clinical outcomes of t-PTK + CXL treatment were the Norwegian researcher Chen et al. (2017) who precented results of a positive effect after treatment.

Through a MEDLINE PICO search most of the existing literature comparing the two methods is from the United States [n=5]: (Gaster et al., 2016; Michael A. Grentzelos et al., 2017; M. A. Grentzelos et al., 2019; George D. Kymionis et al., 2014; G. D. Kymionis et al., 2011), from Canada [n=2]: (Kapasi et al., 2012; Kapasi et al., 2016), one study from Turkey [n=1]: (Sarac et al., 2018) and one Norwegian study [n=1]: (Chen et al., 2017).

Treatment for keratoconic corneas typically involves addressing three main concerns: stopping the progression of the disease, improving the irregular shape of the cornea, and reducing remaining refractive errors. The approach taken depends on factors including whether the keratoconus is worsening, the severity of corneal irregularities and resulting vision problems, and the level of refractive error present (Fernández-Vega-Cueto et al., 2017). This study aims to examine evidence of surgical treatment as an option for keratoconus that achieve both therapeutic and refractive outcomes.

6 Methods

6.1 Study design

The study has a comparative, retrospective design, analyzing, single-center data from patients received combined t-PTK and CXL treatment (from now on called t-PTK+CXL) and patients received C-CXL (from now on called CXL).

6.2 Setting

This study was performed at St. Olavs Hospital, Trondheim University Hospital based on quality assessment of treatment of patients in the period January 2019 to June 2022.

St. Olav's University Hospital is a part of the Norwegian healthcare system located in Trondheim, Norway. The hospital has about 10,000 employees and covers the region of Central Norway. The hospital is affiliated with the Norwegian University of Science and Technology and provides both specialized and general healthcare services. St. Olav's University Hospital is one of the largest hospitals in Norway, and it is known for its advanced medical treatments and research programs. CXL treatment is not performed at local hospitals in the district and the patient ranges from surrounding Ålesund in south to Mo i Rana in north.

Parts of this thesis have been presented in the project protocol as the final exam in MRES019 Research Methods (Pia Victoria Haugum Ekker, 2022) at USN (unpublished).

6.3 Surgical procedure

All treatments are performed at St. Olavs Hospital, Trondheim University Hospital. The t-PTK+CXL treatment was performed by two surgeons (D.S and H.M), and the CXL treatment by procedures were performed by five surgeons (JIL, NN, PE, DS, HM).

6.3.1 Dresden protocol: CXL

Alcaine, Pilocarpine and Cilox are initially applied. Eyelid lock. The epithelium is removed with Amoil's brush. Intraoperative ultrasound pachymetry control performed before initializing Riboflavin 0.1% solution was instilled every 3 minutes for approximately 30 minutes. Penetration of the cornea and presence of riboflavin in the anterior chamber (riboflavin shielding) were monitored by slit-lamp examination. After 30 minutes, uniform saturation of the stroma and flare in the anterior chamber are verified. Intraoperative ultrasound pachymetry control was performed, and

if pachymetry was below 400 microns there would be an elongation of Riboflavin procedure. UVA irradiation was performed using a commercially available UVA optical system (UV-X illumination system version 2000, Beam optimizer) with a light source consisting of an array of UV diodes (365 nm +/- 10 nm) with a potentiometer in series to allow regulation of voltage. UV illumination, 9mW, 10 minutes in a 7.5 mm zone to a total radiation dose of 5.4 mJ/cm2. During treatment, riboflavin solution was applied every 2-3 minutes to saturate the cornea with riboflavin. Postoperative Atropine and Cilox, as well as a silicon-hydrogel bandage contact lens (Lotrafilcon B, Air Optix, Ciba Vision—14.0 mm diameter, 8.6 base curvature, and Dk = 140 barrers) was applied until full re-epithelialization. CXL-epithelium off was used for all the surgeries.

After treatment, on the day of the operation, artificial tear fluid is used every 10 minutes for 3 hours. Spersadex with Chloramphenicol x4 for 10 days. Then Spersadex x3 for a week, then x2 for a week, then x1 for a week. Paralgin Forte up to 3 times a day for the first few days. Artificial tear fluid if needed. Received with 2 ampoules of Oxybuprocaine and Chloramphenicol for use for pain the same day.

6.3.2 Cretan protocol: t-PTK combined CXL

Alcaine, Pilocarpine and Cilox are initially applied. Eyelid lock. Epithelium was removed by t-PTK. An Excimer laser system with a 750 Hz pulse rate and PTK-CAM (Schwind Amaris 750S) was used for the procedure. The t-PTK ablation was performed in an 8.5 mm zone in an intended depth of 65 μm. Intraoperative ultrasound pachymetry control performed before initializing Riboflavin 0.1% solution was instilled every 3 minutes for approximately 30 minutes. Penetration of the cornea and presence of riboflavin in the anterior chamber (riboflavin shielding) were monitored by slit-lamp examination. After 30 minutes, uniform saturation of the stroma and flare in the anterior chamber are verified. Intraoperative ultrasound pachymetry control was performed, and if pachymetry was below 400 microns there would be an elongation of Riboflavin procedure. UVA irradiation was performed using a commercially available UVA optical system (UV-X illumination system version 2000, Beam optimizer) with a light source consisting of an array of UV diodes (365 nm +/- 10 nm) with a potentiometer in series to allow regulation of voltage. UV illumination, 9mW, 10 minutes in a 7.5 mm zone to a total radiation dose of 5.4 mJ/cm2. During treatment, riboflavin solution was applied every 2-3 minutes to saturate the cornea with riboflavin. Postoperative Atropine and Cilox, as well as a silicon-hydrogel bandage contact lens (Lotrafilcon B,

Air Optix, Ciba Vision—14.0 mm diameter, 8.6 base curvature, and Dk = 140 barrers) was applied until full re-epithelialization. CXL-epithelium off was used for all the surgeries.

After treatment, on the day of the operation, artificial tear fluid is used every 10 minutes for 3 hours. Spersadex with Chloramphenicol x4 for 10 days. Then Spersadex x3 for a week, then x2 for a week, then x1 for a week. Paralgin Forte up to 3 times a day for the first few days. Artificial tear fluid if needed. Received with 2 ampoules of Oxybuprocaine and Chloramphenicol for use with pain the same day.

6.4 Patient

All patients with progressive keratoconus who received CXL treatment were include in the period from January 2018 to June 2022 at St. Olavs Hospital, Trondheim University Hospital, Norway. The patients were appropriately informed about possible outcomes, expected result, current clinical experience and given written information about the treatment preoperatively. All eyes treated [n=349] was assigned an ID number for identification. All those who met the criteria of preoperative control, completed treatment, and postoperative control/controls are included [n= 298]. Exclusion criteria were defined as follows: other sight-threatening ocular disease, systemic disease (not including atopic dermatitis), previous surgery, post-LASIK ectasia and pregnancy. Those who met the exclusion criteria was two eyes with postoperative related keratitis, one eye with second time CXL treatment, three eyes with post-LASIK ectasia, and those with incomplete datasets. The t-PTK+CXL group included 155 eyes (30 eyes excluded), and the CXL group 143 eyes were included (21 eyes excluded).

6.5 Examination protocol

Tomographic measures were an important factor to define and diagnose keratoconus. A Pentacam HR, Oculus Optikgeräte GmbH, Münchholzhäuser was used to detect increase in K values: K1, K2 and K max (Pentacam HR, Oculus Optikgeräte GmbH, Münchholzhäuser), and/or change in the map difference in K values between two or several consecutive readings (Pentacam HR, Oculus Optikgeräte GmbH, Münchholzhäuser), decrease in central thickness (Pentacam HR, Oculus Optikgeräte GmbH, Münchholzhäuser), and/or deterioration of CDVA or uncorrected visual acuity (defined as a drop of one or more lines on the Snellen chart, that is not attributed to other ocular disorders), and/or significant changes in the magnitude of spherical equivalence, myopic or

astigmatic refraction (that are not attributed to any other optical system disorders) and/or statistical probability of progression
and/or subjective progression combined with clinical signs.

6.6 Refractive procedure

All patients had full ophthalmological examinations with anterior and posterior examination preoperatively slit lamp exam (Slit Lamp BX 900, Haag-Streit AG), eye fundus examination, intraocular pressure measured by ICare tonometry, corneal tomography (Pentacam HR, Oculus Optikgeräte GmbH, Münchholzhäuser), and corneal thickness (Pentacam HR, Oculus Optikgeräte GmbH, Münchholzhäuser). Patients were asked to not wear their contact lenses 2 weeks prior to the ocular assessment or surgery. All patients were offered "epi-off" standard CXL or t-PTK+CXL procedure after information on steps of the procedure, expected effect of the procedure and possible postoperative complications.

Visual acuity described as "finger count", "<0.05", or "not possible to measure" was noted as 0.0. Visual acuity was expressed as Snellen decimals and at distance. Spherical equivalent (SE) was the refractive error by formula: Sphere + (½ x cylinder) and is referred in diopters (D). K_1, and K_2 was expressions of the flattest meridian, steepest meridian respectively. K-Max is the steepest point over the anterior surface. All measures are in dioptres (D). Pachymetry describes the thickness of the total corneal tissue and is measured in microns (µm). A higher number of values means a thicker cornea, and lower value means thinner. The root mean square (RMS) values for the total high-order irregularity were calculated. Aberrometric values, including RMS total, higher order aberrations (HOAs) and spherical aberrations (Z40) was expressed in micrometers (µm).

6.7 Data collection

All the data was collected retrospectively fromthe St. Olavs Hospitals journal system, "DocuLive". Following surgery codes was filtered in the period 01.01.2018 - 30.06.2022: "CXL"," CXL+PTK", "PTK + CXL" and "PTK" "Operasjonsplanlegger" software. Identifying 349 patients that had CXL *or* PTK-CXL treatment. All dates of treatment, full patient name, date of birth, and the eye treated was systematically organized in an Excel spreadsheet. For identification each patient was assigned a unique id-number ranging from 1 to 349. Personal data was stored as a password secured file in a local server at the hospital.

After patient identification, all patient records were carefully reviewed to retrieve relevant information. Information from the “operasjonsplanlegger”- spreadsheet was crosschecked regarding eye treated and treatment preformed. For each visit, available tomographic measurements were required for the data to be included and eligible for analysis. Data from patient records were manually filtered and validated as eligible data according to following criteria; available data for pre- and post-examination (minimum one and maximum three) including unaided visual acuity (UDVA), spherical power, astigmatic values, axis, and best corrected aided visual acuity (BCVA).

Further a new Excel spreadsheet was created without recognizable patient identification where each patient was identified by a number. The patient's ID number from this stage of collection accompanies the patient throughout the entire analysis process, start to end. Relevant data on each patient was collected from the patient's medical records. Preoperative measures were noted with values closest to the date of treatment. All postoperative data were logged by date and later sorted by time interval. Medical records were not standardized, and each journal was evaluated and matched to the keratometric data in Pentacams viewer tool. On average, it took 20-25 minutes (n 349) to collect data for each patient. Data collected during this procedure included date of Pre-examination, unaided visual acuity (UDVA), spherical power, astigmatic values, axis, best corrected aided visual acuity (BCVA) and date of treatment. Post operatively date of follow-up (minimum one and maximum three), unaided visual acuity (UDVA), spherical power, astigmatic values, axis, and best corrected aided visual acuity (BSCVA). Along with eye treated, sex, age, operator, and optometrist for each visit were all noted.

Tomographic readings were measured with the same Pentacam HR (Oculus Optikgeräte GmbH, Münchholzhäuser) on all patients. Pentacam HR is based on Scheimpflug imaging and creates a series of keratoconus-specific indices. Ocular, corneal, and internal higher-order aberrations were measured through a sixth-order Zernike polynomial decomposition. The maximum diameter in the Zernike analysis was the central 6 mm. To find additional tomographic values, all patients had to be re-searched in Pentacams own Viewer Software. The patient's date of birth and full name were used as identification to locate the patient in Pentacam Viewer software as this information was not connected to the medical records. Dates of valid measurements were paired to Pentacam images where measurements were noted for each visit; pre-examination and follow-ups with associated refractive measurements (minimum one, maximum three postoperatively). Measurements obtained in this step were steepest radius of anterior curvature. K-value (Kmax), pachymetry, flattest

keratometry value (K1), steepest keratometry value (K2), Root mean square aberrations (RMS Total), corneal higher order aberrations (RMS HOAs) and spherical aberrations (Z40).

