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Pathogenesis, presentation, and treatment of keratoconus within the United States

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PATHOGENESIS, PRESENTATION, AND TREATMENTS OF KERATOCONUS
WITHIN THE UNITED STATES

by

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I am truly lucky to have these people in my life and would like to dedicate this thesis to all of them.
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WITHIN THE UNITED STATES

BRIAN THOMAS HUNTINGTON

Boston University School of Medicine, 2013

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ABSTRACT

Keratoconus is a non-inflammatory thinning of the cornea that can lead to an irregular conical shaped protrusion generally of the lower mid-peripheral nasal or temporal hemisphere of the cornea. This degenerative disorder has no known individual cause, nor does it have a known cure. Causes have been theorized to be multifactorial ranging from genetic disorders to environmental stimuli. Overall roughly 1 in 2,000 people suffer from the disorder.

The treatment for keratoconus has generally focused on a broad range of different types of contact lenses, with the patients whose corneas degrade to dangerously thin limits or where visual acuity can no longer be corrected, become candidates for corneal transplant surgery. It is today the third most common cause for corneal transplant.
This study focused on detailing the various treatment options keratoconus patients have, as well as what advances these treatments have each made in recent years. These treatments generally focus on maximizing visual acuity while attempting to retain the corneal protrusion. The other goal of these treatments is to push off the necessity for corneal transplant due to the risks of graft rejection, the risks of surgery, and the overall decrease in quality of life an implant can have on a patient’s life. The studies showed that treatment has come a long way, though there still remains to be a treatment that can appropriately halt the progression of keratoconus. This brings the paper to examine the role and potential impact corneal collagen cross linking could have on keratoconus patients in the U.S.

Corneal Collagen Cross Linking is a procedure where through riboflavin (vitamin B$_2$) and UV-A light, collagen cross links can be induced within the corneal stroma. By linking the collagen polymers, it is theorized that this could permanently halt the progression of keratoconus. This treatment has been approved in Europe since 2006 and in Canada since 2008, but only entered into clinical trials within the U.S. in 2008.

By performing an extensive literature review, it was concluded that corneal cross linking is a safe and effective method of treatment for keratoconus. Enough literature has been published by the international community over the past 15 years that the U.S. could have begun and concluded FDA clinical trials
sooner. The treatment has the potential to halt the progression of keratoconus before it has any debilitating effects, though as of now is not available to most Americans. With the FDA likely to approve the procedure within the next year, keratoconus patients will have a new treatment option that will very likely substantially improve their quality of life.
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## ABBREVIATIONS

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<tr>
<td>CXL</td>
<td>Corneal Cross-Linking</td>
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<tr>
<td>DALK</td>
<td>Deep Anterior Lamellar Keratoplasty</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>ICRS</td>
<td>Intrastromal Corneal Ring Segment</td>
</tr>
<tr>
<td>IL</td>
<td>Interleukins</td>
</tr>
<tr>
<td>LASEK</td>
<td>Sub-Epithelial keratectomy</td>
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<td>LASIK</td>
<td>Laser In-Situ Keratomileusis</td>
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<tr>
<td>LOX</td>
<td>Lysyl Oxidase Gene</td>
</tr>
<tr>
<td>MMP</td>
<td>Matrix Metalloproteinases</td>
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<tr>
<td>pIOL</td>
<td>Phakic Intraocular Lenses</td>
</tr>
<tr>
<td>PKP</td>
<td>Penetrating Keratoplasty</td>
</tr>
<tr>
<td>RGP</td>
<td>Rigid Gas Permeable</td>
</tr>
<tr>
<td>RK</td>
<td>Radial Keratectomies</td>
</tr>
<tr>
<td>SNP</td>
<td>Single Nucleotide Polymorphism</td>
</tr>
<tr>
<td>TMP-1</td>
<td>Tissue Inhibitor of Metalloproteinases-1</td>
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<td>Abbreviation</td>
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<tr>
<td>TNF</td>
<td>Tumor Necrosis Factor</td>
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<td>UV-A</td>
<td>Ultra Violet A</td>
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I. Introduction:

Keratoconus comes from the Greek words of *kerat-* meaning horn (cornea) and *–conus* meaning cone (Wheeler, Hauser, Afshari, Allingham, & Liu, 2012). The phrase comes from the primary characteristic of the disorder in which the cornea of the eye will degrade and become thin enough that it will structurally form a visible cone shaped protrusion (Wheeler et al., 2012). This degenerative disorder has no known individual cause, nor does it have a known cure. Its prevalence within the United States is debated in part to its broad degree of clinical presentation and rate of progression. It has been stated to be as prevalent as 1 in 450 though most studies have the number closer to an average of 1 in 2,000 people within the United States. Sex does not seem to be a determinant though South Asians have been found to be substantially more likely of developing the disorder, with prevalence of 1 in 450 people (Gore, Shortt, & Allan, 2013). Certain other factors have been shown to correlate with its onset such as Down syndrome, certain connective tissue disorders, prevalence of allergies, high UV exposure, genetic inheritance, and compulsive eye rubbing, all which will be discussed more in depth later (Sugar & Macsai, 2012).

Keratoconus is a serious form of corneal dystrophy that results in the thinning and reshaping of the cornea, leading to vision problems of severe myopia and irregular astigmatism. It occurs predominantly with the onset of puberty and generally progresses over the next 1-3 decades of the patient’s life
(Weissman, 2013). Due to the overall prevalence of this disorder, the young age at which it begins to occur, and to the high cost of quality-adjusted life years due to the lifelong treatment and deterioration of sight, this disorder has merited much of the focus and resources from the ophthalmic community (Gothwal et al., 2013).

II. Objectives

The following paper will aim to further explain the presentation, diagnosis, progression, and treatment options of keratoconus. While previous and current treatments have been shown to sometimes alleviate or retard the progression of the disorder, they have been far from perfect in terms of reversing damage or even permanently halting the progression (Gothwal et al., 2013). These treatment options are worth discussing as they all have benefited from very recent technological advances. With the future combination therapies to be seen in the near future potentially with corneal collagen cross linking, a thorough understanding of these treatment options could greatly benefit patients in the future.

This paper will also focus on the novel technique of corneal collagen cross linking. This procedure, though first successfully completed in 1998 in Germany, was not accepted into common practice in Europe till 2006. Despite promising studies from Europe, the U.S. only started FDA clinical trials in 2008 and are still undergoing them today. An examination of the published literature up to the
present is worthwhile in order to determine if corneal cross linking is a worthwhile procedure, and to what effect it will likely have on the keratoconus patients of the United States. The review will focus on the potential benefits as well as the risks of cross-linking while also determining in this author’s own opinion whether or not cross-linking should or is likely to be approved by the FDA in the coming months or years.

A. Structure and Function of the Cornea

To properly understand the pathophysiology of the onset of keratoconus, a basic understanding of the structure and function of the cornea is necessary (Figure 1). The human cornea is the anterior most segment of the eye with its most posterior layer meeting the anterior chamber. It is characteristically divided into five distinct and basic layers, with the anterior most being the epithelium, then Bowman’s layer, the stroma, Descemet’s Membrane, and the posterior most being the corneal endothelium (“ANATOMY OF THE HUMAN EYE: Cornea Histology,” n.d.). Together, the five layers create a roughly 500µm thick transparent cover that plays the greatest role in terms of refracting light onto the retina, with the overall refractive power of the cornea generally about 43 diopters versus the lens itself being only 18 diopters (Piñero, Nieto, & Lopez-Miguel, 2012).
The epithelial layer of the cornea is the outermost layer of the eye and provides the tear interface with the outside world. It is a non-keratinized squamous cell epithelium that is 4-6 cell layers thick (DelMonte & Kim, 2011).

Bowman’s layer is a strong layer of type I collagen that is heavily intertwined. It creates a barrier to the beginning of the stroma and is overall irreplaceable. When damaged, scarring generally occurs due to the following inflammation reaction. It is 8-12µm thick (Morishige, Takagi, Chikama, Takahara, & Nishida, 2011).

