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Review article

Refractive surgical correction and treatment of keratoconus

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ABSTRACT

Keratoconus is an ectatic corneal disorder that causes severe vision loss. Surgical options allow us to correct, partially or totally, the induced refractive error. Intracorneal ring segments (ICRS) implantation represents a minimally invasive surgical option that improves visual acuity, with a high success rate and a low overall complication rate. Corneal allogenic ICRS consists of ring segments derived from allogenic eye bank-processed donor corneas. Selective topography-guided transepithelial photorefractive or phototherapeutic keratectomy combined with CXL is another way in selected cases to improve spectacles corrected distance visual acuity. The microphotoablative remodeling of the central corneal profile is generally planned by optimizing the optical zones and minimizing tissue consumption. Phakic intraocular lens (PIOL) implant is considered in patients with stable disease and acceptable anatomical requirements. The two types of pIOLs, depending on their implantation inside the eye, are anterior chamber-pIOLs, which fixate to the anterior surface of the iris by using a polymethomethacrolate claw at the two haptics, and posterior chamber-pIOLs. In patients with both cataracts and keratoconus, the correct IOL power is difficult to obtain due to the irregular corneal shape and K values. Toric IOL is recommended, but carefully judging the topography and the possible need of subsequent keratoplasties.

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1. Introduction

Keratoconus (KC) is an ectatic corneal disorder affecting up to 1:375 persons in some populations characterized by a progressive deformation and thinning of the cornea.[25] As KC progresses, it causes severe vision loss that can require a surgical approach. We provide information about how surgery can not only treat KC, but also correct, partially or totally, the refractive error, with improvement in binocularity, quality of vision, and quality of life of KC patients. The improvements of older techniques and the development of new techniques that are now available open an interesting panorama for the refractive and corneal surgeon.

We will discuss the risks and benefits of excimer laser photorefractive and phototherapeutic procedures plus corneal collagen cross-linking (CXL), intracorneal ring segments (ICRS) with and without CXL (as they don't stop KC, but can improve the refractive condition in many cases), phakic intraocular lenses (pIOL) and refractive lens exchange with toric IOL implantation.

2. Additive procedures with and without corneal crosslinking

2.1. *Synthetic intrastromal corneal rings segment: surgical techniques and outcomes*

ICRSs were used in the 1980s[18] for low and moderate myopia correction, and anterior cornea curvature flattening occurred by placing ICRS on the stroma. Originally studied as a surgical method to correct low myopia, they have been extended to various pathologies, such as KC, pellucid marginal degeneration, and iatrogenic corneal ectasia.[74,76]

In 2000, Colin and coworkers reported the first results of ICRS technology in KC.[18,19] They found that Intacs technology could reduce the corneal steepening and astigmatism associated with KC and proposed it as an additive surgical procedure for KC management. This surgical option provided an interesting alternative aiming to delay, if not avoid, corneal grafting in ectatic corneal disease. Since then, multiple reports about ICRS for ectatic corneal disorders that show the visual and refractive outcomes of these implants have been published. Nowadays, there are 3 main types of ICRS international available: ring segments with a hexagonal cross-sectional profile (Intacs; Addition Technology, Inc.), ring segments with a triangular profile or variations of this profile (Ferrara rings; Ferrara Ophthalmics Ltda; Keraring; Mediphacos Ltda), and complete rings with a trapezoidal cross-sectional profile (MyoRing; Dioptex, GmBH).[24,78]

As we can see in Table 1, ICRSs are available in different arc lengths, cross-sectional shapes, thickness, and diameters, with greater flattening effects that can be accomplished by thickening the segments or moving a position of the ring segments toward the visual axis.[74]

ICRS implantation is suggested to KC patients who fulfill the following criteria.[86]

1. Age > 18 years
2. Contact lens intolerance
3. Corrected distance visual acuity (CDVA) between 0.3 and 0.6 on the decimal scale
4. Corneal pachymetry > 480 µm in the site of the corneal tunnel
5. Absence of central corneal scarring
6. Alignment of refractive and keratometric axes
7. Not pregnant

Classically, ICRS have been placed in the corneal stroma by creating a channel via mechanical dissection, currently replaced by femtosecond lasers. In the mechanical technique the pupil center is used for ICRS implantation. The site of the incision is usually located in the steep meridian as determined by keratometry. Then, a 1 mm radial incision is performed at the depth of 70–80% corneal thickness (CT) with a calibrated diamond knife, and corneal dissectors are introduced at the base of the incisions on each side to form corneal intrastromal tunnels. A semiautomated vacuum-centering guide is placed, along with the reference point on the corneal surface, at the limbus. Tunnels are created under vacuum, using 2 semicircular dissectors (corneal separators) and by advancing them steadily and rotationally into the lamellar pockets (clockwise and counterclockwise dissection). Once this step is completed, ending with tunnels in the desired directions and diameter, the surgeon removes the suction and inserts the implants into each ostia of the channels.

The femtosecond laser-assisted method requires the use of an infrared laser to create intrastromal cavitations and eventually a dissection plane at the desired depth through the photodisruption process. The laser creates an entry cut followed by tunnel dissection at about 70–80% of the depth determined by corneal pachymetry. In the last step, the segments are inserted into each channel with the aid of special forceps.[88] In addition to being less annoying to the patient, the use of femtosecond lasers is faster and provides greater control of the depth, width, and centering of the tunnel, as well as increased accuracy. In addition, epithelial tissue changes are minimal, and recovery after surgery is faster.[34,1] Channel creation by both methods yields similar visual and refractive results. Nevertheless, increased intraoperative complications occurred with mechanical ICRS implantation.[80,51]

In an ICRS study with the longest follow-up period, Torquetti and coworkers[100] studied the long-term safety and efficacy of ICRS over 10 years in 36 eyes of 30 patients. They analyzed 2 eyes with grade I, 13 with grade II, 14 with grade III, and 7 eyes with grade IV, based on the Amsler–Krumeich classification. This retrospective study showed that 56.6% of eyes gained 2 or more lines of corrected distance visual acuity (CDVA) at 5 years, and 66.7% gained 2 or more lines of CDVA at 10 years of follow-up. They identified advanced KC and reoperation as possible risk factors for loss of visual acuity after ICRS implantation. Also, 10 and 20.7% of eyes that experienced the loss of uncorrected DVA and CDVA, respectively, had grade III or IV KC. Any grade II patient with visual acuity loss had reoperation for ring repositioning, removal, or exchange.

Sadoughi and coworkers[86] also found worse CDVA outcomes in patients with steep preoperative corneas: mean Ks greater than 55.0D and steep Ks greater than 57.0 (i.e., had

Table 1 – Characteristics of different models of intracorneal ring segments.

	Arc length (°)	Cross-section	Thickness (µm)	Optical zone (mm)	Inner diameter (mm)	Outer diameter (mm)
Intacs	150, 210	Hexagonal	210, 230, 250–450 in 50 µm increments	7.0	6.77	8.10
Intacs SK	90, 130, 150	Elliptical	210, 250–500 in 50 µm increments	6.0	6.00	7.00
Keraring	90, 120, 150, 160, 210, 340, 355	Triangular	150–350 in 50 µm increments	5.0 5.5 6.0	5.00	6.00
Ferrara	90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 210, 320	Triangular	150–350 in 50 µm increments	5.0 6.0	4.40	5.60
Myoring	360	Triangular	200–320	No data	5.00–8.00	6.00–9.00

Amsler–Krumeich grade IV). Additionally, Vega-Estrada and coworkers[103] stratified patients by preoperative CDVA and found a significant decrease in CDVA in patients with preoperative CDVA of greater than 0.90.