6.8 Statistical analysis

All data were statistical analysed in Excel Software (Microsoft Corp.) and using R version 4.2.1. A p-value less than 0.05 was considered statistically significant. The data is continuous, sample data do not show normal distribution by The Shapiro-Wiik test and because the data were not normally distributed the non-parametric Wilcoxon signed-rank paired test was considered. However, the sample size indicated that a normality with non-parametric tests were not necessary. The groups are independent meaning they samples contain different set of measures in each sample. Therefore, a paired t-test was the more appropriate to get correct p-values when testing preoperative and postoperative values. To compare postoperatively results between the two treatments in the same interval, the difference was calculated in excel and analysed in a two-tailed independent sample t-test. Descriptive evaluation of data was performed using mean and standard deviation and 95% confidence interval. All preoperative measurements were noted with the measurement closest to treatment date. Postoperative measurements were noted by date, and then include if the follow-up was included within the interval 12±6 months.

6.9 Ethics

This study was approved by NSD with an application for approval through St. Olavs Hospital, Trondheim University Hospital. The study was approved by NSD (Norsk Senter for Forskningsdata) June 2022/ 101050. The approval included an appendix that systematically listed all the measurements that were necessary to retrieve from the patient records to complete the study. Additionally, the application included a time frame of when data was expected to be collected, as well as an end date for collection (set to June 2023). The wording of the approval is that the information collected is based on quality assurance of treatment within the hospital. But the approval also includes permission to present the result in a master's thesis under supervision of the supervisor employed by the University of South-East Norway. The data was processed according to the Helsinki declaration.

7 Result

The mean (SD) age of patients at the time of treatment was 24.56 (±7.33). Mean (SD) age in the t-PTK+CXL group was 24.43 ±6.18 and mean (SD) age in the CXL group was 24.74 ±8.42. Mean age in the t-PTK+CXL group was 24.74 (±8.42).

Of these, 51 % [n=151] were right eyes and 49 % [n=147] were left eyes. There were 298 eyes of 220 patients that met the criteria for inclusion. The distribution between treatments was 48 % [n=143] CXL and 52 % [n=155] t-PTK+CXL. All patients treated in both right and left eye had the same treatment in both eyes, CXL *or* t-PTK+CXL.

In total there were 20 % women [n= 60] and 80 % men [n=238]. In the CXL treatment group there were 21% women [n=31] and 79 % men [n=112]. In the t-PTK+CXL treatment group there were 19 % women [n=29] and 81 % men [n=126].

The t-PTK+CXL treatment was performed by two surgeons, DS (55%) [n=86] and HM (45%) [n=69]. The CXL treatment was performed by five operators NN (50%) [n=72], JIL (25 %) [n=36], PE (11%) [n=15], DS (8%) [n=11], HM (6%) [n=9].

Table 1 Visual, refractive, tomographic, aberrometric, and densitometric parameters at baseline and 12 ±6 months postoperatively in eyes treated with central corneal regularization combined with corneal cross-linking and in eyes treated with corneal cross-linking as a single procedure.

	t-PTK+CXL baseline (n = 155)	t-PTK +CXL 12±6 months (n=107)	P1-value baseline- t-PTK+CXL (12mth±6)	CXL baseline (n = 143)	CXL group 12±6 months (n = 102)	P2-value baseline-CXL (12mth±6)
	Baseline	12 months follow-up		Baseline	12 months follow-up	
	Mean (SD)	**Mean (SD)**		**Mean (SD)**	**Mean (SD)**	
Sex *(% female)*	19%[n=29]	16% ±18		22 %[n=31]	26% ±27	
Age	24.43 ±6.18			24.74 ±8.42		
UDVA *(Snellen)*	0.41 ±0.24	0.67 ±0.32	< 0.001	0.50 ±0.35	0.54 ±0.38	0.001
CDVA *(Snellen)*	0.96 ±0.20	1.03 ±0.19	0.004	0.90 ±0,31	0.92 ±0.31	0.17
Refractive values						
MRSE(D)	0.51 ±1.35	0.08 ±1.36	<0.001	0.30 ±1.74)	0.16 ±2.00	0.41
Sphere (D)	2.30 ±1.68	1.13 ±1.53	<0.001	2.03 ±2.29	1.82 ±2.43	0.1
Cylinder subj.(D)	-3.58 ±1.60	-2.08 ±1.51	<0.001	-3.50 ±2.66	-3.29 ±2.70	0.7
Corneal thickness						
Pachymetry (µ)	477.79 ±28.15	460.47 ±34.40	<.0.001	458.79 ±44.93	451.45 ±50.91	<0.001
Curvature values						
K1 (D)	43.92 ±2.40	43.04 ±2.09	<0.001	45.19 ±4.41	44.72 ±4.19	<0.001
K2 (D)	46.89 ±3.02	46.01 ±2.78	<0.001	48.27 ±5.49	47.86 ±5.21	<0.002
AST.	-2.96 ±1.51	-3.00 ±1.48	0.83	-3.08 ±2.05	-3.13 ±2.19	0.41
K-max (D)	53.15 ±4.3	50.99 ±4.68	<0.001	53.92 ±8.26	53.74 ±8.47	<0.001
Aberrometric Values						
Cornea Total						
RMS Total (µm)	10.605 ±4.265	8.553 ±4.421	<0.001	11.326 ±7.375	10.874 ±9.270	<0.001
HOAs (µm)	2.645 ±1.127	2.162 ±1.151	<0.001	2.884 ±1.917	2.162±1.148	<0.001
Z40 (µm)	-0.245 ±0.570	-0.004 ±0.469	<0.001	-0.441 ±0.959	-0.343 ±0.952	0.002

CXL= corneal cross-linking; t-PTK+CXL= central corneal regularization combined with CXL; UDVA= uncorrected distance visual acuity. The results are expressed as means (standard deviation =SD); CDVA= best spectacle-corrected distance visual acuity; MRSE= mean refractive spherical equivalent. K1= flattest meridian, K2= steepest meridian, AST= corneal astigmatism, K-max= steepest radius of anterior curvature. RMS total= total root mean square; HOAs= higher order aberrations; Z40 Spherical aberrations. The level of statistical significance was set at $p \leq 0.05$. p1= p-value t-PTK+CXL baseline compared to 12±6 months postoperatively, p2: p-value CXL baseline compared to 12±6 months postoperatively.

Table 2 Visual, refractive, tomographic, aberrometric, and densitometric parameters at baseline and 12 ±6 months postoperatively in eyes treated with central corneal regularization combined with corneal cross-linking and in eyes treated with corneal cross-linking as a single procedure.

	P1-value t-PTK+CXL – CXL pre-operatively	P2-value t-PTK+CXL – CXL 12±6mth post-operatively
UDVA *(Snellen)*	0.02	<0.001
CDVA *(Snellen)*	<0.05	0.262
Refractive values		
MRSE(D)	0.25	0.005
Sphere (D)	0.25	<0.001
Cylinder subj.(D)	0.63	<0.001
Corneal thickness		
Pachymetry (µ)	<0.001	<0.001
Curvature values		
K1 (D)	0.003	<0.001
K2 (D)	0.01	<0.001
AST.	0.6	0.69
K-max (D)	<0.05	<0.001
Aberrometric Values		
Cornea Total		
RMS Total (µm)	0.3	<0.001
HOAs (µm)	0.2	<0.001
Z40 (µm)	0.4	0 .002

CXL= corneal cross-linking; t-PTK+CXL = central corneal regularization combined with CXL; UDVA= uncorrected distance visual acuity. The results are expressed as means (standard deviation =SD); CDVA= best spectacle-corrected distance visual acuity; MRSE= mean refractive spherical equivalent. K1= flattest meridian, K2= steepest meridian, AST= corneal astigmatism, K-max= steepest radius of anterior curvature. RMS= root mean square; HOAs= higher order aberrations; Z40 Spherical aberrations. The level of statistical significance was set at $p \leq 0.05$, p1 = the difference between groups at baseline p-values. p2 = the difference between treatments 12 ±6 months postoperatively p-values.

7.1.1 Thinnest pachymetry

Preoperative pachymetry showed significant difference when comparing preoperative measures Table 2. Preoperatively mean (SD) was 468.67 (±38.29) in both groups combined. Postoperative mean (SD) was 456.07 (±43.38) in both groups combined.

Preoperative pachymetry in the CXL group was ranging between 368µm and 562µm. Mean (SD) pachymetry below 400 µm was 386 (±9.0) [n=13]. Preoperative pachymetry in the t-PTK+CXL was ranging between 420µm and 549µm. No eyes had pachymetry measures below 420µm in the t-PTK+CXL group.

The CXL group showed an improvement with a mean (SD) 21.54 (±20.56) [n=73] and a decrease of mean (SD) 9.46 (±7.19) [n=25] when comparing pre- and postoperative results.

The t-PTK+CXL group showed an improvement with mean (SD) 26.11 (±20.63) [n=94] and a decrease of mean (SD) 20.00 (±21.11) [n=8] when comparing pre- and postoperative results.

Both the CXL group and the t-PTK+CXL group showed significant difference postoperatively compared to baseline Table 1 and compared to each other 12±6 months postoperatively Table 2.Table 1.

7.2 Refractive values

7.2.1 Unaided visual acuity (UDVA)

There was no significant difference between treatments preoperatively at baseline Table 2. Preoperatively the UDVA in CXL group ranged between 0.0 and 1.2 Snellen lines. The t-PTK+CXL ranged between 0.0 and 1.0 Snellen lines.

In the CXL group there was significant difference from baseline compared to postoperatively Table 1. In the CXL group the mean (SD) improvement by increase of UDVA was 0.24 (±0.20) [n=45]. In all, 37 eyes had no change and mean (SD) adverse outcome was 0.13 (±0.09) [n=20]. Within the range 0.5 Snellen line to 1.0 Snellen line in the CXL group the mean (SD) of UDVA was 0.81 (±0.22) [n=56]. In the CXL group the mean (SD) increase of 3 Snellen lines or more was 0.48 (±0.2) [n=8]. The mean increase of 2 Snellen lines or more was 0.39 (±0.2) [n=24].

In the t-PTK+CXL group there was significant difference from baseline compared to postoperatively Table 1. In the t-PTK+CXL group the mean (SD) improvement by increase of UDVA was 0.37 (±0.26) [n=83]. In all, 15 eyes had no change in UDVA. Mean (SD) adverse outcome of UDVA was 0.14 (±0.09) [n=9]. Within the range 0.5 Snellen line to 1.2 Snellen line in the t-PTK-CXL group the mean (SD) of UDVA was 0.80 (±0.22) [n=78]. In the t-PTK+CXL group the mean (SD) increase of 3 Snellen lines or more was 0.53 (±0.22) [n=53]. The mean increase of 2 Snellen lines of more was 0.45 (±0.24) [n=71].

In the CXL group 2% showed an improvement of UDVA with an increase between 0.5 to 0.8 Snellen lines. Additionally, 10 % [n=10] in the CXL group went from the 0.4 Snellen line or less to the 0.5 Snellen line or better. In the t-PTK+CXL group 23% showed improvement of UDVA with an improvement in the same interval: increase between 0.5 to 0.8 Snellen lines. Additionally, 36 % [n=39] in the t-PTK+CXL group went from the 0.4 Snellen line to the 0.5 Snellen line or better. In other words, there was over three times the chance to get a visual acuity of 0.5 Snellen line or better in the t-PTK+CXL group compared to the CXL group after treatment.

In a two tailed independent t-test there was significant difference between the two treatments postoperatively Table 2Table 1.

7.2.2 Corrected visual acuity (CDVA)

There was significant difference between treatments preoperatively at baseline Table 2. Preoperatively the CDVA in the CXL group ranged from the 0.1 to the 1.5 Snellen line. In the t-PTK+CXL group the CDVA ranged from the 0.3 to the 1.5 Snellen line. Within the range 0.5 to 1.2 Snellen line the mean (SD) of the CXL group was 0.9 (±0.31) and mean (SD) in the same interval in the t-PTK+CXL the mean (SD) was 0.9 (±0.31). In other words, preoperatively both groups showed similar mean and standard deviation Table 1.

Postoperatively the CXL group showed no significant difference compared to baseline with a total range from the 0.05 to the 1.5 Snellen line Table 1. The mean (SD) increase of CDVA in the CXL group was 0.29 (±0.16) [n=26]. In all, 55 (54%) eyes had no change. Mean (SD) decrease of CDVA was 0.24 (±0.16) [n=21]. In the range between 0.5 and the 1.0 Snellen line in the CXL group the mean (SD) of UDVA was 0.93 (±0.31) [n=93]. In the CXL group the mean (SD) increase of 3

Snellen lines or more was 0.41 (±0.11) [n=9]. The mean (SD) of 2 Snellen lines or more was 0.35 (±0.35) [n=20].