The stroma is the bulk of the corneal tissue accounting for 90% of the thickness of the cornea. It is primarily composed of neatly arranged collagen type I fibrils interspersed with keratocytes, also called corneal fibroblasts. The keratocytes play a major role in the healing and arrangement of the collagen fibrils of the stroma (DelMonte & Kim, 2011). They have also been regarded as a potentially a major player in the onset of keratoconus. As injury is presented to the cornea, keratocytes nearest to the injury will undergo apoptosis, while those on the periphery of the injury will initiate repairing the stroma. In keratoconus patients, it has been found that even keratocytes far from the injury will undergo apoptosis, leading to a greater risk of inflammation, scarring, and overall less wound healing (Sevost’ianov, Giniatullin, Gorskova, & Teplova, 2002).
Descemet’s layer is also a collagen layer, though type IV and serves as the basement membrane to the endothelial layer of the cornea. This layer is crucial to the non-regenerating endothelial cells (Johnson DH, 1982).

The endothelial layer of the cornea is not a true endothelium as it does not border the interior of a blood vessel or part of the lymph system, but rather the aqueous humor filled anterior chamber (DelMonte & Kim, 2011). It’s a single cellular layer whose primary function is to create an osmotic gradient in order to allow a passive flow of water from the stroma into the anterior chamber. This creates an intraocular pressure that helps form the shape of the cornea. When the cells of the endothelium are damaged, the other will grow in size to take over the vacant space (DelMonte & Kim, 2011). When enough are damaged though, the corneal stroma can lose its osmotic gradient thus reversing the osmotic pressure gradient for the flow of water. The stroma will fill with water and lose its transparency. If the endothelium layer is not able to grow in size and shape in order to fix this, the corneal edema will remain, thus necessitating surgical intervention in order to regain vision (DelMonte & Kim, 2011).
B. Keratoconus: Pathogenesis and Causal Factors

The non-inflammatory thinning of the cornea caused by Keratoconus leads to an irregular conical shape generally of the lower mid-peripheral nasal or temporal hemisphere of the cornea (Piñero et al., 2012). While thinning of the inferior periphery and central cornea are the most common, there are some cases where the initial protrusion develops in the superior periphery (Meek et al.,
The thinning of the cornea is due particularly to the degradation of the stromal layer as well as most often the degradation of Bowman’s membrane (Figure 2). In one study, studying the corneal layers of 36 keratoconus patients (Sykakis, Carley, Irion, Denton, & Hillarby, 2012), 92% of the corneas showed breaks in Bowman’s membrane. This was positively correlated with the number of apoptotic keratocytes nearby. In a literature review done by (Sherwin & Brookes, 2004), the basal layer of the epithelium will often become irregular as the cells and intercellular connections degrade. The review found that type XII collagen staining of the basement membrane was markedly less than in normal corneas. The gaps that developed between the basal cells fill with collagen and ECM from the stromal layers in a process that is described as a wound healing process. Because of the invasion of disarranged and disorderly collagen from the stroma, the breaks in Bowman’s membrane can lead to the beginning stages of corneal opacities.
Figure 2: Histopathology of Advanced Keratoconus: Image shows pathology characteristic of each of the five layers of the human cornea. In addition, pathology such as thickened nerve fibers in the sub-basal plexus are shown and indicative of keratoconus.

Breaks in Descemet’s membrane were found in 19% of the corneas, and were correlated with substantially thinner stromal layers (Sykakis et al., 2012). While breaks in Descemet’s is much less common than Bowman’s, they generally coincide with a much more progressed case (Figure 2) (Johnson DH, 1982). Since Descemet’s is the basement membrane of the endothelial cells, ruptures in the membrane will cause a degradation of the endothelial layer through apoptosis. The remaining endothelial cells attempt to fill in the spaces of lost cells, but when failure occurs corneal hydrops can result (Romero-Jiménez, Santodomingo-Rubido, & Wolffsohn, 2010). Hydrops is when the fluid from the anterior chamber is to flow into the stroma and cause it to swell. Unless the eye is able to recover and reseal the endothelium through hypertrophy and remove the excess fluid, surgical intervention and most likely a form of corneal transplant will be necessary (Sharma, Maharana, Singh, & Titiyal, 2010).

The apical portion of the corneal protrusion forming the “cone” of keratoconus, generally represents the thinnest and structurally weakest portion of the cornea. As a result this is the least resistant to maintaining the normal curvature of the cornea. As this protrusion becomes more pronounced, the increased friction and contact with the eyelid sometimes becomes the cause for a buildup of the epithelial layer, though in most cases of keratoconus, the apex will retain the thinnest point of epithelium (Sherwin & Brookes, 2004). The resulting protrusion and deformation of the cornea leads to the associated irregular astigmatism and myopia. (Piñero et al., 2012).
Onset is gradual and generally occurs during puberty. Late-onset keratoconus can also occur in the late 20-30’s but is both much less common and severe. Keratoconus fruste, which is a very mild and stable type of keratoconus, can develop at any point in life and is even less common (Caroline, Andre, Kinoshita, & Choo, n.d.). While keratoconus is almost always bilateral, the progression of the two eyes can differ greatly, leading to only one eye usually being noticed in the initial diagnosis. Upon onset, the disorder will progress for the next 10-30 years until it stabilizes (Weissman, 2013). The speed at which it progresses is dependent on a case by case basis, and necessitates a dramatic spectrum of treatments based on the severity (Gore et al., 2013).

The causes of keratoconus are yet to be proven, though a wide field of factors have been strongly correlated with the disorder over the past several decades. Older studies before the advent of the Pentacam and other forms of corneal topography show that about 6-8% of keratoconus patients have been found to have had close family members who have suffered from the disorder. In a more recent study using the greater diagnostic power of corneal topography, this number is now placed closer to 50% of patients (Romero-Jiménez et al., 2010). Even more striking is a literature review that shows 19 pairs of monozygotic twins where each pair both suffered from keratoconus. This showed a likelihood of genetic inheritance though suggested environmental factors at play due to the variability of severity and progression between the sets of twins (Romero-Jiménez et al., 2010). The form of inheritance is still debated
as some studies have shown keratoconus to behave in a autosomal dominant manner while others have shown more recessive traits (Romero-Jiménez et al., 2010). One rationale for this may be multiple genetic or factors at play that can cause or aid in the development of keratoconus.

Several syndromes have been heavily correlated with keratoconus such as Down syndrome where patients are between 10-300 times more likely to develop keratoconus while other disorders such as diabetes have a protective correlation. There are also multiple inherited connective tissues disorders such as Ehlers-Danlos Syndrome type IV, joint hypermobility syndrome, Marfan’s and Osteogenesis imperfect (Balasubramanian, Pye, & Willcox, 2010; Romero-Jiménez et al., 2010). The association with some of these disorders has lent insight into what genetic factors might be at play within keratoconus cases (Bykhovskaya et al., 2012). Many studies have produced evidence towards genetic errors within the Lysyl Oxidase gene (LOX). LOX is an enzyme that reacts with lysine residues to form aldehydes. These aldehydes are thus able to react with each other and form stabilizing cross links within collagen strands (Bykhovskaya et al., 2012). The impairment of the LOX gene could therefore destabilize the collagen matrix of the stroma. In a study by Bykhovskaya, et al. the researchers examined the activity of LOX via genotyping 222 confirmed keratoconus cases vs. over five thousand case controls. The researchers found several SNP’s with multiple alleles that demonstrated reducing the effectiveness of the two isoforms of LOX located within the cornea. This result strongly
supports the rationale for the effectiveness of corneal cross-linking treatment, which will be discussed later in this paper.

Other proposed genetic factors have been in the genetic and biochemical regulation of proteases, particularly those that have to do with the stromal extracellular matrix and Bowman’s membrane (Balasubramanian et al., 2010). In a literature review done in 2010, it was found that many keratoconus patients had increased levels of proteinases, specifically matrix metalloproteinases (MMP) and cathepsins which can both act as collagenases and gelatinases. The review also found that many keratoconus patients had reduced levels of tissue inhibitor of metalloproteinases-1 (TMP-1), an inhibitor of MMP’s (Balasubramanian et al., 2010).