2.2. *Synthetic ICRS: complications*

ICRS implantation involves intraoperative complications, such as incomplete tunnel creation, corneal surface perforation, or anterior chamber (AC) perforation. In the first case, the complication can be resolved by mechanical dissection. The perforation rates are low, which is one of the most serious complications.[21,93]

Another intraoperative complication is vacuum loss that occurs during femtosecond laser suction; however, it is possible to recreate the same corneal plane and the intrastromal channel. Among postoperative complications, segment migration can occur, which may be due to an excessive ICRS width in a thin cornea. Coskunseven and coworkers and Mounir and coworkers[21,65] reported a high ring migration rate.

ICRS implantation near the incision implies a great risk of corneal melting, and ICRS should be explanted immediately in these cases.[20] Another reason for explantation is poor visual acuity or fluctuations in visual quality. The first to describe an explantation for this reason were Asbell and coworkers.[11] They noted glare, halos, and fluctuating vision. Other surgeons[6,31,12,105,18,71,17] have also reported poor visual acuity as a reason for explantation. One of the main goals of ICRS surgery is to treat KC or ectasia after laser *in situ* keratomileusis. The use of a permanent suture at the incision site and avoiding eye rubbing have been proposed.[46]

Infection risk is noted with ICRS implantation. Multiple microorganisms can cause this complication, and both bacteria and fungi can cause infectious keratitis. For example, *Staphylococcus aureus* 21 appears in up to 25% of cases, followed by *Pseudomonas* species and *Streptococcus pneumoniae*, among others.[95,15]

Several factors have been detected in relation to the onset of this complication, such as previous traumas, ring exposure, use of contact lenses, or systemic diseases such as diabetes mellitus.[42]

The most efficient method to treat infectious keratitis after ICRS implantation is topical antibiotic therapy. Bourcier and coworkers[14] found that topical antibiotic therapy alone was sufficient to treat the infection. On the other hand, in some publications ICRS explantation was considered as the first therapeutic option. Deep corneal neovascularization is another complication that can be caused by the implant and is not associated with the surgical wound. Treatment with topical corticosteroid agents and surgical removal of the ring may induce vessel regression.[9]

Recently, our study group defined the motivating reason for ICRS failure, either anatomic or functional, by reviewing the largest dataset of ICRS explanted up to date.[25]

Explantation due to functional failure represents the main reason for ICRS removal that determines either a worsening of visual acuity more often in mild cases of KC or the need for a keratoplasty to further improve the visual acuity in cases of advanced disease. Spontaneous extrusion of the ring represents the main cause of anatomical failure and happens in implantations performed in advanced cases of KC. We also later reported the largest case series of spontaneous ICRS extrusion after more than 2 years, and we described that the segment can be safely extracted, followed by a reversal of the corneal topographic data to the preoperative level. Of interest, we showed a significant astigmatic change in patients implanted with ICRS before late extrusion of the segment, suggesting the role of this parameter as a prognostic factor of extrusion.[26]

2.3. *Corneal allogenic intrastromal ring segments*

2.3.1. *Introduction*

KC patients with poor spectacle-corrected visual acuity or intolerant to contact lenses may benefit from a new and evolving conservative technique named corneal allogenic intrastromal ring segments (CAIRS) described and introduced for the first time at the international level by Soosan Jacob in 2015.[43,23]

CAIRS represents an additive procedure involving the midperipheral intrastromal transplantation of donor cornea stromal segments. The procedure is growing in popularity due to a relatively simple learning curve, ease of surgery, and safety and effectiveness.[43] It is an allogeneic human donor corneal tissue alternative to synthetic ICRS. CAIRS implantation consists in introducing customized semicircular segments of allogenic tissue into preformed intracorneal channels created manually, or better by a femtosecond laser, in the midperipheral stroma in order to reshape the corneal surface, improving its symmetry, thus combining the morphological and biomechanical benefits of ICRS while eliminating their possible adverse events.[8,25,26] Since its initial conceptualization and introduction, the CAIRS technique has evolved and underwent various modifications to facilitate the surgery and customize it according to different scenarios. The initial pull-through technique was replaced due to mid-depth larger channels dissection facilitating the segments insertion. The CAIRS are pushed in by using a curved Y-rod and drawn in from the opposite incision using a curved reverse Sinskey hook. When a femtosecond laser is not available, manual dissection can be used. Special instruments for the CAIRS procedure were designed such as the CAIRS trephine (Madhu Surgicals, New Delhi, India), the CAIRS marker, the various CAIRS inserters (curved Y-rod, curved reverse Sinskey, pigtail pull-through), and the CAIRS smoothener (Epsilon Eye Care, Mumbai, India) aim at improving accuracy and rapidity of the technique.[43]

2.3.2. *Surgical technique*

CAIRS[43] consists of ring segments created from allogenic eye bank-processed donor corneas with negative serology for HIV, HBV, HCV, and syphilis, with the advantage that corneas not suitable for corneal transplant for endothelial cell count or older donor tissue can be also used. The donor cornea is removed from the storage solution and mounted on an artificial AC. The epithelium is fully debrided and the center is marked and laid upside down on a Teflon block. The endothelium is stripped or eliminated with a sponge, and a double-bladed Jacob trephine (Madhu Surgicals) is used to punch a ring of stromal tissue. The ring is divided in half to yield 2 segments which may be cut to an appropriate size. The breadth and the thickness of these segments can be customized according to severity, KC type, and location, refractive error, pattern of astigmatism, high-order aberrations, and other factors. For this purpose, the trephine comes in different sizes, allowing for thicker or thinner segments of tissue. Parker and coworkers[74] described a CAIRS dry insertion technique, making it easier to insert the segments into the intrastromal channels due to their dehydration which shrinks and stiffens the tissue temporarily. Following the insertion into the channels, the dehydrated CAIRS segments rehydrate immediately. Parker and coworkers also stained the segments with 0.06% trypan blue to enhance their visibility during implantation.[75]

The CAIRS insertion is done under topical anesthesia after femtolaser or manual channels preparation in the recipient's eye. Depending on the patient's requirements, either single segment or double segments may be inserted. The CAIRS segment is flattened with forceps, a gentle push-in/pull-through technique may be used, with the aid of a curved Y-rod and reverse Sinskey hook or curved 23-gauge forceps, or the Jacob CAIRS pig-tail instrument may be used to draw the segment out. It is introduced into the channel and the segment is tied or anchored to the tip of the instrument at the leading end once it reaches the opposite incision or the other side of the same incision. The inserter is then withdrawn from the other side, thereby simultaneously guiding the segment into the channel in a near-circumferential manner.[43]

An almost 360° segment or segment of any desired arc length may thus be placed within the channels. Moreover, an INTACS segment may be used to draw it in as described previously. CAIRS can be combined simultaneously or sequentially with CXL procedure according to minimum CT after CAIRS insertion.[98,59]

Serious complications associated with synthetic ICRS have included segment migration, overriding of segments, stromal thinning leading to melting and necrosis, exposure or extrusion of segments, corneal neovascularization and infectious keratitis.[8,26,46,21]

On the contrary, the advantage of CAIRS vs synthetic ICRS consisted in avoiding the major part of the above-mentioned complications, maintaining the advantage of corneal reinforcing (additive) treatment and remodeling (refractive empowerment) of the corneal surface, plus a higher integration of the allogenic corneal ring into the host corneal stroma. CAIRS may not only be implanted in mild cases but also in patients with more advanced disease.[43,74,75]

Indeed, synthetic ICRS requires a minimum stromal thickness of 400 μm,[59] above the segment in order to prevent stromal necrosis and melt. CAIRS, being allogenic and also less rigid, may be implanted into thinner corneas, so implantable in more advanced cases.[1] CAIRS induces the absence of any reflections with less glare disability. It is possible to customize the arc length, the thickness, the optical zone. and the depth of implant. Naturally, central corneal scarring doesn't benefit from CAIRS implantation.[43]

Patients suitable for CAIRS implant have preliminarily shown improvement in their uncorrected and best-corrected visual acuity, with a reduction in the steepest keratometric value and irregular astigmatism.[43] Those results have been confirmed by several studies, with both manual and femtosecond laser technique for tunnel creation.[74] Recently, 65 keratoconic eyes have been implanted with CAIRS with an improvement in both uncorrected distance visual acuity (UDVA) (from 0.91 ± 0.50 logMAR preoperatively to 0.40 ± 0.24 logMAR postoperatively) and CDVA (from 0.87 ± 0.20 logMAR preoperatively to 0.27 ± 0.06 logMAR postoperatively) and a reduction in the steepest keratometry.[68] Difference map pre- and post-CAIRS showed flattening and regularization of the topography and centralization of the cone together with improvement in the symmetry indices (Fig. 1).