Postoperatively the t-PTK+CXL group showed significant difference compared to baseline with a total range from the 0.5 to the 1.5 Snellen line Table 1. The mean (SD) increase of CDVA in the t-PTK+CXL group was 0.3 (±0.16) [n=48]. In all, 37 eyes (34%) showed no change. Mean (SD) decrease of CDVA in the same group was 0.30 (±0.21) [n=22]. In the range between the 0.5 and the 1.0 Snellen line in the t-PTK+CXL group the mean (SD) of UDVA was 0.9 (±0.31) [n=105]. In the t-PTK+CXL group the mean (SD) increase of 3 Snellen lines or more was 0.42 (±0.12) [n=14]. The mean (SD) of 2 Snellen lines or more was 0.36 (±0.14) [n=34].

The t-PTK+CXL group showed a lower reduction of visual acuity with a maximum reduction of three Snellen lines ranging from 0.05 to 0.3 Snellen lines (with exception form one outliner of 0.7 Snellen lines), while the CXL group showed a greater range of adverse outcomes from 0.05 to 0.6 Snellen lines.

There was no statistically significant difference between treatments 12±6 months postoperatively Table 2.

7.2.3 Manifest spherical equivalent (MRSE)

There was no significant difference between treatments preoperatively Table 2.

Preoperative MRSE in the CXL group was ranging from +4.00 D to -9.88 D. There were 60 % with hyperopic MRSE and a mean (SD) of +1.75 (±1.05) [n=86]. There were 4 eyes (2.8%) with Plano and 37% with myopic MRSE with a mean (SD) of -2.26 (±2.46) [n=53].

Postoperatively the CXL group showed no significant difference compared to baseline Table 1. At 12±6 months follow-up the CXL groups MRSE was ranging from +4.25 D to -11.00 D. The mean (SD) MRSE was 0.16 (±2.00). There were 58% with hyperopic MRSE and a mean (SD) of +1.77 (±1.23) [n=59]. There were 5 eyes (5%) with Plano, and 37% with myopic MRSE with a mean (SD) of -2.38 (±2.60) [n=38].

Preoperative MRSE in the t-PTK+CXL group was ranging from +4.00D to -7.13 D. There were 74 % with hyperopic MRSE and a mean (SD) of +1.56 (±0.97) [n=116]. There were 5 (3%) eyes with Plano, and 22% with myopic MRSE with a mean of mean (SD) -1.92 (±1.9) [n=34].

Postoperatively the t-PTK+CXL group showed significant difference compared to baseline Table 1. At 12±6 months follow-up the t-PTK+CXL groups MRSE was ranging from +4.50D to -5.25D. The mean (SD) MRSE was 0.09 (±1.37). There were 60% with hyperopic MRSE and a mean (SD) of +1.45 (±1.17) [n=65]. There were 11 eyes (10%) with Plano, and 30% with myopic MRSE with a mean (SD) of -1.79 (±1.39) [n=32].

In a two tailed independent t-test there was significant difference between the two treatments postoperatively Table 2.

7.2.4 Spherical refraction (SPH)

There was no significant difference between treatments preoperatively Table 2.

Preoperatively the SPH in the CXL group was ranging from +7.50 D to -8.50 D. There were 87% with hyperopic SPH and a mean (SD) of +3.36 (±2.19) [n=124]. In all, there were 5 eyes (3.5%) with Plano, and 9.5% with myopic SPH mean (SD) of -2.28 (±2.63) [n=14].

Postoperatively the CXL group showed no significant difference compared to baseline Table 1. At 12±6 months follow-up the SPH in the CXL group was ranging from +7.50 D to -8.75 D. There were 79.5% with hyperopic SPH mean (SD) +3.50 (±2.25) [n=81]. There were 7 (7%) with Plano and 13.5% with myopic SPH and a mean (SD) of -2.25 (±2.87) [n=14]. There was 50 % [n=50] with improvement by reduced SPH (n=43 reduced hypermetropia/ n=7 reduced myopia), and 30 % [n=30] with worsening by increased SPH (n= 26 increased hypermetropia/ n=7 increased myopia). There were 18 % [n=18] with no change, and 2% [n=2] that went from Plano to myopia. Further, 1% [n=1] that went from Plano to hypermetropia postoperatively.

Preoperatively the SPH in the t-PTK+CXL group was ranging from +6.75D to -6.25D. There were 93% with hyperopic SPH and a mean (SD) of +3.22 (±1.92) [n=145]. In all, 2 eyes (2%) with Plano, and 5% with myopic SPH mean (SD) of -2.07(±2.02) [n=8].

Postoperatively the t-PTK+CXL group showed significant difference compared to baseline Table 1. At 12±6 months follow-up the SPH in the t-PTK+CXL group was ranging from +5.50 D to -4.25 D. There were 77.6% with hyperopic SPH mean (SD) +2.38 (±1.47) [n=83]. There were 11 eyes (10%) with Plano, and 12% with myopic SPH and a mean (SD) of -1.8 (±1.48) [n=13]. There was 80 % [n=85] with improvement by reduced SPH (n=84 reduced hypermetropia / n=1 reduced myopia), and 12 % [n=13] with worsening by increased SPH (n=11 increased hypermetropia / n=2 increased myopia). There were 6 % [n=6] with no change and 2% [n=2] that went from Plano to myopia postoperatively.

In a two tailed independent t-test there was significant difference between the two treatments postoperatively Table 2.

7.2.5 Refractive astigmatism (CYL)

There was no significant difference between treatments preoperatively Table 2.

Preoperatively CYL in the CXL group was ranging from -0.25 D to -8.50 D. For the CXL group there was 16 eyes with low astigmatism (<1.0 D), 50 eyes with moderate astigmatism (1.0-2.0 D), and 85 eyes with high astigmatism (>2.0 D)

Postoperatively the CXL group showed no significant difference compared to baseline Table 1. At 12±6 months follow-up CYL in the CXL group was ranging from 0.00 D to -9.75 D. There was 40% reduction of CYL with a mean (SD) of 1.68 (1.16) [n=41]. In all, 19 eyes (18%) showed no change, and 37 % showed worsening of CYL by increase with a mean (SD) of 1.31 (0.77) [n=38].

Preoperatively CYL in the t-PTK+CXL group was ranging from -0.75 D to -8.50 D. For the t-PTK+CXL group there was 1 eye with low astigmatism (<1.0 D), 26 eyes with moderate astigmatism (1.0-2.0 D), and 128 eyes with high astigmatism (>2.0 D).

Postoperatively the t-PTK+CXL group showed significant difference compared to baseline Table 1. At 12±6 months follow-up CYL in the t-PTK+CXL group was ranging from 0.00 D to -7.25 D. There was a 57 % reduction of CYL with a mean (SD) of 1.63 (±1.07) [n=41]. In all, 14 eyes

(19.5%) showed no change, and 23.5% showed worsening of CYL by increase with a mean (SD) of 1.11 (±0.70) [n=17].

In a two tailed independent t-test there was significant difference between the two treatments postoperatively Table 2.

7.3 Keratometry values

7.3.1 Kmax

There was significant difference between treatment preoperatively Table 2.

Preoperatively the Max-K in the CXL group was ranging from 43.7 D to 83.7 D. Preoperatively the K-max in the t-PTK+CXL was ranging from 44.6 D to 65.0 D.

Postoperatively the CXL group showed significant difference compared to baseline Table 1. At the 12±6 months follow-up Kmax in the CXL group was ranging from 43.3 D to 78.9 D [n=102]. The mean (SD) improvement by flattening of K-max was 1.93 (±1.45) [n=69]. In all, 4 eyes (4%) showed no change, and mean (SD) worsening by steepening of K-max was 1.02 (±0.75) [n=29]. Mean (SD) improved Kmax ≥ 1.0 D was 2.53 (±1.31) [n=39]. Failure with increase ≥ 1.00 D was 1.67 (±0.63) [n=9].

Postoperatively the t-PTK+CXL group showed significant difference compared to baseline Table 1. At the 12±6 months follow-up the Kmax in the t-PTK+CXL group was ranging from 42.4 D to 68.7 D [n=107]. The mean (SD) improvement by flattening of K-max was 2.92 (±1.81) [n=94]. In all, 3 eyes (6%) showed no change, and mean (SD) worsening by steepening of K-max was -1.06 (±1.05) [n=10]. Mean (SD) improved Kmax ≥ 1.0 D was 3.40 (±1.59) [n=74]. Failure with increase ≥ 1.00D was 2.60 (±1.10) [n=2].

With a Person product-moment correlation test, there was proven a significant correlation between Kmax, K_1 and K_2 (p <.001). In a two tailed independent t-test there was significant difference between the two treatments postoperatively Table 2.

7.3.2 K_1

There was significant difference between treatments preoperatively Table 2.

Preoperatively K_1 in the CXL group was ranging from 38.7 D to 64.3 D. Preoperatively range of K_1 in the t-PTK+CXL was from 36.6 D to 52.6 D.

Postoperatively the CXL group showed significant difference compared to baseline Table 1. At 12±6 months follow-up the K_1 in the CXL group was ranging from 38.3 D to 62.2 D. The mean (SD) improvement by flattening of K_1 was 1.23 (±0.97) [n=65]. In all, 4 eyes (4%) showed no change, and mean (SD) worsening by steepening of K_1 was 0.51 (±0.42) [n=33].

Postoperatively the t-PTK+CXL group showed significant difference compared to baseline Table 1. At 12±6 months follow-up K_1 in the t-PTK+CXL group was ranging from 38.0 D to 48.6 D. The mean (SD) improvement by flattening of K_1 was 1.49 (±1.05) [n=78], 4 eyes (4%) showed no change, and mean (SD) worsening by steepening of K_1 was 0.56 (±0.60) [n=25].

In a two tailed independent t-test there was significant difference between the two treatments postoperatively Table 2.

7.3.3 K_2

There was significant difference between treatments preoperatively Table 2.

Preoperatively K_2 in the CXL group was ranging from 40.4 D to 72.9 D. Preoperatively range of K_2 in the t-PTK+CXL group was 40 D to 56.0 D.

Postoperatively the CXL group showed significant difference compared to baseline Table 1. At 12±6 months follow-up the K_2 in the CXL group was ranging from 40.6 D to 63.7 D The mean (SD) improvement by flattening of K_2 was 1.20 (±1.00) [n=56]. In all, 7 eyes (7%) showed no change, and mean (SD) worsening by steepening of K_2 was 0.70 (±0.60) [n=38]. In the CXL group 35 eyes showed worsening by steepening of ≤ 1 D, and 3 eyes showed a worsening by steepening in the range 1.3 D to 2.6 D post treatment.

Postoperatively the t-PTK+CXL group showed significant difference compared to baseline Table 1. At 12±6 months follow-up the K_2 in the t-PTK+CXL group was ranging from 49.7 D to 54.1 D. The mean (SD) improvement by flattening of K_2 was 1.33 (±0.83) [n=84]. In all, 6 eyes (6%) showed no change, and mean (SD) worsening by steepening of K_2 was 0.73 (±0.68) [n=17]. In the t-PTK+CXL group 16 eyes showed worsening by steepening of ≤ 1 D, and 2 eyes showed an worsening by steepening of 1.2 D and 2.7 D post treatment.

In a two tailed independent t-test there was significant difference between the two treatments postoperatively Table 2.

7.3.4 Corneal Astigmatism (AST)

There was no significant difference between treatments preoperatively Table 2.

Preoperatively the ASTIG. in the CXL group was ranging from -0.2 D to -11.8 D. In the CXL group there was 16 eyes with low astigmatism (<1.0 D), 32 eyes with moderate astigmatism (1.0-2.0 D), and 95 eyes with high astigmatism (>2.0 D).

Postoperatively the CXL group showed no significant difference compared to baseline Table 1. At 12±6 months follow-up the mean (SD) ASTIG. in the CXL group was -3.13 (±2.19) ranging from 0.1 D to -11.7 D. There were 48 eyes (47%) with mean (SD) improvement by reduction of ASTIG with a mean 0.71 (±0.63). In all, 5 eyes (5%) showed no change, and 49 (48%) eyes showed a worsening by increase of ASTIG with a mean (SD) of 0.97 (±0.96).