In addition, studies found that despite keratoconus being a non-inflammatory disease, certain inflammatory signaling factors such as interleukins (IL) and tumor necrosis factor (TNF) were elevated and present in the tears as well as the aqueous humor. Not only were these factors elevated but in some patients, keratocytes in the anterior stroma were found to have as many as four times as many receptors for IL-1 than usual (Balasubramanian et al., 2010; Romero-Jiménez et al., 2010). By IL’s binding to keratocytes, cathepsins were up-regulated. The abundance of cathepsins, as well as TNF, is predicted to signal keratocytes to undergo apoptosis, much as they only normally would under chemical or mechanical trauma (Chwieralski, Welte, & Bühling, 2006).
The apoptosis is likely to cause the release of more IL and other cytokines thus propagating the effect. With the up-regulated cathepsins and additional TNF, the MMP’s are further up-regulated. The overall effect of this chain reaction and up-regulation of proteinases, is the degradation of the epithelial basement membrane (Bowman’s layer) as well as the degradation of the stromal matrix.

An interesting aspect of this cascade is that while it has been demonstrated to be produced through many different genetic mutations, this cascade can also be instigated mechanically. In patients with Tourette syndrome or Leber’s congenital amaurosis, subjects will often compulsively rub their eyes cause self-induced keratoconus. (Nielsen, Hjortdal, Pihlmann, & Corydon, 2013; Romero-Jiménez et al., 2010). It is believed that over time, the continuous rubbing releases enough cytokines from damaged epithelium that keratocytes are triggered into apoptosis in addition to the MMP and cathepsins being up-regulated. While these cases may or may not be an additive effect upon of other aspects of these disorders, some cases of keratoconus are also seen in otherwise healthy individuals who over wear their contact lenses; once again stressing the epithelial layer. The time of onset, speed of progression, and end result of severity, all differ from patient to patient regardless of the suspected causes leaving much speculation as to the true development of keratoconus.

Overall, there have been hundreds of studies on the genetic causes of keratoconus. In an extremely recent publication this year by a team of Danish
ophthalmologists, the past two decades of genetic studies of keratoconus were examined. They found that 16 of the 22 autosomal chromosomes had loci that had a role indicated in keratoconus. The others pointed out that through the conglomereration of the data that it was clear that keratoconus is likely a “characteristic corneal phenotype [that] may be a shared symptom of several different monogenic diseases (Nielsen et al., 2013).” An interesting conclusion by the authors was their determination that keratoconus is not only a polygenic disorder, meaning it is caused by multiple mutations of multiple genes, but rather a multifactorial disorder where its cause is an additive buildup of multiple genetic and environmental factors. This determination would lend explanation to the gross variety of cases that fit the definition of keratoconus.

C. Clinical Presentation, Diagnosis, and Progression

There are overall seven principle clinical presentations that are considered indicative of keratoconus that were established in 1965 by Duke Elder, a former chairman and editor of the British Journal of Ophthalmology (Sherwin & Brookes, 2004). These seven criteria are still used today, though not all need to be present for a diagnosis to be made, as several of them are only seen in moderate to late stage development.
Two features have been discussed already such as the ruptures within Descemet’s as well as Bowman’s membranes. Both of these features can be examined via a slit lamp by an ophthalmologist though, generally will be indicative of more advanced cases.

Another presentation is a brown to yellowish ring that forms around the base of the corneal protrusion called Fleischer’s ring. Fleischer’s ring is a ring of iron deposits made up of hemosiderin that appears in 57% of patients (Edrington, Zadnik, & Barr, 1995). The ring appears at the base of the corneal protrusion and varies in thickness and color. The source of the iron, in one study using electron microscopy, determined that the perilimbal vessels are most likely the source of the ferritin deposits. As the cornea protrudes out, the apex will receive the majority of the pressure and friction form the eyelid. This likely causes minor irritation and inflammation, followed by rupture of the minor vessels. The iron from these cells would be phagocytosed by macrophages where the macrophages are then carried to the epithelial base of the corneal protrusion via the tear film. This deposit via the tears would help explain the concentration of the ring only within the epithelium while also being an area devoid of red blood cells and macrophages (Iwamoto T, 1976).

A fourth presentation is Vogt’s striae (Lee, Hirst, & Readshaw, 1995). These are virtually stress lines that are formed within the stroma as the corneal protrusion bulges away from the normal corneal plane. These stretch marks are
always vertical and form between the individual cellular layers, or lamella, of the stroma (Lee et al., 1995).

A fifth and obvious major presentation through basic exam, is observed through pachymetry. By using a pachymeter, central as well as apical corneal thickness can be determined. Corneas vary from individual so a change in baseline is the most accurate in terms of pachymetry, though lower than normal values can at least indicate the need for further exam or diagnostics. The apex of the protrusion can become as much as 20%-80% thinner than the rest of the cornea (Sherwin & Brookes, 2004).

A sixth clinical presentation of the basic exam is a reflex seen through a retinoscope during a dilated exam. As the light is moved across the pupil, the light reflecting off the retina should refract off the posterior surface of the cornea. The result, even in very early stage keratoconus patients will be a “scissor or oil droplet reflex” that is indicative of the beginnings of the corneal protrusion (Lee et al., 1995).

Lastly, the seventh clinical presentation which also necessitates slit-lamp examination is the thickening of nerve fibers in the sub-basal nerve plexus. This layer of nerves is located between Bowman’s membrane and the epithelial cells and is very densely innervated. When the effects of keratoconus begin to form breaks in Bowman’s membrane, the nerve fibers will thicken to such a degree that they can become visible through close examination. The mechanism or
direct cause of this presentation is still not fully understood (Levin et al., 2011; Sherwin & Brookes, 2004).

The clinical presentation and degree of onset of keratoconus is classified according to Amsler-Krumeich classification (Table 1) (Jorge, 2006). At its most progressed stages, keratoconus can be visibly seen without the aid of a slit lamp by an ophthalmologist, though the very beginning stages can easily be misinterpreted as a minor myopia and/or astigmatism. This can sometimes be aided in diagnosis by a sudden diagnosis of anisometropia, where the two eyes will differ in a great than normal degree of refractive power (Jorge, 2006). The A&M scale is based off four metrics. The degree of myopic and astigmatic refractive error the corneal steepening causes, the mean central K readings, central corneal scarring, and the minimum corneal thickness.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Metrics</th>
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| Stage I | * Eccentric steeping  
* Myopia and astigmatism < 5.00 D  
* Mean central K readings < 48.00 D |
| Stage II | * Myopia and astigmatism from 5.00 to 8.00 D  
* Mean central K readings < 53.00 D  
* Absence of scarring  
* Minimum corneal thickness > 400 µm. |
| Stage III | * Myopia and astigmatism from 8.00 to 10.00 D  
* Mean central K readings > 53.00 D  
* Absence of scarring  
* Minimum corneal thickness 300 to 400 µm. |
| Stage IV | * Refraction not measurable  
* Mean central K readings > 55.00 D  
* Central corneal scarring  
* Minimum corneal thickness 200 µm |

**Table 1: Amsler-Krumeich Classification:** Stages 1-4 with increasing severity of symptoms. Mean central K readings indicate the steepness of the corneal protrusion. Refraction no longer measurable in Stage IV is due to severe corneal scarring.  
The clinical manifestations of keratoconus can vary per patient, though certain characteristics are common, at the very onset of the disorder there may be no clinical presentation other than minute changes within the cornea’s surface. New modern imaging technology has made this more accurate and thus possible to detect.