3. Substractive procedures plus corneal cross-linking

Another alternative, successfully used for over a decade, is expanding the refractive therapeutic options for corneal ectasias, placing itself precisely between the end or the impossibility of using rigid gas permeable (RGP) contact lenses and the execution of a keratoplasty, which in this way can be avoided or postponed, is represented by minimally selective trans-epithelial photorefractive (t-PRK) or phototherapeutic (t-PTK) keratectomy combined with conventional and accelerated CXL, in the so-called CXL Plus therapy. The aim of these treatments is to regularize corneal shape improving the quality of vision with spectacles, consuming the small amount of tissue, minimizing invasiveness. Despite that tissue ablation in KC corneas has never been widely and definitely accepted, it represents a therapeutic reality performed in many countries in selected cases that needs to find a precise and shared place in the modern therapeutic flowchart of KC (Fig. 2).

Numerous studies in the literature, including medium to long-term follow-up, demonstrate the efficacy and safety of

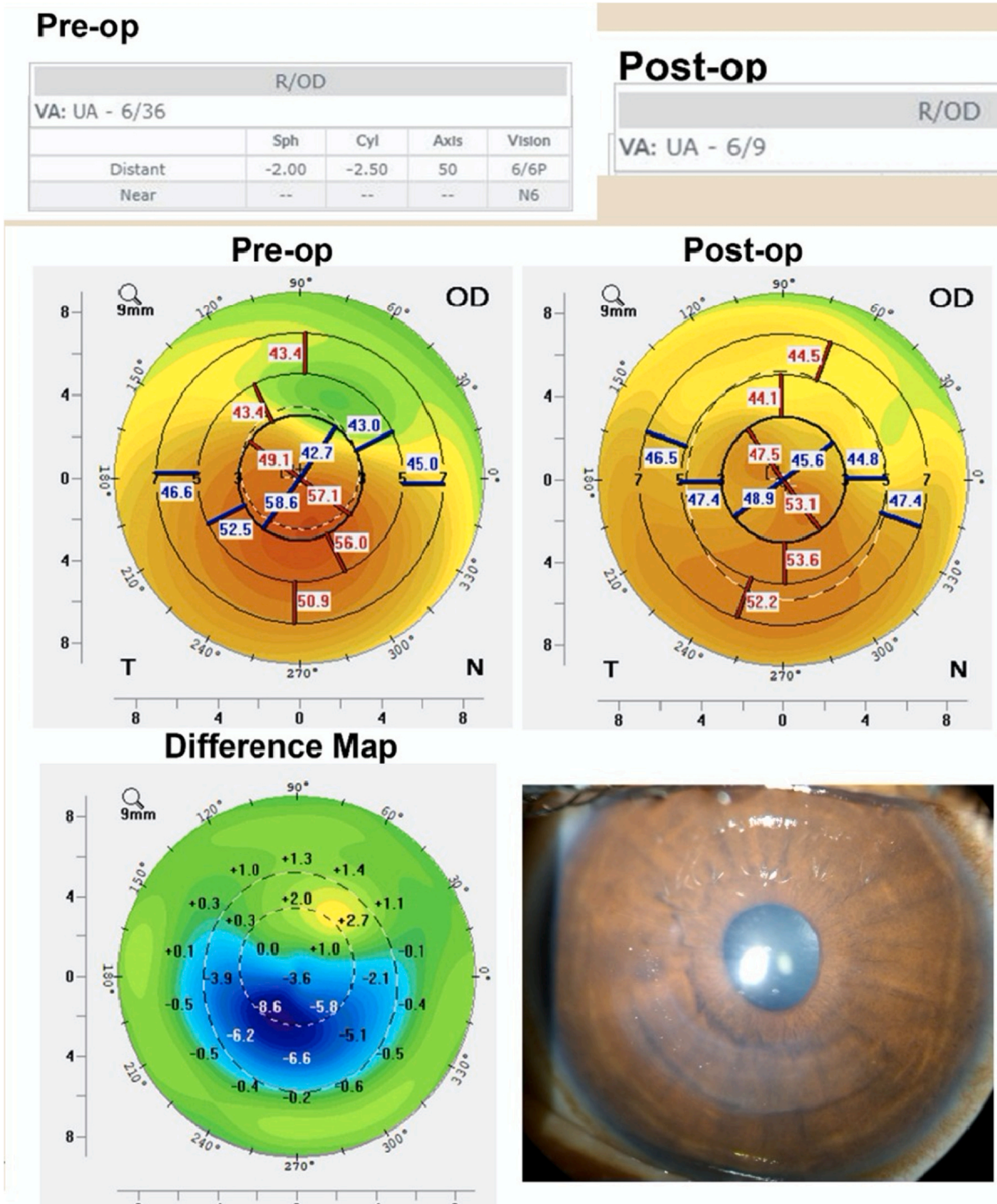

Figure 1 – Corneal allogenic intrastromal ring segments (CAIRS) pre and 6 months postoperative outcomes with differential map and slit-lamp photograph.

the combined topography-guided procedures of excimer laser corneal remodeling and crosslinking that can be performed in selected cases on a same-day basis or sequentially. CXL has paved the way for these treatments by strengthening corneal stroma, stabilizing the progression of ectatic corneas, conferring a higher level of safety and efficacy.[27] This treatment is indicated in selected cases of KC patients intolerant to RGP contact lenses with poor best spectacles corrected visual acuity. The micro-photo-ablative remodeling of the central corneal profile (central corneal remodeling) is generally planned by using topo-guided excimer laser selective ablations, optimizing the optical zones, minimizing tissue consumption (generally less or equal to 55 µm of corneal stroma) and taking into account the contribution of the posterior corneal surface in the determinism of the irregular visual defect and high-order contextual aberrations.

These treatments aimed at improving patients' UDVA and best spectacle corrected visual acuity reducing high order

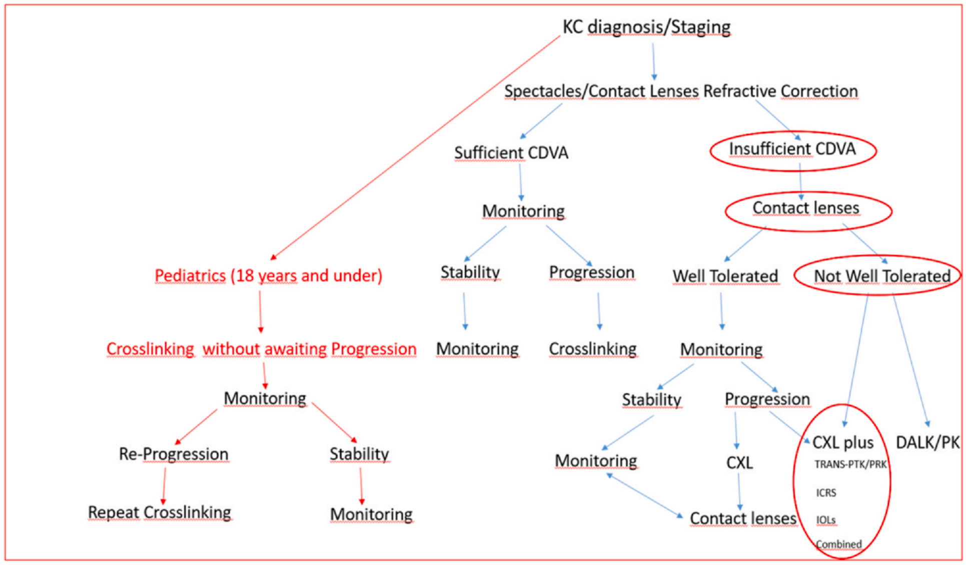

Figure 2 – Mazzotta-D'Oria flow chart for CXL and CXL Plus Therapy.

corneal aberrations (HOA). In addition, another purpose of central corneal remodeling combined with crosslinking consists in improving contact lenses refitting on a more regular reshaped surface. The goal of these treatments is therefore to minimize the need for corneal transplant by improving the quality of vision and life of patients with KC offering a new therapeutic hope in those with contact lenses intolerance or inadequate fitting that represents the best indication of CXL combined refractive empowerment procedures such as t-PRK or t-PTK. Furthermore, this therapy does not prevent performing a deep anterior lamellar or penetrating keratoplasty in case of failure, insufficient visual acuity, ectasia instability, or patient dissatisfaction.