Preoperatively the ASTIG. in the t-PTK+CXL group was ranging from -0.00 D to -6.75 D. In the t-PTK+CXL group there was 12 eyes with low astigmatism (<1.0 D), 34 eyes with moderate astigmatism (1.0-2.0 D), and 109 eyes with high astigmatism (>2.0 D).

Postoperatively the t-PTK+CXL group showed significant difference compared to baseline Table 1. At 12±6 months follow-up the mean (SD) ASTIG. in the t-PTK+CXL group was -3.00 (±1.46) ranging from -0.3 D to -7.10 D. There were 51 eyes (47,5%) with an improvement by reduction of ASTIG with a mean (SD) 0.63 (±0.49) [n=51]. In all, 6 eyes (5,5%) showed no change, and 50 eyes (46%) showed a worsening by increase of ASTIG with a mean (SD) 0.88 (±0.79).

In a two tailed independent t-test there was no significant difference between the two treatments postoperatively Table 2.

7.4 Aberrometric values

7.4.1 Total Root Mean Square (RMS)

There was no significant difference between treatments preoperatively Table 2.

Preoperatively RMS in the CXL group was ranging from 1.805 µm to 35.429 µm. Preoperatively RMS in the t-PTK+CXL group was ranging from 2.275 µm to 19.818µm.

Postoperatively the CXL group showed significant difference compared to baseline Table 1. At the 12±6 months follow-up RMS total in the CXL group was ranging from 1.771 µm to 33.786 µm. There were 74 eyes that showed an improvement by reduction of RMS total with the mean (SD) 1.173 (±1.037) accounting for 72.5% of all the eyes treated with CXL. In all, zero eyes showed no change, and 28 eyes showed a worsening by increase of RMS total with a mean (SD) was 1.045 (±1.415) accounting for 27.5% of all eyes treated with CXL.

Postoperatively the t-PTK+CXL group showed significant difference compared to baseline Table 1. At the 12±6 months follow-up the RMS total in the t-PTK+CXL group was ranging from 2.158 µm to 25.850 µm. There were 94 eyes that showed an improvement by reduction of RMS total with the mean (SD) of 2.569 (±1.531) accounting for 88 % of all eyes treated with t-PTK+CXL. Inn all, 1 eye showed no change, and 12 eyes showed a worsening by increase of RMS total mean (SD) with a mean 1.328 (±2.068) accounting for 11% of all eyes treated with t-PTK+CXL.

In a two tailed independent t-test there was significant difference between the two treatments postoperatively Table 2.

7.4.2 Anterior Total Corneal Higher Order Aberrations (HOAs)

There was significant difference between treatments preoperatively Table 2. Preoperatively HOAs in the CXL group was ranging from 0.368 µm to 9.232 µm. Preoperatively HOAs in the t-PTK+CXL group was ranging from 0.463 µm to 6.740µm.

Postoperatively the CXL group showed significant difference compared to baseline Table 1. At the 12±6 months follow-up HOAs in the CXL group was ranging from 0.418 µm to 9.022 µm. There were 69 eyes that showed improvement by reduction of HOAs with a mean (SD) 0.259 (±0.190). In all, there was zero eyes that showed no change, and 33 eyes that showed worsening by increase HOAs with a mean (SD) of 0.210 (±0.295).

Postoperatively the t-PTK+CXL group showed significant difference compared to baseline Table 1. At the 12±6 months follow-up HOAs in the t-PTK+CXL group was ranging from 0.347 µm to 6.188 µm. The mean (SD) reduction of HOAs was 0.623 (±0.462) [n=92], 1% [n=1] showed no change, and mean (SD) increase of HOAs was 0.276 (±0.2437) [n=14].

In a two tailed independent t-test there was significant difference between the two treatments postoperatively Table 2.

7.4.3 Spherical Aberrations (Z40)

There was significant difference between treatments preoperatively Table 2.
Preoperatively Z40 in the CXL group was ranging from 1.163 µm to -4.563 µm. Preoperatively Z40 in the t-PTK+CXL group was ranging from 1.000 µm to -2.366 µm.

Postoperatively both groups showed significant difference compared to baseline Table 1. At 12±6 months follow-up Z40 in the CXL group was ranging from 0.870 µm to -4.199 µm. At 12±6 months follow-up Z40 in t-PTK+CXL group was ranging from 0.987 µm to -1.777 µm.

In a two tailed independent t-test there was significant difference between the two treatments postoperatively Table 2.

8 Discussion

The average age of patients at the time of treatment showed that treatment was performed in the second to third decade of life. This is also known to be the time keratoconus usually progresses before stabilization in the fourth decade of life (Flockerzi et al., 2021). There was no difference of average age between treatments indicating that age was not an important factor when deciding which treatment that were chosen. Supportively, previous studies have showed that age did not have effect on postoperative results (Baenninger, Bachmann, Wienecke, Kaufmann, & Thiel, 2014). During the data collection period from 2018-2022, a larger percentage of men (80%) received treatment compared to women (20%), as reported by this study. This aligns with the findings of Kristianslund et al. (2021) who conducted a Norwegian study and found that 73% of keratoconic patients in the Norwegian population were male.

According to the study done by Hersh, Greenstein, and Fry (2012), the clinical outcomes of CXL displayed a consistent progression over time. Initially, there was a dip in clinical outcomes after one month, followed by a return to normalcy at three months, and a subsequent advancement at six and twelve months. Furthermore, the same research established that topographic stability became noticeable after one year. Based on these findings, a postoperative interval of 12±6 months was chosen in this study.

Answering the question of which measure holds the most significance to patients is a challenging task due to the intricate nature of visual perceptions. Therefore, it may prove beneficial to consider multiple measures in order to provide the best solution. To achieve optimal visual quality, it is essential to ensure that the entire optical system is functioning correctly to produce a non-distorted image (Wajnsztajn et al., 2022). Additionally, Wajnsztajn et al. (2022) noted that eyes with higher Kmax and MRSE values, as well as lower visual acuity, typically indicate a more severe disease state. Such eyes have a greater probability of displaying improved visual and tomographic outcomes.

The relationship between natural development, progression movement, and patient behaviour is complex. Najmi et al. (2019) proved a strong link between eye-rubbing and the development and progression of keratoconus. By recognizing this connection, we can infer that preventing eye-rubbing and effectively managing conditions such as atopic-, allergy-, and dry eye after consultation and treatment in one eye can indicate a significant role in slowing or halting disease progression in the other eye as well.

8.1 Visual Values

8.1.1 Unaided Distance Visual Acuity (UDVA)

Preoperatively, both groups had similar visual acuity ranges. However, there were differences in UDVA between the groups. In the CXL group, 53% had a visual acuity between 0.5 and 1.2 Snellen lines, while only 40% of the t-PTK+CXL group fell within the same range. This indicates that the CXL group had better visual acuity pre-treatment than the t-PTK+CXL group, implying that the t-PTK+CXL group had a higher potential for improvement of several lines compared to the CXL group. However, considering the high p-values between groups postoperatively Table 2 and between baseline and postoperative measurements in the t-PTK+CXL group Table 1, these findings should not be ignored.

The postoperative results showed that there was a greater improvement of UDVA after treatment for the t-PTK+CXL group compared to the CXL group by 36 % and 14 % respectively. In comparison, the CXL treatment showed over twice a decrease in visual acuity compared to the t-PTK+CXL group with 20% to 8 % respectively. Further, the t-PTK+CXL group showed a lower reduction of visual acuity with a maximum reduction of three Snellen lines (excluding one outliner), while the CXL group showed a greater range of adverse outcomes. Not only was there a greater percentage of increased visual acuity in the t-PTK+CXL group, but this group also added two more positive Snellen lines within its range after treatment.

According to Chambers (2021), a change of three or more lines is generally considered clinically significant, while the Blue Mountains Eye Study (Thiagalingam, Cumming, & Mitchell, 2002) suggests that two Snellen lines indicate clinical significance. As such, an improvement of three Snellen lines, as used in this study, is a restrictive threshold. The t-PTK+CXL group showed that 50% of the total outcome after treatment was attributed to an increase of more than three Snellen lines, whereas for the CXL group, this accounted for only 8% of the total outcome after treatment. Alessio et al. (2013) described the improvement of UDVA after t-PTK+CXL treatment as a supportive result in comparable studies. Additionally, literature presents a correlation between CXL treatment and UDVA, stating a non-significant difference after treatment within this group, as noted by Danesh, Sedaghat, Momeni-Moghaddam, Yekta, and Belin (2021).

Furthermore, the t-PTK+CXL group showed that over three times more eyes that went from <0.5 to ≥ 0.5 compared to the CXL group. This is a significant finding not only because it impacts patients'

subjective perception of their vision, but also because reduced CDVA could limit their choices of profession. Since these patients are often young individuals starting their careers, good vision is particularly important in many occupations. Meeting the 0.5 Snellen line criterion is essential for driving, but there are numerous professions where vision is a specified requirement (Helsedirektoratet, 2023).

Even if we take in account that there was a 10 % difference in rate of Snellen lines preoperatively, and both treatments showed significance compared to baseline and compared to each other at follow-up, we cannot omit the fact that the t-PTK+CXL treatment show better results throughout the analysis of UDVA. So, this indicates that if UDVA is poor, and criteria to perform t-PTK is met, there is a six times higher chance to get an improvement of three Snellen lines or more with the t-PTK+CXL treatment. This should be considered an important factor because visual acuity is considered to be the most commonly used and universally understood measure of visual function (Chambers, 2021).

To discuss this matter even further, a substantial factor is how the improvement of visual acuity in one eye is affecting the total vision. It is evident that the majority of patients [n=182] received treatment for only one eye, leading us to assume that the treatment is focused on the eye with the greatest deterioration. Although there are rare cases that contradict this (Phillips, 2003), it is widely acknowledged that keratoconus affects both eyes with discrepancies in the degree and rate of progression (Santodomingo-Rubido et al., 2022). With very few exceptions (Phillips, 2003), there is stated that keratoconus is a binocular condition with asymmetry in severity and progression (Santodomingo-Rubido et al., 2022).

8.1.2 Corrected Distance Visual Acuity (CDVA)

The fact that these eyes have all undergone treatment tells us that these eyes are not the most advanced (Nassaralla, 2022). This represents the high mean of BCVA in both groups.

Preoperatively both groups showed similar mean and SD in the range between 0.5 and 1.0 Snellen lines Table 1. In the CXL group 90% of the visual acuity ranged between 0.5 and 1.2 Snellen decimals. Compared to the t-PTK+CXL group there were as much as 98 % was within the same range with the same mean (SD) Table 1. For the t-PTK+CXL group all adverse outcomes ranged between one and three Snellen lines, with exception of one outliner with adverse outcome of seven

Snellen lines. To comparison, in the CXL group the adverse outcomes ranged evenly between one to six Snellen lines.

Even though t-PTK+CXL contained a higher percentage of Snellen lines between 0.5 and 1.5 preoperatively, 45 % of the eyes in the t-PTK+CXL group showed an improvement of visual acuity after treatment. In fact, after treatment there were no eyes with CDVA below 0.3 Snellen lines in this group. The CXL group had 25.5 % improvement in the same interval. Both groups showed similar adverse results with 20-21 %. However, the CXL group showed a greater range of adverse outcomes with a maximum of six Snellen lines.

In a the Blue Mountain Eye Study, Thiagalingam et al. (2002) defined clinically significant relevant uncorrected visual activity at 2 or more LogMAR lines in subjects with acuity presenting 0.6 Snellen lines or worse. This study was done an elderly population in a screening setting without differentiation of ocular pathology and described improvement of visual acuity by optimizing correction. Chambers (2021) argued that a change of 3 lines or more is considered clinically significant. None of these two studies describe keratoconic patients, and clinically compared to healthy eyes, keratoconic patients have other visual challenges than visual acuity (Wajnsztajn et al., 2022). There was 19% with a 2 or more Snellen line change and 9 % with a 3 or more Snellen lines improvement in the CXL group. There was 32% with a 2 or more Snellen lines change and 13 % with a 3 or more Snellen lines improvement in the t-PTK+CXL group. In other words, not at very large difference between the groups, supporting the other findings in this category thar describe equality between the groups in this measure.

So, we have established by mean (SD) that most of eyes achieved an acceptable corrected visual acuity in both groups. Nevertheless, even if we take in account that the t-PTK+CXL group preoperatively showed a higher mean of BCVA than the CXL group, improvement in this group still accounted for almost 50 % of the total results after treatment. That is two times the percentage of the CXL group. This is important because even if there is not a detailed evaluation of binocular visual function, it is well known that binocular vision works best with binocular balance. A study done by Dandapani, Padmanabhan, and Hussaindeen (2020) compared binocular vision abnormalities in keratoconic patients with healthy eyes as control group and stated that there was a significant amount of keratoconic patients with binocular abnormalities. They even suggested that the function of binocular vision should be included in clinical examination of all keratoconic patients.