For early and intermediate stages of keratoconus, the most popular and accurate manner in which to diagnose is through computer assisted corneal topography, most commonly using the Scheimpflug Pentacam. The Pentacam is useful in differentiating the normal anterior corneal curvature from that of characteristic signs seen in early to mid-stage keratoconus patients (Figure 3) (Piñero et al., 2012). The Pentacam takes 15-20 pictures about a rotating axis about the center of the cornea. The pictures describe the surface topography in addition to the overall thickness of the cornea at all points. Pinero’s analysis on the corneal topography states there are three features that are most prominent and characteristic of early keratoconus patients. The first being a focal steepening leading up the corneal protrusion. Second, being an irregular astigmatism, and the third being a distinctive bow-tie pattern of the hemimeridians as can be seen in figure XXX below (Piñero et al., 2012).
Figure 3: Pentacam Corneal Topography: Image on the left shows a cornea with moderate keratoconus. Red indicates high K values (very steep) while blue indicates low K values (flat). Note bowtie pattern cause by the corneal protrusion as well as the location within the cornea. This location of lower hemisphere whether nasal or temporal is deemed characteristic. Image on right shows a normal pentacam of a cornea without keratoconus. Source: (Piñero, D. P., Nieto, J. C., & Lopez-Miguel, A. (2012). Characterization of corneal structure in keratoconus. *Journal of Cataract & Refractive Surgery*, 38(12), 2167–2183. doi:10.1016/j.jcrs.2012.10.0)

III. Current Treatments

The progression of keratoconus, as stated before is a widely variable onset. The point at which onset occurs, bilateral vs. unilateral, the overall rate, genetics, environment, and time to stabilization are just some of the major variables. As a result of these characteristics of the disorder, the treatment plans that are developed for keratoconus patients are also varied.

A. Contacts

In virtually all keratoconus cases, the first method of treatment attempted will be contact lenses. The use of contacts has two major benefits towards keratoconus patients. First, it helps improve the visual acuity that is lost from the
changing corneal topography and second, it provides a barrier which helps halt the progression of the corneal protrusion (Lembach, 2003). For use in the United States today, this is the only non-surgical approach that has been cleared by the FDA (Romero-Jiménez et al., 2010). As a result, more than 75% of keratoconus patients will wear contacts from early diagnose on up to advanced cases of corneal protrusion. The ability to treat the broad range of corneal irregularities keratoconus presents is due to the technological development of an arsenal of different types of contact lens that fit the person and degree of development (Barnett & Mannis, 2011). As a result of the use of contact lenses, 99% of wearers are shown to be able to push back the need for surgery (Barnett & Mannis, 2011). This is an important factor as the most common form of surgical intervention for patients is still penetrating keratoplasty (PKP), also known as a corneal transplant. PKP, which will be addressed later, has high graft failure rates when measured out to 20 years (Thompson, Price, Bowers, & Price, 2003). As a result, pushing off the need for this radical treatment can preserve quality of life as well as lend to better overall outcomes (Gothwal et al., 2013).

The treatment plans for contact lenses generally start with the cheapest option as well as the most comfortable fit for long term comfort and use. This option is soft contact lenses. This option will only work when the corneal protrusion is minimal. The other benefit is if the astigmatism is small enough, the contact between the cornea and the contact lens itself can mask the surface
irregularity. As the progression continues, toric contact lenses can be used to help with the further pronounced astigmatism (Barnett & Mannis, 2011).

Soft contact lenses, though effective for vision and comfort, do little to slow the progression of the corneal protrusion. As the keratoconus progresses, ophthalmologists will generally switch patients to a rigid gas permeable (RGP) contact lens which also have the benefit of allowing more oxygen and tears to reach the cornea. The drawback to these lenses can be an increase of corneal scarring over the long term (Barnett & Mannis, 2011). One randomly controlled trial between RGP contact wearers and a control group showed there was a 69% increase in corneal scarring over the course of 8 years (Zadnik et al., 2005). This drawback is offset by the controlled progression of the cone as well as better overall acuity.

A large aspect of the total gain in acuity and benefits will come from the fit of the contact lens. In the past there have been three methods of fitting RGP lenses. The first method was apical clearance which focused on using the periphery of the central cornea as a rest to keep the lens from touching the protrusion. This had the drawback of losing the benefits of retaining the size and shape of the protrusion and also lacked in the visual gains of other methods. The second fit method was to place the majority of support on the apex of the protrusion. This was found to degrade the epithelial layer and lead to substantially higher rates of corneal scarring. The primary method utilized today
is called the three point touch, in which the contact will bear down on two or more peripheral points around the cornea while it will in addition lightly rest upon the apex of the protrusion as well. This aids in minimal movement when blinking, maximum gain for visual acuity, better stabilizes the protrusion, and also reduces the risk of scarring (Barnett & Mannis, 2011; Zadnik et al., 2005).

Many patients wearing RGPs will eventually become unable to tolerate the lenses for extended periods, and in many cases the protrusion will continue to grow outwards, creating a worse fit. New technology has led to variety of options to delay this point. Rose-K ™ contact lenses are custom made to the contour of the protrusion so that the entire contact can distribute is surface area yet retain the shape of the cornea (Betts, Mitchell, & Zadnik, 2002). While visual results and the proportion that suffer from corneal scarring is not changed from regular RGP, 72% of patients are more comfortable wearing them and prefer them (Betts et al., 2002). Despite this, most patients will reach a point that RGP’s regardless the type no longer fit right due to the expanding protrusion and/or epithelial stress.

Other options for this include “piggy backing” a soft contact under a RGP or wearing hybrids which are a RGP lens with a soft contact lens material “skirt” that helps aid in comfort and distribute the weight of the RGP off the cornea. These options provide more comfort and protection to the eye yet are substantially more expensive, cumbersome to utilize, and can cause neovascularization as a trade-off (Barnett & Mannis, 2011). The final option for
advanced keratoconus patients who either don’t have surgical intervention as an option, or are nearing it, is to wear limbic or scleral contacts. These RGP reach over and past the edges of the cornea either onto the limbus, or for even more advanced cases where the cone is large and decentered, the sclera.

The overall goal of contact lenses is to try and stabilize the protrusion of the cornea while providing maximal visual acuity. When these attempts fail to slow or retard the progression, surgical intervention is often required. The most common procedure in the past, and even today has been a complete penetrating keratoplasty.

B. Penetrating Keratoplasty (Full Thickness Corneal Transplant)

The term penetrating keratoplasty refers to a complete removal of all five layers of the host cornea and replacing them with those of a healthy cornea donated from a recently deceased individual. Overall, about 20% of keratoconus patients will at some point undergo a corneal transplant. Depending on the geographic region it can range between the first and third most common need for corneal transplant. In the United States, Keratoconus is the third most common reason for PKP, likely due to variance in genetic demographics as well as the technological advances of contact lenses discussed previously. The sudden need for PKP can be due to a variety of symptoms. It generally is required if the
corneal protrusion becomes large enough that contact wear is no longer possible. It is often required when scarring occurs whether from breaks in Descemet’s or Bowman’s membranes, or due to epithelial stress from contact lenses or frequent eye rubbing. Another indicator can simply be dangerously thin overall thickness of the stroma or even corneal hydrops developed from endothelial cell apoptosis. Any of these symptoms can cause a patient to become a candidate for transplant.

This procedure of PKP has been around since 1844, but it only became the dominant form of treatment for keratoconus in the late 1950’s (Siganos et al., 2010). Corneal transplant is the most common and widely utilized form of human transplant surgery, even today. It is unique and overall more simplistic compared to other transplant procedures due to the minimized potential of graft rejection. The minimized risk is because the cornea is one of the few tissues with immunologic privilege, meaning it lacks the majority of machinery and mechanisms needed to illicit an immune response (Niederkorn, 2013). Much of this is due in part to the cornea being avascular, and thus not bearing the usual actors involved with such a reaction. In addition, within the anterior chamber, there are even cells that will naturally act to suppress any immune response detected (Stein-Streilein & Streilein, 2002). The sudden apoptosis of keratocytes within an injured cornea is predicted to be in line with this response since they are virtually the only cells present in the stroma, and will thus self-destruct so as to avoid spreading any viruses that potentially could have contracted due to
exposure (Wilson et al., 1996). All these attributes lend to the transparency of the cornea, but also therefore allow for a relatively simplistic procedure to carry out successful and long lasting transplant (Niederkorn, 2013).