Kanellopoulos and coworkers[45,58,48] in 2007 published the first case series of combined CXL with sequential topography-guided PRK as an alternative therapeutic approach for KC, providing a personalized protocol also known as the "Athens protocol," followed by the "Cretan protocol" published by Kymionis and coworkers in 2009.[52]

The Athens protocol, recommended 70% treatment of the cylinder and up to 70% treatment of the sphere so as not to exceed an ablation depth of 50 μm and achieve an expected CT of no less than 350 μm after PRK. The larger study included a total of 325 eyes with KC comparing a group of 127 eyes that underwent CXL with subsequent topography-guided PRK performed 6 months later (sequential group) and a second group of 198 eyes that underwent CXL and PRK in a combined procedure on the same day (simultaneous group) showed that same-day simultaneous topography-guided PRK and CXL appears to be superior to sequential CXL with later PRK in the visual rehabilitation of progressing KC.[47]

The simultaneous technique seemed to overcome the drawbacks of the initial two-step CXL-PRK procedure due to its main advantage that laser ablation does not interfere with already cross-linked corneal tissue. On the contrary, other retrospective, noncomparative consecutive case series in patients that underwent corneal-wavefront guided TransPRK for the correction of aberrations at least 4–6 months after CXL reported that corneal-wavefront guided transepithelial PRK ablation profiles after conventional CXL also yields to good visual, optical, and refractive results. Indeed, a prospective uncontrolled interventional case series study including a total of 34 consecutive eyes of 25 patients with KC previously treated (at least 1 year) with CXL showed a significant improvement in the uncorrected and corrected distance visual acuities proving the efficacy and safety of performing excimer laser photoablation also after CXL as an effective option to partially correct the sphero-cylindrical errors and to minimize the level of higher order aberrations in mild and moderate KC.

These data are further confirmed by the so-called "Topolink study" performed in 62 eyes where the topography-guided PRK followed the CXL treatment, there were significant improvements in corneal astigmatism, maximum keratometry, mean keratometry, SE, posterior astigmatism, and total HOAs without significant correlations between age, sex, time elapsed between CXL and PRK, and age at the time of either procedure on final visual acuity. These studies show, contrary to what was believed, that the execution of the excimer laser at least 6–12 months after CXL, determines functional results comparable to the sequential laser/CXL treatment in the absence of adverse effects or complications without inducing errors due to the rate of ablation of cross-linked tissue. These results pave the way for the possibility that even patients already treated with CXL can perform a TG-guided or WF-guided excimer laser ablation to improve their visual acuity.

These treatments were safe and efficacious for the correction of refracto-therapeutic problems in keratoconic patients and demonstrate the usefulness of performing laser ablation after CXL thus evaluating the impact of CXL-induced modifications in patient refraction and aberrations which may induce unwanted hypercorrections. The long-term outcomes of CXL for the treatment of KC in a prospective, comparative, interventional case series of 30 eyes with progressive KC using 2 different

Table 2 – Differences of the different treatment planning for phototherapeutic keratectomy + corneal cross-linking.

Authors (years)	KC st	Age incl	Thinnest point tot	Stromal abl depth	Optic zone	Gain CDVA	Follow-up	Eyes	CXL protocol
Kymionis et al (2009) (2011) (2014)	I-II	18 (30)	> 400	50 µm epithel T-PTK	6.5–7	+1.3	4 y (7) 3 y (11) 2 y (23)	41	CXL conv 3–30 5.4 J Medio 30 R
Kanellopoulos et al (2009) (2010) (2014) (2019)	I-II	17	> 300	50 µm epithel 50 µm stromal (70% ref)	5.5–6.5	+0.2	Up to 10 y	231	ACXL 10-9 5.4 J
Shetty et al (2013) (2015)	I-II	23 (25)	> 400	50 µm epithel 40 µm stromal	5.5–6.5	+0.3	1 y	29	ACXL 4–30 7.2 J
Alessio et al (2013)	I-II	18	> 450	50 µm epithel 50 µm stromal	2.1–5.4	+0.2	2 y	17	CXL 3–30
Sakla et al (2014)	I-II	18	> 450	50 µm stromal T-PRK	5.5	+4	1 y	31	CXL conv 3–30 5.4 J
Aslanides et al (2013)	I-II	21	> 400	50 µm 80% cyl 60% sph	5.5	+3	1 y	22	CXL 3–30 5.4 J Medio R or R hypo
Nattis et al (2019)	I-II	17	> 300	50 µm	6	+2	1 y	62	
Mulè et al (2019)	I-II	14	> 400	55 µm CCR	1–1.5 9.8	+3.2	1 y	24	CXL 9–10 Ribo 0.1%
Rabina et al (2020)	I-II	21	> 400	50 µm	6.5	+1	3 y	50	CXL 5.4 J 9–10
Rechichi et al (2021)	I-II	18	> 400	50 µm	6	+2	2 y	100	ACXL 7.2 J 8–30

KC = keratoconus; CCR = Central corneal regularization; CDVA = corrected distance visual acuity; T-PTK = trans-epithelial phototherapeutic keratectomy; T-PRK = trans-epithelial photorefractive keratectomy.

techniques for epithelial removal: an excimer laser-assisted t-PTK vs the standard mechanical epithelial debridement by a blunt metal spatula, showed no intraoperative and postoperative complications in any of the patients with the advantage that epithelial removal with t-PTK during CXL resulted in statistically significant better visual (CDVA, UDVA), refractive (astigmatism reduction), and keratometric outcomes compared with the mechanical epithelial debridement over a long-term follow-up.[44,57]

Definitely, according to the Cretan protocol, the functional results and outcomes the combined trans-epithelial PTK and CXL were effective and safe in KC patients over a long-term follow-up and is particularly indicated in patients with RGP lens intolerance and poor spectacles CDVA with high order aberration that can improve their quality of vision avoiding or postponing the need of corneal transplant.[53]

The results of the Cretan protocol were confirmed by other retrospective cohort studies,[35] proving that simultaneous topography-guided partial PRK or PTK and CXL were effective, safe, and stable in KC patients significantly reducing the higher order aberrations and astigmatic error.[90,50]

The comparative long-term reports between combined t-PRK with a solid-state laser (maximum ablation depth, 50 µm) followed by simultaneous CXL vs CXL alone in progressive KC patient groups, well matching in terms of age and KC stage, demonstrated the superiority of simultaneous t-PRK followed by CXL in improving vision of treated patients vs those treated with CXL alone, and similar results regarding postoperative stability.[16] The main limiting factors concerning safety regarding CT that must be taken into account in treatment planning correcting aberrations removing the small amount of tissue and postoperative haze due to excessive wound-related stimuli in combined simultaneous procedures.

Table 2 displays the differences between the different treatment planning showing inhomogeneous protocols and

Table 3 – Common parameter extrapolated from the different CXL plus excimer laser surface ablation protocol.