8.2 Refractive Values

8.2.1 Manifest Refractive Spherical Equivalent (MRSE)

Preoperatively there was a greater percentage of hyperopic MRSE in both the CXL – and the t-PTK+CXL group by 60 % and 75 % respectively. However, the mean MRSE was considerably lower in the t-PTK+CXL group compared to the CXL group. Preoperatively the CXL group had a higher range of dioptric power than the t-PTK+CXL group, indicating that there the visual impairment was more severe in the CXL group.

Postoperatively the mean of the CXL group was decreased, but the standard deviation was increased, this was also reflected in the expand of dioptric range within this group. The other parameters as the percentage of hyperopic-, myopic- and Plano MRSE remained unchanged from pre- to postoperatively. There was no statistical significance when comparing pre- and postoperative values for the CXL group. These findings are supported by Danesh et al. (2021) that stated that the geometric and functional parameters showed stability of corneal status one year after treatment.

For the t-PTK+CXL group the mean MRSE changed drastically when comparing pre- and postoperative values. The standard deviations were also slightly decreased in the same comparison. The range of dioptric power changed with improvement by reduction of 2.35 dioptres. In contrast, the CXL group had a worsening by increased power change with 6.75 dioptres when comparing pre-and postoperative values. The trend of improved MRSE after t-PTK+CXL treatment is supported by Chen et al. (2017) and Alessio et al. (2013) that showed similar findings.

Besides the significant disparity between pre- and postoperative MRSE values in the t-PTK+CXL group, as demonstrated in Table 1 and Table 2, it is worth mentioning that the percentage of Plano MRSE increased after treatment. The t-PTK+CXL group had twice as many outcomes of Plano postoperatively compared to the CXL group.

8.3 Curvature Values

8.3.1 Kmax

A study Alshehri et al. (2022) reported mean K-max values of normal eye was 42.91 ± 1.40 D. It was important to note that these values may vary depending on the population and the measurement technique used. In 2017, a crucial study was published that played a major role in the FDA's approval of the CXL treatment in the United States. This study stated that an elevation of 1.00 D or higher in the steepest keratometry measurement is deemed significant (Smadja & Krauthammer, 2023).

There was a significant difference in Kmax in both groups compared to baseline Table 1. Postoperatively the CXL group and the t-PTK+CXL group showed a flattening of 68 % and 88 % respectively. Compared to baseline, the worsening of Kmax by steepening post-treatment in the CXL group was almost three times higher compared to the t-PTK+CXL group with 28 % and 10 % respectively. Even so, we saw by the range in the CXL group that the highest numbers of Kmax were reduced after treatment. This phenomenon was confirmed in a study by Kuechler, Tappeiner, Epstein, and Frueh (2018) where they looked at Kmax outcomes in the steep corneas (≥ 58.0 D) after CXL treatment. They concluded that there was a significant decrease in steepness after one year, but also that these corneas showed a significant (≥1.0 D) progression long term compared to the moderate stages of kerataoconus. Further, the t-PTK+CXL group showed a larger total of reduced Kmax from pre- to postoperatively. The t-PTK+CXL treatment had a greater mean of failure (increase of Kmax) than the CXL group ≥ 1.00 D. However, in the t-PTK+CXL group there was only two observations (1.8%) in this range, whereas in the CXL group there was 9 observations (9 %) in the same interval.

The findings of this research indicate that, in comparison to baseline, both CXL and t-PTK+CXL demonstrate statistically significant results 12±6 months following the procedure. Prior studies have demonstrated an improvement of K-Max using both methods (Chen et al., 2017; Wajnsztajn et al., 2022). However, there was in fact a 3.16 D improvement of Kmax in the t-PTK+CXL group with an almost 90 % improvement post-treatment. And there were also three times more adverse outcomes in the CXL group than in the t-PTK+CXL group.

8.3.2 Corneal- and refractive Astigmatism

By using Fu's astigmatism severity grading scale (Fu et al., 2018) and comparing refractive and tomographic corneal astigmatism, distinct patterns emerged. The measure of refractive astigmatism showed a greater prevalence of severe astigmatism in the t-PTK+CXL group compared to the CXL group. In the CXL group of corneal astigmatism the low, medium, and high astigmatism in the CXL group was 11%, 22 %, and 65 % respectively. The low, medium, and high astigmatism in the t-PTK+CXL group was 8 %, 22 % and 70 % respectively. In the CXL group of refractive astigmatism the low, medium, and high astigmatism in the CXL group was 11%, 35 %, and 59 % respectively. In the t-PTK+CXL group the low, medium, and high astigmatism was 0.6 %, 17% and 83 % respectively. In other words, there was a big difference between treatments in refractive astigmatism, but similar results between treatments in corneal astigmatism. This was interesting because progression of keratoconus was measured by refractive astigmatic progression and not by corneal astigmatic progression. This could be attributed to the fact that there are different categories of astigmatism, such as corneal, lenticular, and total. Corneal astigmatism is caused by the curvature of the cornea which can be measured through keratometry, while lenticular astigmatism is a result of the shape of the crystalline lens. Total astigmatism is the combination of both corneal and lenticular astigmatism and can be identified through retinoscopy and refraction (D. D. Koch et al., 2012). Nonetheless, considering the threshold set at “greater than 2.00 D” for defining "high," it can be assumed that the majority of the eyes selected for laser treatment had a visual irregularity that was possible to correct. Furthermore, traditional CXL treatment was probably given to individuals with mild to moderate refractive anomalies who were identified at an early stage, and visual rehabilitation was not an objective of the treatment.

Essentially, despite the significant attention being given to refractive astigmatism, the choice of treatment based on disease severity by refractive astigmatism appears to be relatively homogeneous when evaluating tomographic measurements and the degree of astigmatism. In my opinion this is in fact a very interesting finding because a high grade of refractive astigmatism, reduced UDVA, good CDVA *and* a moderate tomographic picture may indicate that the refractive error has recently occurred, and that morphological sign are not yet permeant or pronounced. According to G. Kymionis et al. (2015) partial removal of Bowman's layer on the cone can induce local UVA penetration in the corneal stroma, resulting in a heightened effectiveness of CXL treatment in the area most in need of corneal strengthening.

8.4 Aberrometric Values

To the authors knowledge aberrometric values as a consideration when grading of keratoconus are not systemized. Most of the studies on the subject focus on differentiating healthy eyes from keratoconic eyes, preferably to detect the disease at early stage (Heidari et al., 2020; Salman et al., 2022). The traditional grading methods, as Amsler-Krumeich classification, grades the severity of keratoconus with the mean K readings (based on topography and *not* tomography), myopia/astigmatism, morphological signs and pachymetry. In other words, there is a huge gap between traditional grading methods and today's technological ability to detect, classify and treat keratoconus. Three articles were identified through a PICO search in Medline regarding alternative methods for grading the severity of keratoconus that included tomographic values. However, only one of these articles was comparable to the present study (J. L. Alió & M. H. Shabayek, 2006; T. McMahon et al., 2006; S. Ortiz-Toquero, Fernandez, & Martin, 2020). But even J. L. Alió and M. H. Shabayek (2006) suggestion of an alternative grading was based on Amsler-Krumeichs classification, and also only included the third order aberrations (described as RMS of coma-like aberrations) from the Zerinke analysis. Stated differently, it is commonly accepted that individuals with keratoconus experience significant visual impairment due to higher order aberrations. Yet, there is no agreement regarding the extent to which these aberrations contribute to the visual disturbance. We can still agree that an improvement by reduced higher order aberrations is interpreted as a positive effect after treatment.

8.4.1 Total Root Mean Square (RMS)

Zernike polynomials and coefficients are complex to comprehend and make sense of in regard to wavefront aberrations. The RMS measure proves valuable in measuring the wavefront error. By comparing deviations between the wavefront surface and its mean, the RMS generates a single, easily interpretable number to represent the wave front error. In basic terms, RMS wavefront error is the divergence of the wavefront from a planar one, exemplified by a single numerical value (Unterhorst & Rubin, 2015).

According to Lim, Wei, Chan, and Tan (2007) the average RMS total for normal, healthy eyes is approximately 0.49 +/- 0.16. However, keratoconic eyes demonstrate a higher value in this regard, also well proved in this study, with no eyes at the average measure. It is a well-established fact that keratoconic eyes have a greater quantity of higher order aberrations on their anterior corneal surface (J. L. Alió & M. H. Shabayek, 2006; Lim et al., 2007).

Both treatments showed significant difference compared to baseline and compared to each other at 12±6 months postoperatively. The range of RMS total in the CXL group was slightly higher compared to the t-PTK+CXL group, which is consistent with previous observations on the severity level within the groups. However, in the t-PTK+CXL group the improvement by reduction of RMS total accounted for 88 % of all eyes treated with t-PTK+CXL, with only 11% worsening by increase postoperatively. In comparison, the CXL group showed almost three times greater worsening by 28%, and with an improvement accounting for 72.5 % for all eyes treated with CXL. While both groups demonstrated a significant reduction in RMS total, the t-PTK+CXL group showed a slightly superior outcome, indicating a greater reduction of total RMS with the alternative t-PTK+CXL treatment.

8.4.2 Higher Order Aberrations HOAS (Z3-Z7)

According to a study conducted by J. L. Alió and M. H. Shabayek (2006), the average HOAs for healthy eyes is 0.52 µm. Detection of high-order aberrations can only be done by wavefront aberrometers. Inferior corneal steepening cases the rays to travel across this area in a defocus, causing visual symptoms which result from the spread of the light at the retinal plane (Lin et al., 2013).Even with the greater range within the CXL group, it was better results in the t-PTK+CXL group in terms of reduction of HOAs of 68% and 86 % respectively. Additionally, a worsening by increase of HOAs was twice a high in the CXL group compared to the t-PTK+CXL group with 32 % and 14 % respectively. Eyes suffering from keratoconus demonstrate substantially greater levels of corneal higher order aberrations, particularly those resembling coma. Utilizing a corneal aberrometry map, the identification and classification of keratoconus in its initial stages can be accurately determined through the presence of coma-like aberrations (J. L. Alió & M. H. Shabayek, 2006).

Refractive values

8.5 Best Corrected Subjective Refraction

Best corrected subjective refraction is just that – subjective. Therefore, it may sometimes be a challenge ensure the measurement to be correct and repeatable. Davis, Schechtman, Begley, Shin, and Zadnik (1998) test- retested The Collaborative Longitudinal Evaluation of Keratoconus Study (CLEK) to determine the repeatability of the CLEKs refraction protocol on correct visual acuity in keratoconus. The compared repeatability of subjective refraction was allegiantly good. However,

compared to the control group with normal eyes there was found a somewhat lower repeatability than with the keratoconic eyes. In the same period of time Gordon et al. (1998) did det same test-retest, and made the same conclusion. They also pointed out that the repeatability was slightly reduced when different practitioners tested at baseline, follow-up and between follow-ups. Nevertheless, it should be commented that the possibility of improved visual acuity can be affected by other factors as cognitive function, dry eyes, practitioner related differences and so on (Spierer, Fischer, Barak, & Belkin, 2016).

There were found significant differences between baseline and t-PTK+CXL group and *not* in the same interval for the CXL group. There was also significance between the groups postoperatively Table 2. This only tell us that there is a difference, not if the difference is positive or negative. But let's look at the numbers. There was no change in range observed in the CXL group, but the t-PTK+CXL group demonstrated a reduction in power resulting in a 3.25 D range shift. This was evidenced by twice as many eyes in the t-PTK+CXL group displaying a reduction in hypermetropia compared to the CXL group. Specifically, the t-PTK+CXL group showed an over 80% reduction in SPH, which was 0.5 times greater than the reduction observed in the CXL group. Furthermore, the t-PTK+CXL group demonstrated almost three times less worsening by SPH increase than the CXL group, with rates of 30% and 12%, respectively. These numbers compare well with the MRSE results that also indicate a greater reduction of power in the t-PTK+CXL group compared to the CXL group.

Both groups showed that approximately 90 % of the spherical power was hyperopic, with a slightly higher percentage of hyperopic eyes in the t-PTK+CXL group. This contradicts with the CLAK study's data of manifest refraction in keratoconic eyes which reported a mean sphere of -6.405, and with a cylinder of -2.361 (Zadnik et al., 1998). A theory of why that is might be purely geographical reasons. Myopia is often referred to as epidemic-like situation (Morgan et al., 2018). At the same time, a Norwegian study form Kongsberg, Norway, stated that this was not the case in Norwegian children. It was, in fact, the opposite; Norwegian children turns out to be mainly hyperopic (Hagen et al., 2018).