In one of the first studies to track and follow up on long term success rates of corneal transplants, Thompson, et al. tracked the success and complications of 3,992 eyes. Of these transplants, 449 of the eyes were of keratoconus patients with an overall, 11 of those 449 eyes subsequently failing. Three of these failed due to endothelial failure, three due to endothelial rejection, one to surface complications, and the other four to miscellaneous reasons (Thompson et al., 2003). While this subgroup of the analysis had a substantially higher success rate at ten years than most other studies, it does show that despite the corneas resistant to graft rejection is minimal, there are still risks of it occurring.

Comprehensively, over the range of publication over the past couple decades, including the most recent, PKP is generally listed as having an 80% success rate out to 10 years. Overall, 17% total PKP recipients experience graft failure within the first three years, with the remaining 3% scattered out to the 10 year mark. For those whose grafts fail, the only option has generally been to re-graft a new cornea. The success rate for secondary or tertiary PKP is only a 41% success rate at the 10 year mark, and a 53% failure rate at the 3 year mark (Thompson et al., 2003). A current theory is that the host immune system will become primed to foreign cornea tissue and will thus be more sensitive to
subsequent attempts (Thompson et al., 2003). One explanation for this has been that the transplantation of the endothelial cells and thus their interaction with the anterior chamber increases the odds of host resistance. Evidence was found when PKP procedures were done simultaneously with a phakic intra-ocular lens extraction. The disruption of the iris and the particularly the posterior capsule potentially released many of the inflammation and immunological factors that could have added to the likelihood of rejection (Cassidy, Beltz, Jhanji, & Loughnan, 2013; Jonuscheit, Doughty, & Ramaesh, 2013).

In response to this possibly, and to the evidence that the native endothelial cell layer suffers at an accelerated rate when part of a transplanted cornea, new techniques have been recently developed to more directly address these issues (Jonuscheit et al., 2013).

C. Deep Anterior Lamellar Keratoplasty (DALK)

Deep anterior lamellar keratoplasty (DALK) is a relatively new technique that though was first proposed in 1959 became more commonplace only in the past two decades. The primary difference between DALK and PKP is the number and depth of the layers of the cornea that are removed and then replaced with a donor graft (Daneshgar, 2012). Rather than excise all layers from the epithelium to the endothelium, DALK, as the name implies, only excises
from the epithelial layer up to, but not including Descemet’s membrane. The rationale for this lies in most keratoconus patients that undergo corneal transplants, require them due to corneal scarring or opacities within the anterior part of the stroma (Cassidy et al., 2013). By removing all parts of the stroma, and grafting the three donor layers on, surgeons can hope to reduce the risk of graft rejection. Via this method, the operation is able to remain outside of the anterior chamber of the eye, where the immune reaction is most likely thought to originate (Daneshgar, 2012). Another benefit that stems from this method is the preservation of the longevity of the endothelial cells. In grafts, the endothelial cells can drop in density per square millimeter by more than 50%, though with DALK, the host is able to retain their own endothelial cells (Jonuscheit et al., 2013). In addition, since the bottom two layers of the host cornea remain intact, the grafting of the host cornea become more structurally sound as compared to the PKP (Feizi, Javadi, & Kanavi, 2012). As DALK doesn’t penetrate into the anterior chamber, it also benefits from less post-operative care and complications. The regimen of drugs used post-op can lead to future secondary comorbidities such as glaucoma or cataracts, likely from high and long term doses of steroids (Cassidy et al., 2013). Together these benefits are pushing DALK to become the forefront of corneal transplant therapy over PKP, though there are still drawbacks or barriers that have slowed it from getting there yet (Akdemir, Kandemir, Sayman, Selvi, & Kamil Dogan, 2012).
The most striking difference between the two procedures is the substantial learning curve required to successfully strip the entire stromal layer without perforating Descemet’s membrane. Studies comparing the outcome of PRK versus DALK procedures reported perforating Descemet’s membrane generally 15% though sometimes as much as 40% of the time. In these cases, the DALK procedure is simply converted to a PRK procedure (Noble et al., 2007). In addition, the overall visual acuity results compared to PRK have not been shown be statistically significant in any literature reviews that this author found (Noble et al., 2007).

Overall, advances in technology have once made this treatment for keratoconus more effective than it once was. By utilizing femtosecond laser technology (the same lasers utilized for LASIK surgery) surgeons are able to create more accurate and precise cuts for both the host and donor tissue. Zig-zag patterns show a more structurally sound bond between the graft, as well as shorter healing times (Reinhart et al., 2011). The “bubble technique” has also reduced perforation of Descemet’s membrane, by having air injected into the stroma, thus causing the lamella to lift and expand. This has made it easier to mechanically debride the stromal layers than earlier (Braun, Hofmann-Rummelt, Schlötzer-Schrehardt, Kruse, & Cursiefen, 2013). As more evidence is brought out regarding DALK as a more resilient form of corneal transplantation, we can expect to see it as a more common procedure within the U.S. over the coming years (Cassidy et al., 2013).
D. Intrastromal Corneal Ring Segments

With the progression of keratoconus, there are two primary goals for treatment in progressive cases. The first is to halt the progression of the thinning of the cornea, as well as the protrusion of the cornea. As the cornea thins past 400μm, many treatment options become dangerous with such a thin cornea. The ability to control progression is currently very limited. RGP contacts aid in stalling progression a little, though overall there is nothing on the market that can properly halt the progression of keratoconus other than corneal transplant (whether in the form of PKP or DALK) (FDA, 2004). The other goal of treatment is to preserve the patient’s vision until there is no other option left but corneal transplant. This course of treatment is fairly successful as only about 20% of keratoconus cases continue on to have PKP or DALK. The other 80% progress slowly enough for various types of contact to help maintain a high enough quality of life.

In 2004 a new device was approved for use in keratoconus patients who can no longer tolerate contacts. This type of device has been generically named an intrastromal corneal ring segment (ICRS), though and even today, only one company has secured FDA approval. Their product, called INTACS® is currently the only version of this technology used today. INTACS® are two curved plastic rings that each make up 150° of a complete circle around the pupil (FDA, 2004).
Each ring segment is surgically inserted into the peripheral stroma of the cornea. By placing the ring segments opposite each other, an almost full circle is created causing tension across the entire cornea. This tension pulls the surface of the cornea taunt, and will flatted out the surface of the cornea, including most astigmatisms caused by the keratoconus. The device was made and approved for mild to moderate keratoconus with vision correction of around 3 diopter spherical correction and up to around 1 diopter of astigmatism, though recent studies have shown impressive results with patients up to 12 diopters of necessary vision correction (Khan, Injarie, & Muhtaseb, 2012). If the INTACS® are not able to achieve near 20/20 vision by themselves, by flattening the cornea, they make it more possible again for the use of RGP again. This combination of therapy allows for the maximum possible corrective vision, and is the newest approved method of delaying the need for corneal transplant.

In a study that came out mid-2012 from the Iris Advanced Eye Centre in Chandigarh, India, 105 eyes from 85 patients were followed up over 5 years after having had INTACS® implanted. The group was categorized according to three subgroups. Specifically of note was the subgroup that was noted as having preoperative progression. Of the 56 eyes that had noted pre-op progression, five years later only 4 of the eyes had continued this progression. The other 52 eyes had no statistical difference in the slope or protrusion of the cornea (Bedi, Touboul, Pinsard, & Colin, 2012). Further research into this may yield more
substantial results in INTACS® being a viable method for helping halt or at least slow the progression of keratoconus.