Average KC stage at inclusion	Stage II (I-II)
Average age at inclusion	18.5 years (14–30)
Average stromal thinnest point at inclusion	435 µm (300–450)
Average stromal ablation	50 µm (40–55)
Average optical zone diameter	5.5–6.5 mm
Average CDVA gain	+2.35 S Lines (1–4 SL)
Average follow up	3 years (1–10)

KC = keratoconus; CDVA = corrected distance visual acuity.

setting that still represents the most important limitation of these approaches requiring standardization of the indications and settings such as age at inclusion, volume of tissue ablation, programmed residual stromal bed, optical zones, accelerated crosslinking protocols, intraoperative use of mitomycin C and postoperative therapeutic regimen.

Beyond some main parameters, however, each case is different so the protocols may change according to each KC baseline parameters such as patient's age (children not indicated), baseline and residual minimum CT, apex cone localization. Table 3 displays the common parameter extrapolated from the different CXL plus excimer laser surface ablation protocol studies displayed in Table 2.

The prospective comparative studies evaluating the effect of KC apex location on the change in refractive outcomes, UDVA, CDVA, l acuity, total corneal aberrations, and corneal biomechanics (corneal hysteresis and corneal resistance factor) after combined topography-guided PRK CXL demonstrated in the group were the cone was located within the central 2-mm zone a superior postoperative best-corrected distance visual acuity than in patients were the cone was located outside the central 2-mm zone. On the contrary, interestingly, the increases in corneal hysteresis and corneal resistance factor were greater in peripheral cones addressing the fact that cone location impacts in visual acuity and biomechanics after the combined procedure paving the way also to customized CXL profiles in the future such as elastic modulus guided CXL with variable energy or stromal pachymetry gradient CXL profiles conferring higher resistance in the most ectatic steepest areas and reducing energy deliver to the less ectatic ones so sparing energy and stromal wound related stimulation.

A recently published study evaluated the changes in refractive outcomes and corneal aberrations in central and paracentral KC after selective transepithelial topography-guided photorefractive keratectomy combined with accelerated corneal crosslinking, the so-called "STARE-X Protocol."[84] This prospective, interventional, multicenter study was performed in 100 KC eyes and patients were subdivided into 2 groups: group 1 with cone located within the central 3 mm zone (50 eyes) and group 2 (50 eyes) with cone located outside the central 3 mm zone with a 2-year follow-up. Main outcome measures included UDVA, CDVA, corneal tomography and corneal wavefront aberrations compared at baseline and 2 years after the treatment. One hundred eyes of 100 patients underwent STARE-X protocol at 2 years, UDVA and CDVA improved, and sphere, cylinder, and Kmax were reduced after treatment in both groups. Moreover, a statistically significant reduction of total higher-order aberrations HOA was observed in both groups. In accordance with the observation of other authors, the best CDVA was achieved in central cones.

Topo-guided custom surface ablation followed by CXL using a trans-epithelial approach was preferred to minimize stromal consumption, taking into account the masking effect of the corneal epithelium in ectatic corneas. The combination of topography-guided custom ablation and CXL improved patients' visual, refractive, and topographic outcomes and halted the progression of keratectasia. More recently this approach combining corneal customized transepithelial therapeutic ablation to treat irregular corneal optics and accelerated CXL named central corneal regularization or remodeling "Central corneal regularization protocol" has been published.[70,96] This interesting series of 24 eyes included the selective ablation aimed to transform the preoperative irregular corneal morphology into a regular aconic shape of desired curvature, defined as the expected postoperative anterior corneal curvature according to the programmed treatment. Different from other protocols, to achieve minimal tissue removal from the biomechanically compromised cornea, a full regularization was aimed at setting a narrow optical zone (1.0–1.5 mm in diameter), while the quality of the postoperative corneal optics was addressed by gradually fading custom ablation effect towards the periphery, within a total ablation zone of up to 9.8 mm in diameter. The large "connecting refractive zone" between the central optical zone and the untreated periphery features offered a smooth customized transition with a constant slope in each radial direction, resulting in linear increase or decrease of curvature.[97,99,67]

The programmed customized ablation was achieved by a software based on ray-tracing calculation of the total corneal power balancing the refractive contribution of the posterior corneal surface with the anterior. All the treatments in this case were planned to leave at least a 400 µm of residual stromal bed followed by 9 mW/5.4 J/cm^2 accelerated CXL, thus minimizing the wound-related stimulation and haze.[60]

The "Tel Aviv protocol" consists of t-PRK, and 9 mW/5.4 J/cm^2 accelerated CXL. In this series of 50 eyes, half of the manifest refractive astigmatism (on the same axis) was planned in the programmed excimer laser ablation, while the spherical ablation is added so as not to exceed a total of 50 µm ablation of the epithelium and anterior stroma in a 3-year follow-up. The Tel Aviv protocol for progressive KC patients provided good improvement in visual acuity and astigmatism while halting the progression of KC without adverse events.[81]

Another important feature recently demonstrated was that the use of mitomycin C after CXL and particularly in combined simultaneous topography-guided t-PTK or t-PRK with CXL should be avoided because it increases corneal haze. Current studies suggest that CDVA, UDVA, and HOA in low-to-moderate KC patients improved in a combined treatment without sacrificing the biomechanical stability of the cornea. Long-term results have a follow-up period of 68 months. Basically, the techniques that remove epithelium manually or by alcohol, without considering that epithelium is a masking agent compensating morphological irregularities of corneal curvature, induce higher tissue volume ablation and a higher risk of overcorrections, with potential hyperopic shift, without considering the contribution of the posterior corneal surface aberration that differs case by case in the heterogeneous phenotypes of KC. Transepithelial selective excimer laser photoablation procedures are superior to achieving a small amount of tissue consumption and in customized central cornea remodeling.[82]

Moreover, software based on the calculation of mean pupillary power or raytracing technology compensating anterior and posterior corneal surfaces is mandatory to avoid bad surprises. Concerning CXL protocols, not the same protocol for all is indicated. There are pachymetry-guided protocols actually available to customize also CXL presetting the depth of demarcation line, according to residual postablation stromal pachymetry, thus sparing endothelium and reducing the risk of haze that is higher with Dresden protocol. Indeed, the original 3 mW/cm^2 Dresden protocol is not a good indication for these combined procedures that require also CXL customization.[60]

4. Phakic intraocular lenses

4.1. *Introduction*

It is a well-established fact that refractive surgery in the form of corneal laser refractive surgery is contraindicated in KC patients. Combined PRK-CXL protocols aim to regularize the cornea and reduce RG contact lens dependence, but such treatments do not target emetropia since this would usually involve an unacceptable amount of stromal ablation, even in the presence of a crosslinked tissue.[50] Because of this, phakic intraocular lenses (pIOL) play a critical role in the visual rehabilitation of the KC patients, usually suffering from high refractive errors with significant levels of anisometropia, limiting the use of spectacles.[4]

Thus, pIOLs are an essential tool in the last stage of the visual rehabilitation of the KC patient once the cornea has been reshaped and refraction shows stability.

The main benefits of pIOLs in the KC eye are that cornea biomechanics remain unaltered, not interfering with the natural evolution of the disease.[54,3] It involves a reversible procedure, so pIOL exchange could be an option in the presence of an unexpected refractive change in the long-term observation; and accommodation is preserved, in contrast to pseudophakic IOLs. The key element at the preoperative assessment is to understand that pIOLs just correct low-order aberrations (spherical and cylindrical refractive errors), but not HOAs, usually present in a large amount in such patients (with high levels of coma and coma-like aberrations) deteriorating the visual acuity and quality of vision. These HOAs, which remain uncorrected with pIOLs, need to be approached in advance by "reshaping" procedures such as PRK-CXL protocols or ICRS implantation[22] in order to regularize as much as possible the existing irregular astigmatism and so improve the quality of vision and bring the spectacle-CDVA to an acceptable level (CDVA > 0.5) before considering any pIOL implantation (Fig. 3).