Curvature values

8.6 K_1 and K_2

There was significant difference in both treatment when comparing baseline to follow-up Table 1. In general, the t-PTK+CXL treatment showed a higher improvement by greater flattening and less steepening that the CXL treatment. K_1 is highly correlated with K_2.

Preoperatively the CXL group showed a greater range of K_2 compared to the t-PTK+CXL group. The lowest value was the same in both groups, but the highest value was steeper in the CXL group by 16.9 D compared to the t-PTK+CXL group. Since steepening of K_2 is one of central measures to diagnose and following progression of keratoconus it is again possible to claim that the CXL group contained eyes with a more severe grade of keratoconus at time of treatment (Smadja & Krauthammer, 2023). The K_2 values seemed to cluster more in a low- to moderate stage of keratoconus in the t-PTK+CXL group eyes compared to the CXL group. This can probably be explained by the fact that the patient was offered treatment regardless of severity of the keratoconus and when in doubt, the conventional treatment was chosen.

In the CXL group there was a flattening of 63 % post treatment, and for the t-PTK+CXL group there was 79 % flattening of K_2. This suggest that both treatments create at significant flattening of K_2 compared to baseline, also confirmed by a paired t-test in Table 1.

When it comes to progression of K_2 after treatment the CXL group shows twice the percentage of steepening by 37 % compared to the t-PTK+CXL group with 16 %. This correlates to the Kmax results. The literature and classification of keratoconus does not define threshold for when progression of K_2 is considered significant. A theory to this is; the high correlation to flattest meridian K_1 and corneal astigmatism create a complexity which make it difficult to define progression from a single K_2 measure (Cunha et al., 2021). However, steepest keratectomy measure (cf. K-max) is defined as progression in the literature as $\geq$ 1 D in 1 year (Raiskup-Wolf, Hoyer, Spoerl, & Pillunat, 2008; Smadja & Krauthammer, 2023). If these definitions are somehow comparable, that means that approximately 90 % of the eyes that showed steepening was below threshold for what is described as significant in both groups.

8.7 Corneal Thickness

Pachymetry is an important factor when deciding to treat combined CXL with vision rehabilitation techniques as PTK. Haque, Jones, and Simpson (2008) reported in their study on 'Thickness mapping of the cornea and epithelium using optical coherence tomography' that the changes in central thickness were not uniform across the cornea, with the thinnest point being the most affected. They concluded that central corneal thickness was thinnest in keratoconic eyes (447 +/- 68 micron) with a central epithelial thickness of 44 +/- 7 micron and 42.1 +/- 4.5 micron thinner at the apex. That is highly consistent with the results of this study, that in both groups combined showed a preoperatively mean (SD) of 468.67 (±38.29) at thinnest point.
Table 1 reveals that baseline pachymetry values in the CXL group were lower than in the t-PTK+CXL group. None of the corneas in the t-PTK+CXL group had pachymetry readings below 420 µm, whereas 25% of the eyes in the CXL group did. Additionally, 9% of the eyes in the CXL group had readings below 400 µm, suggesting a more advanced stage of keratoconic progression compared to the t-PTK+CXL group at the time of treatment. After 12±6 months of follow-up, 12% of the CXL group still had pachymetry readings below 400µm.

Although there was a statistically significant difference in corneal pachymetry, the clinical significance remains unclear. Greenstein, Shah, Fry, and Hersh (2011) reported that the overall corneal pachymetry stabilizes closer to its baseline level over time. Research indicates that the minor changes in corneal thickness resulting from CXL, and laser refractive surgery do not typically have lasting effects on corneal health or visual acuity. Nevertheless, patients should receive meticulous evaluation and monitoring to ensure the best possible outcomes and the implications of changes in corneal thickness after CXL require further investigation (Greenstein et al., 2011).

Aberrometric Values

8.8 Spherical Aberrations Z40 (Z4)

It has been reported that Zernike coefficients can vary from -0.579 µm to 0.572 µm for spherical aberration (Unterhorst & Rubin, 2015). Spherical aberration is included as one the most disturbing factors when it comes to visual perception (Koh et al., 2022). "Negative" spherical aberration means peripheral rays are not bent enough. "Positive" spherical aberration means peripheral rays are bent too much. We see that the range of spherical aberration is slightly reduced in both groups,

indicating a positive effect after treatment by reducing the spherical aberrations. Even though this is statistically significant Table 1, the level of clinically significance is uncertain.

9 Conclusion

This study indicates that t-PTK+CXL provides better visual quality than CXL treatment. Both t-PTK+CXL and CXL treatment appears to effectively halt the progression of keratoconus while also improving UDVA, CDVA, MRSE, flattening curvature values, and reducing aberrometric values.

While using a surgical approach to treat keratoconus through refractive therapy may appear promising, larger controlled and randomized studies with longer monitoring periods are needed to determine the best refractive procedure or sequence for individual cases. Further randomized controlled trials are required to validate the findings of this study.

10 Further research

The dataset included a multitude of parameters, which increased the reliability of the non-randomized data. After thorough consideration, it was evaluated that it was not possible to analyse all the data regarding the complex disease and its impact on visual perception and quality within the limitations of this project. However, the extensive amount of data gathered allows for further comprehensive studies to be conducted. In particular, a follow-up with several intervals in the same patient would be interesting to analyse.

This study is retrospective and has limitations in terms of recommending further treatment. The inclusion of a conventional treatment (CXL) and an alternative treatment (t-PTK+CXL) makes it apparent that obtaining the alternative treatment was more challenging. Despite this, an equal number of eyes were treated with each method, as shown in Table 1, suggesting a favourable attitude towards the alternative treatment by the surgeons and follow-up team. A blinded, randomized comparison study would be necessary for more conclusive results. However, the aim of the study may not be to replace the conventional treatment but to provide more viable treatment options within specific criteria.

Comparable prospective clinical trials and studies have chosen to assign t-PTK+CXL treatment for the worst eye and CXL treatment for the best eye (Alessio et al., 2013). Future research could preferably very well have this approach since it is likely to assume that early diagnosis and binocular treatment will including subclinical keratoconus in at least one eye, especially in young people.

Retrospectively, it might look like one of the main criteria to choose PTK + CXL was pachymetry >420 microns and protentional to achieve good visual acuity. This threshold of pachymetry is also seen in comparable studies (Chen et al., 2017; Kapasi et al., 2012). For example, large refractive error with anisometropia and astigmatic anisometropia seemed to be to be favoured to the PTK + CXL treatment. However, this was not systemized or documented, nor investigated in this study. But for further research, this would be an interesting to focus on this matter.

Further, through the application of vector mathematics, the Alpins Method establishes a target for correcting astigmatism while assessing potential factors that may impede success in achieving this goal. Additionally, this approach may facilitate the enhancement of surgical procedures and

adjustment of laser settings for future interventions. Among other techniques employed to evaluate surgical outcomes, the Alpins Method is recognized as a highly sophisticated approach (Douglas D. Koch, 1997). Fu et al. (2018) study is an example of studies that already report vectors in their analyses of astigmatism. In the authors opinion, to truly know the success of refractive and visual outcomes, these numbers should be considered used in further studies that report visual outcome after treatment.

To fully answer the question of visual quality a quality-of-life questionnaire of the matter should have been tested simultaneously with the treatment process. These number also affect the fact that visual acuity below 0.05 Snellen lines are not graded. So, improvement between finger count and measurable visual acuity is noted as an improvement of 0.05 (from 0.00 to 0.05). Even if this study showed relatively high visual acuity, a LogMAR (logarithm of minimum angel of resolution) would assumably give more precise numbers over the true effect on improvement and decrease of visual acuity, especially where the visual acuity was poor.

Although not addressed in this thesis, an undoubtedly significant consideration is the public health implications of the visual impairment resulting from keratoconus. Kymes, Walline, Zadnik, and Gordon (2004) demonstrated that keratoconus has a greater impact on quality of life than its clinical severity might suggest.

11 References/bibliography

Alessio, G., L'Abbate, M., Sborgia, C., & La Tegola, M. G. (2013). Photorefractive keratectomy followed by cross-linking versus cross-linking alone for management of progressive keratoconus: two-year follow-up. *Am J Ophthalmol, 155*(1), 54-65.e51. doi:10.1016/j.ajo.2012.07.004

Alió, J. L., Piñero, D. P., Alesón, A., Teus, M. A., Barraquer, R. I., Murta, J., . . . Uceda-Montanes, A. (2011). Keratoconus-integrated characterization considering anterior corneal aberrations, internal astigmatism, and corneal biomechanics. *Journal of Cataract & Refractive Surgery, 37*(3), 552-568. doi:10.1016/j.jcrs.2010.10.046

Alió, J. L., & Shabayek, M. H. (2006). Corneal Higher Order Aberrations: A Method to Grade Keratoconus. *Journal of Refractive Surgery, 22*(6), 539-545. doi:doi:10.3928/1081-597X-20060601-05

Alió, J. L., & Shabayek, M. H. (2006). Corneal higher order aberrations: a method to grade keratoconus. *J Refract Surg, 22*(6), 539-545. doi:10.3928/1081-597x-20060601-05

Alshehri, O., Abdelaal, A. M., Abudawood, G., Khan, M. A., Alsharif, S., Hijazi, H., & AlQassimi, A. (2022). Normative Values for Corneal Tomography and Comparison of Both Eyes in Young Saudi Males with 20/20 Vision Using Pentacam-HR Scheimpflug Imaging. *Clin Ophthalmol, 16*, 2631-2637. doi:10.2147/opth.S376411

Arance-Gil, Á., Villa-Collar, C., Pérez-Sanchez, B., Carracedo, G., & Gutiérrez-Ortega, R. (2021). Epithelium-Off vs. transepithelial corneal collagen crosslinking in progressive keratoconus: 3 years of follow-up. *J Optom, 14*(2), 189-198. doi:10.1016/j.optom.2020.07.005

Aydin Kurna, S., Altun, A., Gencaga, T., Akkaya, S., & Sengor, T. (2014). Vision Related Quality of Life in Patients with Keratoconus. *Journal of Ophthalmology, 2014*, 694542. doi:10.1155/2014/694542

Baenninger, P. B., Bachmann, L. M., Wienecke, L., Kaufmann, C., & Thiel, M. A. (2014). Effects and adverse events after CXL for keratoconus are independent of age: a 1-year follow-up study. *Eye (Lond), 28*(6), 691-695. doi:10.1038/eye.2014.56

Bak-Nielsen, S., Ramlau-Hansen, C. H., Ivarsen, A., Plana-Ripoll, O., & Hjortdal, J. (2019). Incidence and prevalence of keratoconus in Denmark - an update. *Acta Ophthalmol, 97*(8), 752-755. doi:10.1111/aos.14082

Belin, M. W., & Duncan, J. K. (2016). Keratoconus: The ABCD Grading System. [Keratokonus: Das ABCD-System zur Stadieneinteilung]. *Klin Monbl Augenheilkd, 233*(06), 701-707. doi:10.1055/s-0042-100626

Chambers, W. A. (2021). Methods for Evaluating Drug-Induced Visual Side Effects. In F. F. T. Fraunfelder & F. R. W. Fraunfelder (Eds.), *Drug-Induced Ocular Side Effects (Eighth Edition)* (pp. 13-18). London: Elsevier.