E. Laser Refractive Surgery (LASIK, LASEK, & PRK)

Laser refractive surgery has become increasingly more common since the early 1990’s when it came into common practice. Laser surgery has several benefits over the older style of refractive surgery, which was radial keratectomies (RK). In RK, radial scours of the cornea would be made in a spoke like pattern so as to change the cornea’s shape as it healed. This would correct myopic vision though was less accurate and substantially more susceptible to infections (Ozulken, Cabot, & Yoo, 2013). With the introduction of LASIK (laser in-situ keratomileusis) the reshaping of the cornea is controlled by a laser. This is even more accurate today with the use of femtosecond lasers that are utilized in cutting open a flap within the stroma so that the interior layers of the stroma can be ablated by another laser (Ozulken et al., 2013). For cases of keratoconus, ophthalmologists at the time saw LASIK as an effective method to reshape the protruding cornea by cutting a flap into the cornea and ablating away part of the stroma. It took about five years before researchers determined the potentially devastating effects of this treatment (Binder et al., 2005).
In 1995 a patient developed a case of keratoconus immediately having had LASIK. This later became known as the first of many iatrogenic keratoconus cases that would be later designated as LASIK induced ectasia (Binder et al., 2005). In effect, it was determined that when creating the flap, which allows surgeons to reshape the interior of the stroma, the wound initiated the onset of keratoconus. Since 1995, there have been determined numerous risk factors associated with LASIK induced ectasia (Binder et al., 2005). The prominent factors have been correlated with myopia >8 diopters, thin corneas, and increasing age (Randleman, Russell, Ward, Thompson, & Stulting, 2003). The overall rate of ectasia was low, but for the popularity that LASIK has taken on in the United States, the risks subsequent to testing for ectasia associated risk factors were about 1 in 2,000. With the introduction of corneal topography and avoiding high risk patients, the incidence is now better than 1 in 5,000 (Binder et al., 2005).

As the method LASIK fell out of favor in keratoconus suspects, another technique of laser refractive surgery was attempted in remodeling the cornea of such patients. Photorefractive keratectomy (PRK) is a procedure where the epithelium of the cornea is removed using a high concentration of alcohol. The underlying Bowman’s membrane and stroma are then ablated to a depth necessary to achieve the desired focus prescription. The epithelium regrow from stem cells in the limbus over the next 7-10 days. Laser assisted sub-epithelial keratectomy (LASEK) is the same technique as PRK except the removed epithelium is placed
back over the freshly ablated stroma as a form of natural bandage while the epithelium regrows (Guedj, Saad, Audureau, & Gatinel, 2013).

Multiple studies, including a recent 2013 publication in the Journal of Cataract & Refractive Surgery had a five year follow on keratoconus patients who received PRK. The results followed 42 patients, and found that only 2 patients out of the 42 regressed considerably following the procedure. Their conclusion was that PRK “may be safe and effective for myopia and astigmatism in carefully selected patients,” regarding keratoconus patients (Guedj et al., 2013).

F. Phakic Intraocular Lens

The final currently FDA approved method for treating keratoconus discussed in this paper is also very recent within the American ophthalmic community. Phakic intraocular lenses (pIOL) were only approved at the end of 2004 by Abott Medical Optics and even since then have only received one competitor in the field (“Phakic IOLs (Implantable Lenses) - Verisyse and Staar Visian ICL,” n.d.). This is another method in which was determined to help people with medium to high levels of myopia including when due to keratoconus. The pIOL is surgically implanted in the eye, depending on which companies’ pIOL is used, either between the iris and the natural lens of the eye, or in the anterior chamber of the eye, right on top of the iris. The operation itself is similar
to that of a cataract surgery, except the eye’s natural lens is left in place while the new pIOL is placed just in front of the lens (M.D, M.D, & Hauranieh, 2012).

The benefits of this surgery is having a contact lens that never has to be removed or taken care of. The lens is able to compensate for myopia between -5 and -20 diopters, substantially higher than what a RGP lens would be able to compensate for. This is especially ideal for patients who can no longer comfortably wear contact lenses, yet are still trying to push off a undergoing a corneal transplant. It is also an alternative to LASIK or PRK/LASEK since the corneal stroma does not have to be ablated away, which as discussed earlier, is higher contraindicated for keratoconus patients (Sedaghat, Ansari-Astaneh, Zarei-Ghanavati, Davis, & Sikder, 2011). As long as the protrusion is not over the center of the cornea, and as long as there is no scarring, the pIOL can even be toric, and thus compensate for basic astigmatism created by the keratoconus (M.D et al., 2012). This unfortunately has not been met with nearly the wide scale acceptance as LASIK in terms of vision correction.

As the FDA approval is so recent, no comprehensive long term reports exist as yet that indicate the safety of a pIOL. Those that do, are less than five years and of small sample sets. Some research is has shown common side effects of lenses being placed in the anterior or posterior chamber leading to cataracts, severe endothelial cell damage, or even glaucoma (Pechméja, Guinguet, Colin, & Binder, 2012). For specifically keratoconus patients, the
disorder has to be relatively stable before a pIOL will be considered for implanti ng. Despite being a relatively simple procedure much like cataract surgery, surgeons try to keep an intraocular procedures to a minimum so as to minimize the increased surgical risks of actually entering the eye. As a result of these factors, pIOL are still a growing field as ophthalmologists wait for longer term results to arise. Newer versions are currently being tested by the FDA that include being foldable so to be inserted through much smaller incisions, as well as other models that are made for substantially higher astigmatisms such as those seen in keratoconus (Ozerturk et al., 2012). Unfortunately, this method for regaining sight, is once again contraindicated for advanced cases of keratoconus, where the cornea has either become too scarred, become too thin, or has had Descemet’s rupture and resulted in corneal hydrops. For all these cases, corneal transplant would unfortunately still be indicated as the only approved treatment within the U.S. (Center for Devices and Radiological Health, n.d.).

IV. Proposed New Treatment- Corneal Cross-Linking

The newest and potentially most revolutionary treatment for keratoconus is called corneal cross-linking (CXL). The idea came from Dr. Theo Seiler, M.D. of the University of Dresden back in a paper published in 1994. In 1998, he and a team from the University of Dresden completed the first treatment of CXL on a
human subject. From the results of the first patient and the many that followed, they garnered the “Dresden Protocol,” which became the published step by step methodology for how they achieved their results. These results have since become the gold standard for the procedure. Since this first procedure, hundreds of studies have followed up on his results with all twenty five countries of Europe having officially approved the procedure by 2006. Canada followed suit in 2008 along with a myriad of Asian countries. As of today though, the FDA is still awaiting the results of several American clinical trials that are currently underway, several of which will be discussed later. The remainder of this paper will examine the most up to date research that has shown the potential benefits and drawbacks of CXL for keratoconus patients, as well as to what questions have yet to be answered with this novel technology and procedure.

The name or term “corneal cross-linking” is used in reference to cross linked polymers of collagen that the procedure is meant or at least thought to induce within the stroma of the cornea.* As previously mentioned in this paper, no FDA approved treatment currently exists that is able to specifically halt the progression of keratoconus other than corneal transplant. CXL is unique in being able to fill this niche without being nearly as risky, expensive, or debilitating as a corneal transplant.

The procedure itself is of the same degree of invasiveness as PRK and lasts roughly 30 minutes. The Dresden Protocol, or the most commonly
practiced methodology of the procedure is as follows. The epithelium is removed, generally using a high concentration of alcohol much again like PRK. A 0.1% solution of Riboflavin (vitamin B$_2$) with a 20% dextran solution is administered for 30min at increments of 3-5min. These steps are so the riboflavin can properly penetrate the surface of the cornea and permeate through the lamella of the stroma. A lamp that emits ultra violet A radiation (UV-A) at a wavelength of 365nm for 30minutes. The epithelium can then be placed back over the stroma or be discarded. A bandage contact is placed on the eye for a week so as to protect the regenerating epithelial cells. In practice, this need be performed on each eye only once for the effects to be permanent. The overall understanding of how this works though is of ongoing debate, even today.