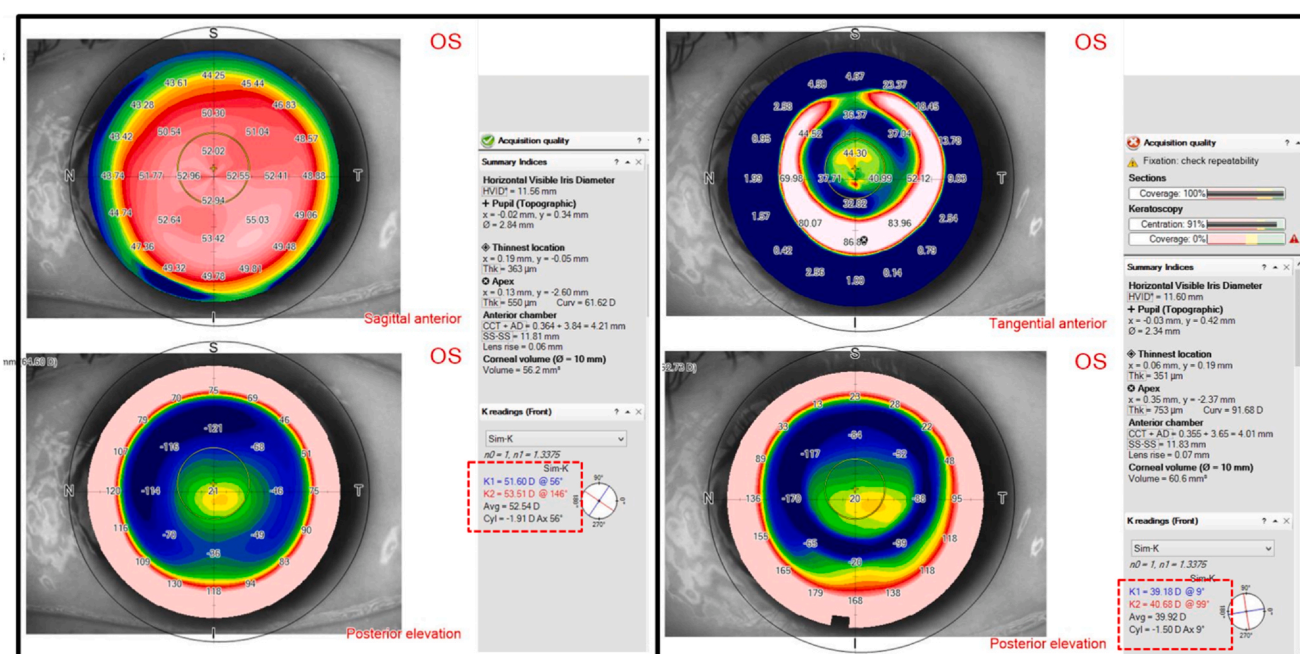

Figure 3 – Case of a 50-year-old male with progressive loss of vision after myopic laser *in situ* keratomileusis (LASIK) 20 years before for high myopia correction. On the left side of the image it can be observed a severe ectasia on the anterior curvature map with pathological posterior elevation, confirming the diagnosis of post-LASIK ectasia. At this point, uncorrected distance visual acuity (UDVA) was counting fingers at 2 months, and corrected distance visual acuity (CDVA) was 0.2 with a myopia of – 20.5D. A 320° intracorneal ring was implanted, obtaining a strong flattening on the anterior curvature map (right image), with an improvement of the UDVA to 0.15, and CDVA to 0.6, with a refraction of – 12D – 1D × 180°. A nontoric Artiflex anterior chamber-phakic intraocular lens (implantation through the steep axis with an opposite incision) was programmed after demonstrating refractive stability, obtaining a final postoperative UDVA of 0.9 and plano refraction. Visual, refractive, and keratometric stability is maintained after more than 2 years of observation.

4.2. Implantation criteria

1. Stable disease: pIOLs may be considered in KC when facing a stable KC with demonstrated refractive stability. Otherwise, a progressive cone will affect to the visual and refractive stability in the long term, and so a CXL procedure may be performed in advance.
2. Acceptable CDVA: as stated before, pIOLs don't rehabilitate corneal irregularity and HOAs, so pIOLs may be implanted as far as the patient shows an acceptable CDVA (> 0.5, decimal scale), and being this vision subjectively appreciated as "acceptable" by the patient. Otherwise, corneal reshaping procedures such as PRK-CXL or ICRS may precede in order to reduce RGP dependency and enhance the visual outcome expected with the pIOL.
3. Meet the usual pIOL anatomical requirements: usual anatomical recommendations according to the preferred pIOL model need to be addressed before implantation (minimal anterior chamber depth - ACD and angle aperture, lens rise, endothelial cell density, etc).

Since the cornea and the crystalline lens remain unchanged with pIOL implantation, IOL power calculation is based on the subjective refraction preoperatively and the specific IOL calculation nomogram provided from the different pIOL companies. To the best of our knowledge, no specific pIOL calculation nomograms have been developed for KC to optimize the resulting vault (space between the posterior surface of the pIOL and the anterior lens capsule) in case of posterior chamber pIOLs (PC-pIOL). AC-pIOLs don't present the limitation of a variable vault since they are fixed to the anterior surface of the iris.

4.3. pIOL models

1. AC-pIOLs: Artilens (Ophtec BV) is the only commercially available AC-pIOL today (Fig. 4-Left). It presents 2 formats according to the amount of targeted spherical equivalent: Artisan, a nonfoldable polymethyl methacrylate (PMMA) lens (requires 5.5 mm incision, ideally through a scleral tunnel), and Artiflex, a foldable polysiloxane lens with PMMA haptics (requires 3.2 mm corneal/limbal incision). Both AC-pIOLs fixate to the anterior surface of the iris by using a PMMA claw at the two haptics. Due to this mechanism of implantation, there is no chance of postoperative pIOL rotation, but still requires the performance of a superior peripheral iridotomy in order to avoid the risk of pupillary block. Artilens can correct up to 23.5D of myopia and 7.5D of astigmatism.
2. PC-pIOLs: among the different commercially available models, the implantable collamer lens (ICL, Staar) concentrates almost all available scientific evidence about the use of PC-pIOL in KC[10] (Fig. 4-Right) (Table 4). ICL is a plate-haptic foldable collamer IOL implanted at the ciliary sulcus, between the iris and the crystalline lens, through a 3.2 mm corneal/limbal incision. ICL latest model (V4c) incorporates a tiny hole in the middle of the lens to prevent aqueous flow blockage and so further placement of a peripheral iridotomy is no longer required.[77] Its diopter range goes up to 18D of myopia and 6D of astigmatism.

Recently, new PC-pIOL models (none of them FDA approved) have reached the market, such us intraocular posterior chamber lens (Care Group) and Eyecryl Phakic IOL (Biotech Vision Care). These are hydrophilic acrylic IOLs that offer a broader diopter range than ICL; however, the available scientific data in peer-reviewed journals about them is scanty.

The main advantage of PC-pIOLs over the iris claw AC-pIOLs is the easiness of their implantation, reason why they are usually preferred by the majority of surgeons. On the other hand, with PC-pIOLs there exist the risk for postoperative IOL rotation (see below), what is inexistent with Artilens as far as they are correctly implanted. Moreover, vault should be considered with PC-pIOLs, since an excessive vault can compromise the iridocornea angles, and an insufficient vault may imply a risk for secondary cataract. Vault prediction in KC eyes may be negatively influenced by a potential overestimation of the ACD if this is measured considering the apex of the cone, what could occasionally generate the selection of a larger diameter IOL than really needed, and so a higher vault than expected.[2] Although no specific calculation nomograms have been suggested for KC, careful measurement of the ACD is advised during the IOL selection for such patients.