Chanbour, W., El Zein, L., Younes, M. A., Issa, M., Warhekar, P., Chelala, E., & Jarade, E. (2021). Corneal Cross-Linking for Keratoconus and Post-LASIK Ectasia and Failure Rate: A 3 Years Follow-Up Study. *Cureus, 13*(11), e19552. doi:10.7759/cureus.19552

Chen, X., Stojanovic, A., Eidet, J. R., & Utheim, T. P. (2015). Corneal collagen cross-linking (CXL) in thin corneas. *Eye Vis (Lond), 2*, 15. doi:10.1186/s40662-015-0025-3

Chen, X., Stojanovic, A., Xu, Y., Zhou, W., Raeder, S., Enayati, S., & Utheim, T. P. (2017). Medium- to Long-Term Results of Corneal Cross-Linking for Keratoconus Using Phototherapeutic Keratectomy for Epithelial Removal and Partial Stromal Ablation. *J Refract Surg, 33*(7), 488-495. doi:10.3928/1081597x-20170504-03

Cifariello, F., Minicucci, M., Di Renzo, F., Di Taranto, D., Coclite, G., Zaccaria, S., . . . Costagliola, C. (2018). Epi-Off versus Epi-On Corneal Collagen Cross-Linking in

Keratoconus Patients: A Comparative Study through 2-Year Follow-Up. *J Ophthalmol, 2018*, 4947983. doi:10.1155/2018/4947983
Colin, J., & Velou, S. (2002). Utilization of refractive surgery technology in keratoconus and corneal transplants. *Curr Opin Ophthalmol, 13*(4), 230-234. doi:10.1097/00055735-200208000-00007
Cunha, A. M., Correia, P. J., Alves, H., Torrão, L., Moreira, R., Falcão-Reis, F., & Pinheiro-Costa, J. (2021). Keratoconus enlargement as a predictor of keratoconus progression. *Scientific Reports, 11*(1), 21079. doi:10.1038/s41598-021-00649-0
Dandapani, S. A., Padmanabhan, P., & Hussaindeen, J. R. (2020). Spectrum of Binocular Vision Anomalies in Keratoconus Subjects. *Optom Vis Sci, 97*(6), 424-428. doi:10.1097/opx.0000000000001517
Danesh, Z., Sedaghat, M. R., Momeni-Moghaddam, H., Yekta, A. A., & Belin, M. W. (2021). Corneal Stability and Visual Acuity 1 Year After Corneal Cross-linking Assessed Using the ABCD Keratoconus Staging System. *J Refract Surg, 37*(10), 700-706. doi:10.3928/1081597x-20210712-09
Davis, L. J., Schechtman, K. B., Begley, C. G., Shin, J. A., & Zadnik, K. (1998). Repeatability of refraction and corrected visual acuity in keratoconus. The CLEK Study Group. Collaborative Longitudinal Evaluation of Keratoconus. *Optom Vis Sci, 75*(12), 887-896. doi:10.1097/00006324-199812000-00011
Deshmukh, R., Reddy, J. C., Rapuano, C. J., & Vaddavalli, P. K. (2020). Phototherapeutic keratectomy: Indications, methods and decision making. *Indian Journal of Ophthalmology, 68*(12). Retrieved from https://journals.lww.com/ijo/Fulltext/2020/68120/Phototherapeutic_keratectomy__Indications,_methods.32.aspx
Efron, N. (2017). Contact lens wear is intrinsically inflammatory. *Clinical and Experimental Optometry, 100*(1), 3-19. doi:10.1111/cxo.12487
Fagerholm, P. (2003). Phototherapeutic keratectomy: 12 years of experience. *Acta Ophthalmol Scand, 81*(1), 19-32. doi:10.1034/j.1600-0420.2003.00015.x
Fernández-Vega-Cueto, L., Romano, V., Zaldivar, R., Gordillo, C. H., Aiello, F., Madrid-Costa, D., & Alfonso, J. F. (2017). Surgical Options for the Refractive Correction of Keratoconus: Myth or Reality. *Journal of Ophthalmology, 2017*, 7589816. doi:10.1155/2017/7589816
Flockerzi, E., Xanthopoulou, K., Goebels, S. C., Zemova, E., Razafimino, S., Hamon, L., . . . Seitz, B. (2021). Keratoconus staging by decades: a baseline ABCD classification of 1000 patients in the Homburg Keratoconus Center. *British Journal of Ophthalmology, 105*(8), 1069-1075. doi:10.1136/bjophthalmol-2020-316789
Fu, Y., Yu, X., Savini, G., Huang, J., Lian, H., Song, B., . . . Zhao, Y. (2018). Assessment of Corneal Keratometric and Astigmatism Measurements Using Verion System and Other Instruments in Cataract Patient. *Curr Eye Res, 43*(10), 1205-1214. doi:10.1080/02713683.2018.1488264
Gaster, R. N., Ben Margines, J., Gaster, D. N., Li, X., & Rabinowitz, Y. S. (2016). Comparison of the Effect of Epithelial Removal by Transepithelial Phototherapeutic Keratectomy or Manual Debridement on Cross-linking Procedures for Progressive Keratoconus. *J Refract Surg, 32*(10), 699-704. doi:10.3928/1081597x-20160712-01
Gatinel, D. (2007). 9 - Wavefront analysis. In D. T. Azar (Ed.), *Refractive Surgery (Second Edition)* (pp. 117-145). Edinburgh: Mosby.
Gediz, F., Yüksel, B., Küsbeci, T., Akmaz, O., & Kartı, Ö. (2019). The Effect of Donor- and Recipient-Related Factors on Corneal Graft Survival in Penetrating Keratoplasty. *Semin Ophthalmol, 34*(1), 11-18. doi:10.1080/08820538.2018.1549681
Gherghel, D., Hosking, S. L., Mantry, S., Banerjee, S., Naroo, S. A., & Shah, S. (2004). Corneal pachymetry in normal and keratoconic eyes: Orbscan II versus ultrasound. *J Cataract Refract Surg, 30*(6), 1272-1277. doi:10.1016/j.jcrs.2003.11.049

Godefrooij, D. A., de Wit, G. A., Uiterwaal, C. S., Imhof, S. M., & Wisse, R. P. (2017). Age-specific Incidence and Prevalence of Keratoconus: A Nationwide Registration Study. *Am J Ophthalmol, 175*, 169-172. doi:10.1016/j.ajo.2016.12.015

Gomes, J. A., Tan, D., Rapuano, C. J., Belin, M. W., Ambrósio, R., Jr., Guell, J. L., . . . Sangwan, V. S. (2015). Global consensus on keratoconus and ectatic diseases. *Cornea, 34*(4), 359-369. doi:10.1097/ico.0000000000000408

Gordon, M. O., Schechtman, K. B., Davis, L. J., McMahon, T. T., Schornack, J., & Zadnik, K. (1998). Visual acuity repeatability in keratoconus: impact on sample size. Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study Group. *Optom Vis Sci, 75*(4), 249-257. doi:10.1097/00006324-199804000-00021

Greenstein, S. A., Shah, V. P., Fry, K. L., & Hersh, P. S. (2011). Corneal thickness changes after corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. *J Cataract Refract Surg, 37*(4), 691-700. doi:10.1016/j.jcrs.2010.10.052

Grentzelos, M. A., Kounis, G. A., Diakonis, V. F., Siganos, C. S., Tsilimbaris, M. K., Pallikaris, I. G., & Kymionis, G. D. (2017). Combined transepithelial phototherapeutic keratectomy and conventional photorefractive keratectomy followed simultaneously by corneal crosslinking for keratoconus: Cretan protocol plus. *Journal of Cataract & Refractive Surgery, 43*(10), 1257-1262. doi:10.1016/j.jcrs.2017.06.047

Grentzelos, M. A., Liakopoulos, D. A., Siganos, C. S., Tsilimbaris, M. K., Pallikaris, I. G., & Kymionis, G. D. (2019). Long-term Comparison of Combined t-PTK and CXL (Cretan Protocol) Versus CXL With Mechanical Epithelial Debridement for Keratoconus. *J Refract Surg, 35*(10), 650-655. doi:10.3928/1081597x-20190917-01

Hagen, L. A., Gjelle, J. V. B., Arnegard, S., Pedersen, H. R., Gilson, S. J., & Baraas, R. C. (2018). Prevalence and Possible Factors of Myopia in Norwegian Adolescents. *Scientific Reports, 8*(1), 13479. doi:10.1038/s41598-018-31790-y

Haque, S., Jones, L., & Simpson, T. (2008). Thickness mapping of the cornea and epithelium using optical coherence tomography. *Optom Vis Sci, 85*(10), E963-976. doi:10.1097/OPX.0b013e318188892c

Hefner-Shahar, H., Erdinest, N., & Barbara, A. (2016). *High-order Aberrations in Keratoconus*.

Heidari, Z., Mohammadpour, M., Hashemi, H., Jafarzadehpur, E., Moghaddasi, A., Yaseri, M., & Fotouhi, A. (2020). Early diagnosis of subclinical keratoconus by wavefront parameters using Scheimpflug, Placido and Hartmann–Shack based devices. *International Ophthalmology, 40*(7), 1659-1671. doi:10.1007/s10792-020-01334-3

Helsedirektoratet. (2023). Førerkortveileder. doi:https://www.helsedirektoratet.no/veiledere/forerkortveileder

Henein, C., & Nanavaty, M. A. (2017). Systematic review comparing penetrating keratoplasty and deep anterior lamellar keratoplasty for management of keratoconus. *Cont Lens Anterior Eye, 40*(1), 3-14. doi:10.1016/j.clae.2016.10.001

Hersh, P. S., Greenstein, S., & Fry, K. (2012). Clinical Timecourse of Corneal Collagen Crosslinking. *Investigative Ophthalmology & Visual Science, 53*(14), 4124-4124.

Kandel, H., Pesudovs, K., & Watson, S. L. (2020). Measurement of Quality of Life in Keratoconus. *Cornea, 39*(3), 386-393. doi:10.1097/ico.0000000000002170

Kankariya, V. P., Dube, A. B., Grentzelos, M. A., Kontadakis, G. A., Diakonis, V. F., Petrelli, M., & Kymionis, G. D. (2020). Corneal cross-linking (CXL) combined with refractive surgery for the comprehensive management of keratoconus: CXL plus. *Indian Journal of Ophthalmology, 68*(12), 2757-2772. doi:10.4103/ijo.IJO_1841_20

Kankariya, V. P., Kymionis, G. D., Diakonis, V. F., & Yoo, S. H. (2013). Management of pediatric keratoconus – Evolving role of corneal collagen cross-linking: An update. *Indian Journal of Ophthalmology, 61*(8), 435-440. doi:10.4103/0301-4738.116070

Kapasi, M., Baath, J., Mintsioulis, G., Jackson, W. B., & Baig, K. (2012). Phototherapeutic keratectomy versus mechanical epithelial removal followed by corneal collagen crosslinking for keratoconus. *Can J Ophthalmol, 47*(4), 344-347. doi:10.1016/j.jcjo.2012.03.046

Kapasi, M., Dhaliwal, A., Mintsioulis, G., Jackson, W. B., & Baig, K. (2016). Long-Term Results of Phototherapeutic Keratectomy Versus Mechanical Epithelial Removal Followed by Corneal Collagen Cross-Linking for Keratoconus. *Cornea, 35*(2), 157-161. doi:10.1097/ico.0000000000000679

Kim, K. H., & Mian, S. I. (2020). Refractive approaches to visual rehabilitation in patients with keratoconus. *Current Opinion in Ophthalmology, 31*(4), 261-267. doi:10.1097/icu.0000000000000675

Koch, D. D. (1997). Excimer laser technology: New options coming to fruition. *Journal of Cataract & Refractive Surgery, 23*(10), 1429-1430. doi:10.1016/s0886-3350(97)80001-6

Koch, D. D., Ali, S. F., Weikert, M. P., Shirayama, M., Jenkins, R., & Wang, L. (2012). Contribution of posterior corneal astigmatism to total corneal astigmatism. *J Cataract Refract Surg, 38*(12), 2080-2087. doi:10.1016/j.jcrs.2012.08.036

Koh, S., Inoue, R., Maeno, S., Mihashi, T., Maeda, N., Jhanji, V., & Nishida, K. (2022). Characteristics of Higher-Order Aberrations in Different Stages of Keratoconus. *Eye Contact Lens, 48*(6), 256-260. doi:10.1097/icl.0000000000000897

Kontadakis, G. A., Kankariya, V. P., Tsoulnaras, K., Pallikaris, A. I., Plaka, A., & Kymionis, G. D. (2016). Long-Term Comparison of Simultaneous Topography-Guided Photorefractive Keratectomy Followed by Corneal Cross-linking versus Corneal Cross-linking Alone. *Ophthalmology, 123*(5), 974-983. doi:10.1016/j.ophtha.2016.01.010

Kristianslund, O., Hagem, A. M., Thorsrud, A., & Drolsum, L. (2021). Prevalence and incidence of keratoconus in Norway: a nationwide register study. *Acta Ophthalmol, 99*(5), e694-e699. doi:10.1111/aos.14668

Kuechler, S. J., Tappeiner, C., Epstein, D., & Frueh, B. E. (2018). Keratoconus Progression After Corneal Cross-Linking in Eyes With Preoperative Maximum Keratometry Values of 58 Diopters and Steeper. *Cornea, 37*(11), 1444-1448. doi:10.1097/ico.0000000000001736