The exact biochemical series of events CXL induces is still not fully understood today and is still under study. Two predominate theories exist as to the total series of events with both sharing the same basic mechanisms. Riboflavin is a micronutrient that is extremely light sensitive and breaks down into multiple components when exposed. The first theory therefore believes the UV-A breaks the riboflavin into free radicals. These free radicals are believed to interact with different amino acids of collagens and thus forming covalent bonds between the different polymers. The other theory is similar though with an additional step. It believes the riboflavin in the presence of O$_2$ will react and form single molecular oxygen ($^{1}$O$_2$). These single molecular oxygen molecules then do the same thing as the riboflavin free radicals, inducing covalent bonds
between the collagen molecules. One aspect of this that a recent literature review from this past January (2013) in the Journal of the College of Optometrists is that most researchers agree that collagen crosslinking does not target a specific amino acids of the collagen, nor just the collagen polymers either. *In vivo* human cells will exports tropocollagen, a precursor to collagen. Lysine oxidase then reacts with lysine and hydroxylysine residues of the tropocollagen molecules, forming aldehydes that will then be able to form covalent crosslinks. Both theories as to how CXL works believe the UV-A induced radicals likely act on the lysine and hydroxylysine residues in a similar manner, but researchers believes it goes well beyond this. They believe there are multiple different residues acted on the collagen molecules in addition to proteoglycans of the extra cellular matrix. What likely occurs with CXL is a broad stroke of covalent bonds being created across the stroma, though without altering the transparent nature of the stroma.

The overall results of this procedure have been very favorable. In general studies have not only shown CXL to halt the progression of keratoconus in 98% of cases, but to also improve the overall visual acuity of in 50% of patients as well. This phenomenon of increasing visual acuity has been routinely observed in CXL studies and has several hypotheses as to its occurrence. Despite the favorable results though, much like the disorder of keratoconus itself, there is a great deal of mystery regarding CXL. The FDA has delayed approval based on a variety of factors, the majority of which stem from determining the
most efficacious manner as well as the safest in which to perform the procedure. In addition, there are a very large number of exclusion criteria that have traditionally been followed. One of the most controversial ones in the past has been for children as they have been traditionally exempted from FDA clinical trials in the past due to ethical concerns, in the case of keratoconus.

As a result of these debates and the potential benefits of CXL, there has been a large degree of research activity focused on the subject of keratoconus. In just the past two years, Medline has over 200 publications on corneal cross linking, with over 50 of those published just in 2013. The gross majority of these though are from outside the United States since it has yet to approve the procedure. The clinical studies that are ongoing in the U.S. are from the various device manufacturers of the UV lamps and are all struggling to be the first approved. Currently there are 79 studies registered with the U.S. National Institute of Health focused on keratoconus, with 39 still recruiting today. The gross majority of these are examining the many different aspects of CXL that have yet to be answered even after more than 20 years of international practice.
V. Recent and Current Studies on Corneal Collagen Cross-Linking

A. Benefits

The overall benefits of CXL have been reported over hundreds of individual studies as well as dozens of standardized clinical studies held internationally. In one of the most recent literature reviews regarding CXL, “Corneal Cross-Linking - A Review” published in the *Journal of the College of Optometrists* shows 17 clinical trials all using the Dresden Protocol for CXL (Table 1). The studies range from 10 to 241 eyes per study with follow ups ranging from 6 months to 6 years. The primary columns to examine when determining the effects of CXL are the 5th and 6th columns assessing the % of halted or improved changes in $K_{\text{max}}$ as well as the mean overall reduction of $K_{\text{max}}$. $K_{\text{max}}$ is referring to the maximum K value meaning the maximum keratometry value measured in diopters. Keratometry assesses the axis as well as the steepness, or extent, of an astigmatism, which in the case of keratoconus is the extent of the corneal protrusion. The $K_{\text{max}}$ should stop increasing after CXL, or in ideal cases, actually regress, showing the protrusion has flattened. As can be seen in column 5 between 81% and 100% halted regression in addition to having between 23% and 77% actually improve. Column 6 shows overall reduction in $K_{\text{max}}$ was between 0.16 D and 2.47 D (Meek & Hayes, 2013).
Table 2: Literature Review of Standard CXL Studies using Dresden Protocol: Columns 5 and 6 illustrate the overall success rate in arresting the progression of keratoconus. Columns 7 and 8 display the overall improvements in uncorrected and correct visual acuity. 


In another literature review done in 2012 by a group that was published in the Journal of the American Optometric Association, “Corneal Collagen Cross-Linking: An Introduction and Literature Review” had 20 out of 50 clinical trials found were included after passing through predetermined exclusion criteria (Dahl, Spotts, & Truong, 2012). The studies were similar to table 1. 14 of the 20 studies measured decreases in Kmax values. Values ranged from stabilization (no change) to 4.34 D decrease with follow up ranging from 6 to 36 months. A series of subanalyses were also determined (Dahl et al., 2012).
A novel aspect of CXL is the fact it can be combined with virtually any of the therapies discussed earlier in this paper. Intrastromal Ring Segments can be implanted and within the same procedure have the cornea immediately undergo CXL. This procedure would benefit from the ability to help flatten the cornea using one of both part of the INTACS® ring and then CXL the cornea so as to prevent any further progression. The results seen in Table 3 can be seen across the board to favor the INTACS® with the CXL.

<table>
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<tr>
<th>Measurement</th>
<th>Intacs only</th>
<th>Intacs/CXL</th>
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<tbody>
<tr>
<td>UCVA*</td>
<td>1.9</td>
<td>3.19</td>
</tr>
<tr>
<td>BCVA*</td>
<td>1.7</td>
<td>3.09</td>
</tr>
<tr>
<td>Spherical refraction</td>
<td>2.08 D</td>
<td>2.58 D</td>
</tr>
<tr>
<td>Cylindrical refraction</td>
<td>0.47 D</td>
<td>0.62 D</td>
</tr>
<tr>
<td>Mean K value</td>
<td>2.22 D</td>
<td>2.57 D</td>
</tr>
<tr>
<td>Steepest K value</td>
<td>1.27 D</td>
<td>2.03 D</td>
</tr>
</tbody>
</table>


This dual treatment was also seen for patients who received PRK. As the epithelium is already removed from the stroma, the patient can easily undergo PRK immediately before CXL. Results were once again across the board in terms CXL with PRK being more favorable for improvements in visual acuity (Dahl et al., 2012).

Another study has also postulated the idea of utilizing CXL with PKP or DALK patients. As some cases of keratoconus are recurring despite a new
transplanted cornea, CXL has been proposed to stop the recurrences and aid in helping the new graft last longer (Richoz, Schutz, Pajic, Coskunseven, & Hafezi, 2012).

Overall, CXL has shown an overwhelming degree of evidence that it not only halts the progression of keratoconus but that it also aids in regressing the corneal protrusion and flattening the cornea. These results show virtually permanent avoidance of corneal transplant, and with the combination of other simultaneous procedures such as PRK or INTACS, shows a promising method in which to avoid contacts as well. Despite these results, the FDA and other researchers are still trying to determine to what extent the side effects are of CXL, as well as to what risk factors exist that exacerbate those factors.

B. Potential Harms and/or Risks

One of the largest concerns with the idea of corneal cross linking has always been the fact that a UV light is being shone directly onto the open cornea for such a long period of time. UV light has long been established as being dangerous for virtually every tissue in the human body. As referenced earlier, some of the most sensitive and delicate cells in the human eye are the endothelial cells. A study published in 2007 determined that endothelial cell death began to occur after being irradiated at 0.36mW/cm² at 370nm (Spoerl, Mrochen, Sliney, Trokel, & Seiler, 2007). As referenced earlier, the UV-A light
used according to the Dresden Protocol method of CXL is 370nm with the energy of the UV-A delivering 3mW/cm² for 30min (Wollensak, Spörl, & Seiler, 2003). The authors determined though that two factors prevented the endothelial cells from receiving this toxic degree of UV-A radiation. First, the riboflavin actually acts to absorb about 50% of the UV-A light. Second, since the endothelial cells are at the very posterior edge of the cornea, the stroma absorbed the majority of the rest of the lights energy. By the time it reached the endothelial cells, the authors determined they were receiving only 0.18 mW/cm². What this study did help determine though, was despite the copious amounts of riboflavin that soak the cornea in order to help absorb the UV-A light, a minimum thickness of around 400um was important in order to preserve the health of the endothelial layer.