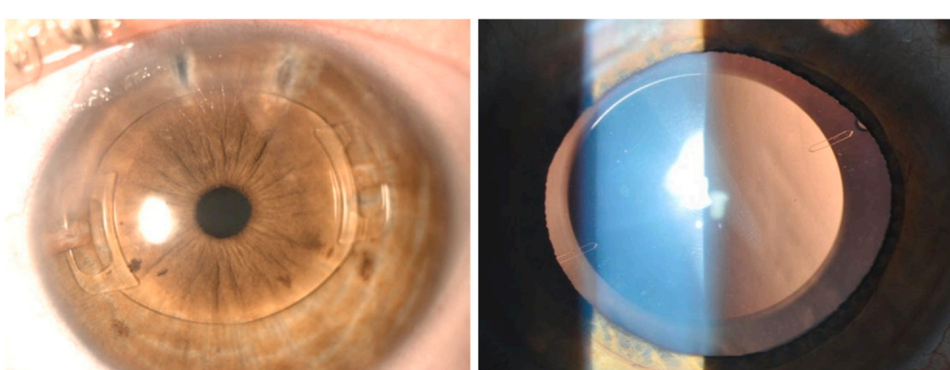

Figure 4 – Toric iris-claw anterior chamber-phakic intraocular lens (pIOL) (Artiflex; left), and toric posterior chamber-pIOL (implantable collamer lens; right).

4.4. *Efficacy and safety*

In order to simplify and focus the extensive evidence regarding the safety and efficacy profile of pIOL for the visual rehabilitation of KC patients, we have analyzed the scientific evidence published within the last 10 years (from 2012; Table 4). pIOL models have progressively been changed and improved along the years, as well as the preoperative anatomic safety inclusion criteria for each type of pIOL has also been progressively refined. Thus, we believe that the available evidence from the last decade reflects more accurately current tendencies and obtained results with the use of pIOL in KC eyes (Table 4).

As can be seen in Table 4[4,89,33,28,30] both types of pIOL (iris claw and PC-pIOLs) offer good results in terms of efficacy, with indices close to or even exceeding 1, which means that postoperative UDVA approximates and may exceed the preoperative CDVA. Nevertheless, these results are worse (in terms of efficacy and predictability) than those expected in eyes with normal corneas, where reported efficacy indexes are systematically exceeding 1 and more than 90% of eyes show a final spherical equivalent within 0.5D from target correction (vs less than 70% generally reported in KC).[73,49]

Regarding safety, all analyzed articles report indexes well over 1, reflecting that CDVA is significantly improved after pIOL implantation. These safety indexes seem similar or even better than those previously reported for non-KC eyes.[73,49]

Within the last decade, a majority of authors have focused on reporting the outcomes of ICL as pIOL for KC, with only four papers using iris-claw AC-pIOLs. Despite that Artilens and ICL have shown similar efficacy and safety performance (Table 4), there is a general trend towards the use of PC-pIOLs, probably in relation with their easier implantation and less demanding surgical skills. One study directly compared the outcomes of toric ICL and toric Artilens in a retrospective study in KC patients.[4]

They demonstrated that both implants provided equivalent results, with no statistically significant differences between them in terms of efficacy, safety and stability of the refractive result, although they reported a trend toward better effectiveness results in the iris-fixated pIOL group in relation with a better astigmatic outcome. To the best of our knowledge, there are no studies reporting the outcomes of intraocular posterior chamber lens PC-pIOL in KC patients, and only one using the EyeCryl PC-pIOL, were reported outcomes were comparable to those previously reported with ICL.[13]

4.5. *Complications*

Regarding PC-pIOL complication rates, the majority of studies do not mention the obtained vault or state that no pIOL rotation was needed in any patient. Only Shafik and coworkers[94] and Fairaq and coworkers[29] specified this, reporting a mean vault of 509.75 (range: 320–900) and 421 (range: 98–926) μm. However, Alhamzah and coworkers[2] found that improper vault size was the most common cause of ICL exchange/explantation among patients with or without KC, and showed a tendency toward higher vaults in KC patients, highlighting the need for more accurate methods to calculate ICL size when facing KC eyes. As stated before, this may be linked with a potential overestimation of the ACD if it is measured considering the posterior curvature of the cone apex.

There is one report of a case of secondary anterior subcapsular cataract (ICL model was not specified),[29] although

Table 4 – Summary of outcomes of phakic intraocular lens implantation for keratoconus studies.

Author (year)	Lens	Eyes	Follow-up (months)	Preop SE (D)	Preop astigmatism (D)	Postop SE (D)	Postop astigmatism (D)
Sakla et al (2021)[89]	Toric ICL after PRK + CXL	46	12	− 7.35 ± 5.20	− 2.90 ± 2.21	− 0.32 ± 1.42	− 1.47 ± 1.46
Balparda et al (2021)[13]	Toric EyeCryl	20	6	− 10.31 ± 6.18	− 3.82 ± 1.62	+ 0.09	− 0.66 ± 0.18
Fairaq et al (2021)[29]	Toric ICL	32	15.3	− 7.87 (median)	− 3 (median)	− 0.31 (median)	− 1.12 (median)
He et al (2020)[40]	Toric ICL after ICRS + CXL	31	12	− 3.13 ± 3.32	− 3.14 ± 1.71	− 0.08 ± 0.72	− 0.63 ± 0.67
Emerah et al (2019)[28]	Toric ICL after CXL	14	6	− 4.8 ± 2.25	− 2.3 ± 1.60	− 0.3 ± 0.4	− 0.6 ± − 0.5
Abdelmassih et al (2017)[1]	Toric ICL after ICRS + CXL	16	24	− 4.58 ± 3.47	− 4.13 ± 1.64	− 0.73 ± 1.07	− 1.23 ± 1.11
Antonios et al (2015)[10]	Toric ICL after CXL	30	12	− 6.81 ± 3.48	− 2.74 ± 1.33	− 0.83 ± 0.76	− 1.03 ± 0.60
Kamiya et al (2015)[56]	Toric ICL	21	36	− 9.70 ± 2.33	− 3.21 ± 1.56	− 0.02 ± 0.53	− 0.62 ± 0.79
Shafik Shaheen et al (2014)[94]	Toric ICL after CXL	16	36	− 5.98 ± 4.39	− 4.91 ± 1.51	0.00 ± 0.18	− 0.05 ± 0.14
Hashemian et al (2013)[37]	Toric ICL	22	6	− 4.98 ± 2.63	− 2.77 ± 0.99	− 0.33 ± 0.51	− 1.23 ± 0.65
Fadlallah et al (2013)[30]	Toric ICL after CXL	16	6	− 7.24 ± 3.53	− 2.64 ± 1.28	− 0.89 ± 0.76	− 1.16 ± 0.64
Alió et al (2014)[4]	Toric ICL	28	15	− 10.01 ± 3.82	− 2.67 ± 1.79	− 0.62 ± 0.92	− 1.13 ± 0.84
Alió et al (2014)[5]	Toric Artiflex	20	15	− 8.91 ± 4.57	− 2.29 ± 1.90	− 0.28 ± 0.81	− 0.70 ± 0.80
Güell et al (2012)[36]	Toric Artilens after CXL	17	37	− 6.99 ± 3.2	− 3.54 ± 1.38	− 0.22 ± 0.33	− 0.62 ± 0.39
Ferreira et al (2014)[32]	Toric Artilens after ICRS	21	12	− 10.76 ± 6.86	− 3.25 ± 1.2	− 0.46 ± 0.8	− 1.2 ± 1.18
Fischinger et al (2021)[33]	Toric Iris Claw after CXL	38	1.5	− 5.71 ± 4.96		− 1.25 ± 1.20	

SE = spherical equivalent; ICL = implantable collamer lens; pIOL = phakic intraocular lens.
For those studies combining procedures such as corneal collagen crosslinking (CXL) or intracorneal ring segments (ICRS), preoperative data shown is before pIOL implantation (thus, after combined procedures have been performed).

from the introduction of the latest ICL model with central aquaport (V4c) secondary cataract risk has been estimated to be close to 0%.[72]

Finally, mean endothelial cell loss reported has been 1.41% at 6 months, 1.11% at 12 months,[29] 4.4% at 3 years, and 8.98% at 3 years[96] in general comparable to the one observed in non-KC eyes.