Kymes, S. M., Walline, J. J., Zadnik, K., & Gordon, M. O. (2004). Quality of life in keratoconus. *Am J Ophthalmol, 138*(4), 527-535. doi:10.1016/j.ajo.2004.04.031

Kymionis, G., Grentzelos, M., Klados, N., Xanthopoulou, N., Paraskevopoulos, T., & Detorakis, E. (2015). Corneal Collagen Cross-Linking Mushroom Shape Demarcation Line Profile After Limited Bowman's Membrane Removal by Phototherapeutic Keratectomy. *The open ophthalmology journal, 9*, 17-19. doi:10.2174/1874364101509010017

Kymionis, G. D., Grentzelos, M. A., Kankariya, V. P., Liakopoulos, D. A., Karavitaki, A. E., Portaliou, D. M., . . . Pallikaris, I. G. (2014). Long-term results of combined transepithelial phototherapeutic keratectomy and corneal collagen crosslinking for keratoconus: Cretan protocol. *Journal of Cataract & Refractive Surgery, 40*(9), 1439-1445. doi:10.1016/j.jcrs.2014.01.040

Kymionis, G. D., Grentzelos, M. A., Kounis, G. A., Diakonis, V. F., Limnopoulou, A. N., & Panagopoulou, S. I. (2012). Combined transepithelial phototherapeutic keratectomy and corneal collagen cross-linking for progressive keratoconus. *Ophthalmology, 119*(9), 1777-1784. doi:10.1016/j.ophtha.2012.03.038

Kymionis, G. D., Portaliou, D. M., Kounis, G. A., Limnopoulou, A. N., Kontadakis, G. A., & Grentzelos, M. A. (2011). Simultaneous topography-guided photorefractive keratectomy followed by corneal collagen cross-linking for keratoconus. *Am J Ophthalmol, 152*(5), 748-755. doi:10.1016/j.ajo.2011.04.033

Lim, L., Wei, R. H., Chan, W. K., & Tan, D. T. (2007). Evaluation of higher order ocular aberrations in patients with keratoconus. *J Refract Surg, 23*(8), 825-828. doi:10.3928/1081-597x-20071001-13

Lin, H.-Z., Chen, C.-C., & Lee, Y.-C. (2013). Comparisons of wavefront refraction, autorefraction, and subjective manifest refraction. *Tzu Chi Medical Journal, 25*(1), 43-46. doi:https://doi.org/10.1016/j.tcmj.2013.01.006

Matthaei, M., Sandhaeger, H., Hermel, M., Adler, W., Jun, A. S., Cursiefen, C., & Heindl, L. M. (2017). Changing Indications in Penetrating Keratoplasty: A Systematic Review of 34 Years of Global Reporting. *Transplantation, 101*(6), 1387-1399. doi:10.1097/tp.0000000000001281

McGhee, C. N., Kim, B. Z., & Wilson, P. J. (2015). Contemporary Treatment Paradigms in Keratoconus. *Cornea, 34 Suppl 10*, S16-23. doi:10.1097/ico.0000000000000504

McMahon, T., Szczotka-Flynn, L., Barr, J., Anderson, R., Slaughter, M., Lass, J., & Iyengar, S. (2006). A New Method for Grading the Severity of Keratoconus. *Cornea, 25*, 794-800. doi:10.1097/01.ico.0000226359.26678.d1

McMahon, T. T., Szczotka-Flynn, L., Barr, J. T., Anderson, R. J., Slaughter, M. E., Lass, J. H., . . . Group, a. t. C. S. (2006). A New Method for Grading the Severity of Keratoconus: The Keratoconus Severity Score (KSS). *Cornea, 25*(7), 794-800. doi:10.1097/01.ico.0000226359.26678.d1

Meiri, Z., Keren, S., Rosenblatt, A., Sarig, T., Shenhav, L., & Varssano, D. (2016). Efficacy of Corneal Collagen Cross-Linking for the Treatment of Keratoconus: A Systematic Review and Meta-Analysis. *Cornea, 35*(3), 417-428. doi:10.1097/ico.0000000000000723

Mohammadi, S. F., Khorrami-Nejad, M., & Hamidirad, M. (2019). Posterior corneal astigmatism: a review article. *Clin Optom (Auckl), 11*, 85-96. doi:10.2147/opto.S210721

Morgan, I. G., French, A. N., Ashby, R. S., Guo, X., Ding, X., He, M., & Rose, K. A. (2018). The epidemics of myopia: Aetiology and prevention. *Prog Retin Eye Res, 62*, 134-149. doi:10.1016/j.preteyeres.2017.09.004

Morgenstern, A., Chang, C., & Eiden, B. (2020). 10 things you need to know about manageing keratoconus.

Nagpal, R., Maharana, P. K., Roop, P., Murthy, S. I., Rapuano, C. J., Titiyal, J. S., . . . Sharma, N. (2020). Phototherapeutic keratectomy. *Surv Ophthalmol, 65*(1), 79-108. doi:10.1016/j.survophthal.2019.07.002

Najmi, H., Mobarki, Y., Mania, K., Altowairqi, B., Basehi, M., Mahfouz, M. S., & Elmahdy, M. (2019). The correlation between keratoconus and eye rubbing: a review. *Int J Ophthalmol, 12*(11), 1775-1781. doi:10.18240/ijo.2019.11.17

Nassaralla, B. A. (2022). Corneal Cross-Linking: Indications and Contraindications. In E. Almodin, B. A. Nassaralla, & J. Sandes (Eds.), *Keratoconus : A Comprehensive Guide to Diagnosis and Treatment* (pp. 373-391). Cham: Springer International Publishing.

Niu, K., & Tian, C. (2022). Zernike polynomials and their applications. *Journal of Optics, 24*(12), 123001. doi:10.1088/2040-8986/ac9e08

Ortiz-Toquero, S., Fernandez, I., & Martin, R. (2020). Classification of Keratoconus Based on Anterior Corneal High-order Aberrations: A Cross-validation Study. *Optom Vis Sci, 97*(3), 169-177. doi:10.1097/opx.0000000000001489

Ortiz-Toquero, S., Perez, S., Rodriguez, G., de Juan, V., Mayo-Iscar, A., & Martin, R. (2016). The influence of the refractive correction on the vision-related quality of life in keratoconus patients. *Quality of Life Research, 25*(4), 1043-1051. doi:10.1007/s11136-015-1117-1

Phillips, A. J. (2003). Can true monocular keratoconus occur? *Clin Exp Optom, 86*(6), 399-402. doi:10.1111/j.1444-0938.2003.tb03085.x

Pinto, R. D. P., Abe, R. Y., Gomes, F. C., Barbisan, P. R. T., Martini, A. F., de Almeida Borges, D., . . . Alves, M. (2021). Quality of life in keratoconus: evaluation with Keratoconus Outcomes Research Questionnaire (KORQ). *Scientific Reports, 11*(1), 12970. doi:10.1038/s41598-021-92346-1

Raiskup-Wolf, F., Hoyer, A., Spoerl, E., & Pillunat, L. E. (2008). Collagen crosslinking with riboflavin and ultraviolet-A light in keratoconus: long-term results. *J Cataract Refract Surg, 34*(5), 796-801. doi:10.1016/j.jcrs.2007.12.039

Raiskup, F., Theuring, A., Pillunat, L. E., & Spoerl, E. (2015). Corneal collagen crosslinking with riboflavin and ultraviolet-A light in progressive keratoconus: ten-year results. *J Cataract Refract Surg, 41*(1), 41-46. doi:10.1016/j.jcrs.2014.09.033

Rapuano, C. J. (2010). Phototherapeutic keratectomy: who are the best candidates and how do you treat them? *Curr Opin Ophthalmol, 21*(4), 280-282. doi:10.1097/ICU.0b013e32833a8e0d

Salman, A., Kailani, O., Marshall, J., Ghabra, M., Balamoun, A. A., Darwish, T. R., . . . Alhaji, H. (2022). Evaluation of Anterior and Posterior Corneal Higher Order Aberrations for the Detection of Keratoconus and Suspect Keratoconus. *Tomography, 8*(6), 2864-2873. doi:10.3390/tomography8060240

Salmon, J. F. (2018). KANSKI'S Clinical Ophthalmology *Book*(9), 601-602.

Santodomingo-Rubido, J., Carracedo, G., Suzaki, A., Villa-Collar, C., Vincent, S. J., & Wolffsohn, J. S. (2022). Keratoconus: An updated review. *Cont Lens Anterior Eye, 45*(3), 101559. doi:10.1016/j.clae.2021.101559

Sarac, O., Kosekahya, P., Caglayan, M., Tanriverdi, B., Taslipinar Uzel, A. G., & Cagil, N. (2018). Mechanical versus transepithelial phototherapeutic keratectomy epithelial removal followed by accelerated corneal crosslinking for pediatric keratoconus: Long-term results. *J Cataract Refract Surg, 44*(7), 827-835. doi:10.1016/j.jcrs.2018.04.039

Savini, G., Carbonelli, M., Barboni, P., & Hoffer, K. J. (2011). Repeatability of automatic measurements performed by a dual Scheimpflug analyzer in unoperated and post-refractive surgery eyes. *J Cataract Refract Surg, 37*(2), 302-309. doi:10.1016/j.jcrs.2010.07.039

Schechter, R. J. (1977). Snell's Law: optimum pathway analysis. *Surv Ophthalmol, 21*(6), 464-466. doi:10.1016/s0039-6257(77)80002-7

Smadja, D., & Krauthammer, M. (2023). Chapter 8 - Clinical Course and Progression of Keratoconus. In L. Izquierdo, M. Henriquez, & M. Mannis (Eds.), *Keratoconus* (pp. 103-112). New Delhi: Elsevier.

Spierer, O., Fischer, N., Barak, A., & Belkin, M. (2016). Correlation Between Vision and Cognitive Function in the Elderly: A Cross-Sectional Study. *Medicine (Baltimore), 95*(3), e2423. doi:10.1097/md.0000000000002423

Spoerl, E., Huhle, M., & Seiler, T. (1998). Induction of cross-links in corneal tissue. *Exp Eye Res, 66*(1), 97-103. doi:10.1006/exer.1997.0410

Subasinghe, S. K., Ogbuehi, K. C., & Dias, G. J. (2018). Current perspectives on corneal collagen crosslinking (CXL). *Graefes Arch Clin Exp Ophthalmol, 256*(8), 1363-1384. doi:10.1007/s00417-018-3966-0

Thiagalingam, S., Cumming, R. G., & Mitchell, P. (2002). Factors associated with undercorrected refractive errors in an older population: the Blue Mountains Eye Study. *Br J Ophthalmol, 86*(9), 1041-1045. doi:10.1136/bjo.86.9.1041

Unterhorst, H. A., & Rubin, A. (2015). Ocular aberrations and wavefront aberrometry: A review. *2015, 74*(1). doi:10.4102/aveh.v74i1.21

Wajnsztajn, D., Shmueli, O., Zur, K., Frucht-Pery, J., & Solomon, A. (2022). Predicting factors for the efficacy of cross-linking for keratoconus. *PLoS One, 17*(2), e0263528. doi:10.1371/journal.pone.0263528

Walker, M. K., Lema, C., & Redfern, R. (2020). Scleral lens wear: Measuring inflammation in the fluid reservoir. *Contact Lens and Anterior Eye, 43*(6), 577-584. doi:https://doi.org/10.1016/j.clae.2020.02.017

Wilson, S. E., Marino, G. K., Medeiros, C. S., & Santhiago, M. R. (2017). Phototherapeutic Keratectomy: Science and Art. *J Refract Surg, 33*(3), 203-210. doi:10.3928/1081597x-20161123-01

Wollensak, G., Spoerl, E., & Seiler, T. (2003). Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. *Am J Ophthalmol, 135*(5), 620-627. doi:10.1016/s0002-9394(02)02220-1

Wu, Y., Tan, Q., Zhang, W., Wang, J., Yang, B., Ma, W., . . . Liu, L. (2015). Rigid gas-permeable contact lens related life quality in keratoconic patients with different grades of severity. *Clin Exp Optom, 98*(2), 150-154. doi:10.1111/cxo.12237

Zadnik, K., Barr, J. T., Edrington, T. B., Everett, D. F., Jameson, M., McMahon, T. T., . . . Gordon, M. O. (1998). Baseline findings in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study. *Invest Ophthalmol Vis Sci, 39*(13), 2537-2546.

Zhang, X. H., & Li, X. (2020). Effect of rigid gas permeable contact lens on keratoconus progression: a review. *Int J Ophthalmol, 13*(7), 1124-1131. doi:10.18240/ijo.2020.07.17

List of tables and charts