Another concern that developed with the use of UV-A light during the course of CXL has to do with the limbal epithelial cells. These cells are important since the epithelium is debrided away during CXL. The stem cells for the epithelium are located in the limbus. The authors found that if the limbal cells are irradiated at the dosage utilized in CXL, the stem cells were more likely to enter into an early and irreversible stage of apoptosis. The riboflavin solution was found to substantially lower the mortality rate of the limbal cells, though was not found to eliminate the risk. These findings support finding a lowest effective amount of time and power setting for the UV lamp through future clinical studies.

Another complication or risk factor has been the results of hazing of the cornea in CXL patients. In a decent sized study involving 127 patients of which
163 eyes were involved, a rate of 8.6% of hazing was found. The hazing it
turned out was a change in refractive index between the cross-linked anterior
stroma and the less cross-linked posterior stroma. Risk factors for this hazing
were determined to be age, how late of progression the keratoconus was,
including factors of $K_{\text{max}}$ and corneal thickness (Raiskup, Hoyer, & Spoerl, 2009).

This minor complication has led fuel to a raging and ongoing debate on
the topic of CXL. As stated before, the epithelium generally is removed during
CXL so as the riboflavin is able to penetrate deep into the stroma. A 2009 study
in the Journal of Cataract and Refractive Surgery showed that when the
epithelium was left on, only about 20% of the rigidity of the post-CXL cornea was
achieved (Raiskup et al., 2009). Despite this, other papers have shown
equivalent or even better results by leaving the epithelium intact during the
procedure (Magli et al., 2012). Most though have shown substantially longer
loading times with the riboflavin as well as using different chemicals so as to
loosen the epithelial cell junctions and make the cell layer more permeable.
Either way, for the patients, the epithelium-off method would present a much
lower list of risks as the procedure would be much less invasive. Post-op care
and comfort would be much more comfortable and the risk and rates of infection
would likely be less since the protective epithelium would still be protecting the
stroma (Dahl et al., 2012; Meek & Hayes, 2013). In fact, one study showed that
by leaving the epithelium intact, surgeons were able to safely cross-link 16
patient’s corneas that would otherwise been determined too thin for the
procedure. The corneas ranged from 331-389um and by 18 months later were able to show endothelial counts were unaffected by such a closer proximity to the UV-A lamp (Thorsrud, Nicolaissen, & Drolsum, 2012). The major U.S. trials underway currently are not looking at this issue as all are examining other factors CXL just to get it approved. Based off the completed and currently underway American trials, the U.S. National Institute for Health assert that the FDA will likely only pass the epithelium-off method of CXL initially.

The last worthwhile risk of CXL worth mentioning in this paper regards specific risk factors that have been identified within patients who have poor outcomes. Several studies have shown that older, more progressed cases, with steeper $K_{\max}$, and thinner corneas tend to fare worse overall than people over the age of 35. Specifically, people over the age of 35 who already had vision greater than 20/25 where listed as having the least gains. In contrast, people under the age of 26 were shown to have the greatest improvements. This result supports finding and diagnosing patients as early as possible and treating keratoconus with CXL as a first line treatment. Overall the authors of these studies believed that if these exclusion criteria were met, success rates of over 99% could be attained (Koller, Mrochen, & Seiler, 2009).
V. Discussion and Conclusion

Through the course of this paper the various forms of treatment options for keratoconus were examined. The general goal of treatment for these patients has generally been simply to keep their visual acuity as good as possible for as long as possible. RGP contact lenses were the closest thing to a form of treatment that actually slowed the progression of keratoconus or at least the extent of the corneal protrusion. This treatment cannot have its importance underscored since only 20% of keratoconus patients undergo corneal transplant in their lives, this means almost all of the rest of the 80% will have contacts as their only form of treatment (Romero-Jiménez et al., 2010). For the 20%, options have increased for them too with the introduction of INTACS® in 2004 as well as procedures such as DALK where the likelihood of graft rejection is lessened in the long term and the risks to the survival of endothelial cells is decreased. Despite these advances, patients still have concerns of their keratoconus progressing without anything to stop it. Some patients even have recurrent keratoconus, where even after transplant, the graft cornea undergoes the same dystrophic process. The overall disorder is not well understood, and overall isn’t well controlled. Corneal collagen cross linking fills this niche (Meek & Hayes, 2013). While it is not a cure in any sense of the word, CXL is indeed a permanent form of treatment that is going to allow the majority of keratoconus patients to no longer have to worry about regression. An issue that becomes
apparent when met with the overwhelming display of evidence that CXL is beneficial in the gross majority of cases is simply, why didn’t the United States start clinical trials sooner?

As can be seen in the references of this paper, the majority of papers cited are from 2012 and 2013. The field of corneal refractive surgery has been very active these years potentially due to such advances as femtosecond lasers which have lent them unprecedented accuracy and precision in a myriad of procedures, but also due to the acceptance of corneal cross linking in almost every country in the world. CXL has finally given ophthalmologists a weapon against one of the most uncontrollable disorder in ophthalmology. What is surprising when gleaming the references cited though, is the great lack of papers that were written in the United States. Despite the procedure first having been successfully completed in 1998, with all of Europe having accepted and approved it by 2006, and Canada by 2008, the United States hadn’t even started clinical trials on CXL till 2008 (Ashwin & McDonnell, 2010). With such a mountain of evidence that was available several years earlier, it is unfortunate not to already see CXL as part of the common medical practice.

Currently, some ophthalmologists around the country are already doing CXL, the gross majority though are signed on with the various clinical trials currently going on. What this means for keratoconus patients is that while they may have an opportunity to get the treatment within the United States, none of it
is covered by insurance. It currently costs between $2,000-$4,000 to get CXL done in the U.S (“CXL-USA,” n.d.). It’s speculated that by the time CXL is pushed through the FDA, the various device manufacturers will have spent over $50 million over the course of testing. Unfortunately many of these studies aren’t testing novel aspects of CXL but rather testing basic tenets of the treatment that were studied in Germany over a decade ago. Avedro, Inc. one manufacturer of one of the 6 versions of the UV-A lamp has two trials currently underway. One has the intervention group receiving the riboflavin and UV-A exposure while the control group just receives the UV-A light in one trial and just the riboflavin in the other (Avedro, Inc., n.d.).

In scanning the U.S. National Institute for Health clinical trial registry, no clinical trial was found that was testing whether CXL was more effective depending on the method of epithelium removed or left intact. This is one of the most debated aspects in CXL where efficacy vs. risk of patient complications are being played against each other. Topics such as this should be the subject of U.S. clinical trials at this stage, not just simple overall efficacy trials when the academic community already has ample CXL trials and literature reviews with 6 year follow ups.

In addition, many of the FDA trials have through standard protocol, excluded the involvement of children under 18 from the trials. Unfortunately, this procedure as, mentioned earlier, isn’t only just more effective in people under 26,
but the benefits to halting the progression of keratoconus at an early age have already been widely shown through studies in Europe (Zotta et al., 2012). The amount of time necessary before the FDA approves the use of the device may take even longer than the general acceptance. This will continue to put domestic keratoconus patients at a distinct disadvantage in care compared to their European and Canadian counterparts.

Overall being at the advent of the United State’s approval of CXL will be an exciting time for both patients and researchers. There are many questions left to be determined and by having the FDA approval more Universities and researchers will independently be able to become involved. Researchers have already postulated that CXL may be utilized as a prophylactic therapy for patients undergoing LASIK to as to entirely avoid LASIK induced keratoconus. In addition, researchers have pointed out that there may be cross therapies for CXL due to the bactericidal aspect of UV-A light. Corneal infections therefore may benefit from the CXL therapy (Ashwin & McDonnell, 2010). And lastly with the wide spectrum of additional treatments for keratoconus, it is highly likely and already internationally supported that CXL used in combination with other therapies gives the maximum likelihood of halting the regression of keratoconus while providing best corrected vision. With FDA approval hopefully to come by the end of 2013, the domestic medical options for keratoconus patients should greatly improve.
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