Iris claw AC-pIOLs totally skip the complications of secondary cataract formation and inadequate vaulting since they have the advantage of "one lens size fits all" however, this pIOL has been related to an increased endothelial cell loss, greater than the physiological rate, and subsequent risk for corneal decompensation requiring corneal transplantation.[49,101]

On the other hand, it has been reported that, if the anatomical inclusion criteria for these pIOLs is strictly met (ACD > 3 mm from corneal endothelium), endothelial cell loss may not be different than physiological with up to 10 years of follow-up.[66]

Artilens studies included in Table 4 didn't observe a significant decrease in central endothelial cell density in such KC population.[4,36,33]

Iris claw AC-pIOLs fixates to the iris, preventing any risk of potential pIOL rotation and subsequent loss of astigmatic correction; however, PC-pIOLs can suffer from this postoperative complication, and the higher is the targeted astigmatism, the stronger will be the cylinder undercorrection in the advent of pIOL rotation. Kamiya and coworkers[56] reported toric ICL axis rotation > 10° in one eye (5%), requiring ICL repositioning, while Fairaq et al[29] reported this complication in 3 eyes (9.4%).

5. Refractive lens exchange-cataract surgery

5.1. *Which biometry to target the right power*

The peculiar optical structure of KC explains the interest that this condition has in clinical practice as regards the calculation of the IOL power, in the preoperative setting of a refractive lens exchange or cataract surgery (as both procedures have the same problems with the calculation in KC). This measurement in patients with KC has a significant variability of refractive results due to the optical properties of the cornea, the inhomogeneity in the depth of the AC and the lower accuracy in the detection of the axial length (AL). These limits are partially reduced by the ongoing development of technology and data science that can improve the accuracy of IOL selection.[7]

Hashemi and coworkers[39] examined the repeatability of keratometry measurements with 5 different devices (Pentacam, Eyesys, Orbscan, IOLMaster, Javal manual keratometer) based on 5 different measurement techniques in 78 eyes with different grades of KC. Their study found that in patients with K values up to 55.0D keratometry readings had good repeatability among all the devices and Pentacam had the highest repeatability, while Orbscan had the lowest. In group 3 (K > 55D) all 5 devices had low repeatability. The same authors found that the lowest mean absolute error was obtained with the SRK/T formula in patients with mild to moderate KC, and SRK/T and SRK II formulas in patients with severe KC.[39]

Vergence formulas use up to 6 biometry parameters, introducing a series of modifications to know how IOL power changes with the varying corneal curvature and AL of the eye.[103] Recently, Savini and coworkers,[93] comparing 5 different formulas, showed that SRK/T is the most accurate formula, yielding an acceptable percentage of patients with a prediction error within ± 0.5D, which reached a rate of 61.9% in eyes with a grade I keratoconus (KCN). The outcomes reported by the authors were even worse in eyes with more advanced degrees of the disease, suggesting caution when targeting any refractive outcome in eyes with preoperative K value higher than 48D.[91,83]

This finding agrees with what has been observed by our research group in a previous study that showed a higher refractive accuracy when the SRK/T formula was used[5] and probably depends on the fact that the SRK/T tends to overestimate the IOL power in eyes with steep corneas.[61] Such overestimation can be useful in eyes with KC since it counterbalances the average trend toward hyperopic refraction observed with most formulas. Moreover, the AL was, on average, relatively high, and it was longer than 26.0 mm in 34.1% of eyes. This might be another factor contributing to the good performance of the SRK/T because this formula has been shown to be one of the most accurate in long eyes.[41,5] Alio and coworkers[5] showed that the AL had a stronger correlation with the final spherical equivalent than the preoperative keratometry in 17 eyes of 10 patients diagnosed with stable KCN who had microincision cataract surgery (MICS) with toric IOL implantation.

Reitblat and coworkers[85] analyzed the performance of commonly used IOL power calculation formulas in a subgroup of eyes with steep corneal geometry (K > 46D). They found that IOL power calculations for eyes with an average K value greater than 46D yielded myopic prediction errors with the SRK/T and Hill-RBF formulas and hyperopic errors with Haigis and Olsen-C formulas. Compared with all other formulas, the SRK/T showed a higher systemic error. The authors described then a new regression formula for K value adjustment to be used with the SRK/T formula (optimized $K = -1.91 + 1.05 \times$ measured K), in order to reduce the refractive error using the SRK/T formula for IOL power calculation in eyes with extreme corneal measurements (K > 46D).

The Barrett Universal II is becoming accepted as one of the most accurate IOL formulas in use today, contributing to its increasing popularity among surgeons. The formula is based on a theoretical model eye and retains the positive correlation of AL and keratometry to ACD. Importantly, the Barrett Universal II is able to maintain its accuracy across a wide range of ALs and ACD.[61]

Newer methodologies are being applied to IOL calculation with promises of improved accuracy.[104] As opposed to vergence-based equations, the Olsen formula uses both exact and paraxial ray tracings of optical light through the refractive media in the eye, including the specific optics of a particular IOL, to derive the postoperative position of that lens.[72]

In the Olsen formula, the lens constant is no longer related to AL and corneal power but to the characteristic of the crystalline lens and the dimension of the AC. In the 2020 study of 10,930 eyes, the Barrett Universal II had larger overall mean absolute errors compared with the Olsen formula and Hill-RBF (2.0 version) calculator, and was comparable with the AL-adjusted Holladay 2 formula; however, when analyzed by different categories of AL, the Barrett had less error than Olsen and Hill-RBF 2.0 in long eyes (AL > 26.0 mm) and is equivalent to the Olsen for medium eyes (22.0–26.0 mm).[24]

We should expect a poor refractive result with a higher hyperopic shift in eyes with advanced KCN (stage II or III), based on three mayor motivating reasons.[92]

First, calculating the corneal power with the standard keratometric index (n = 1.3375) may lead to erroneous results. This fictitious index can be correctly used to achieve the refractive power of the whole cornea based from just the anterior corneal curvature, but only on the condition that the ratio between the anterior and posterior corneal curvature is within normal limits: in KCN eyes, the standard keratometric index overestimate corneal power.[79,55]

Second, keratometers and corneal topographers provide measurements of corneal curvature that might be inaccurate because of asymmetry of corneal curvature. Every keratometer, in fact, assumes that the corneal curvature is constant along a given meridian, but this is not the case in most KC eyes.[91]

Third, KC can alter the usual relationship between corneal curvature, ACD and IOL position, thus reducing the accuracy of any formula in predicting the effective lens position.

5.2. *Choice of the intraocular lens*

An important moment in the intraoperative planning is the choice of the IOL to be implanted. Whenever planning RLE surgery in a KC eye, the surgeon will have to decide whether a toric IOL is more suitable than a monofocal IOL.

Hashemi and coworkers[38] reported the results using an AcrySof toric IOL in 23 eyes of 17 patients with KCN and cataract. They showed that toric IOLs improved vision and refraction in all types of KCN including mild, moderate, and even severe KC; however, in case of severe KC, the refractive outcomes had less predictability. Similarly, Nanavaty and coworkers[69] showed that the use of pseudophakic toric IOL in KC cataract patients was effective and resulted in an acceptable and stable vision in patients with mild and moderate KC. Alio and coworkers[5] retrospectively evaluated 17 KC eyes of 10 patients that underwent MICS and reported a significant improvement in UDVA, CDVA and cylinder but not in the sphere.

When considering the lower predictability and outcomes in severe KCN, one should take into account that, the astigmatism of those corneas is more irregular, this aspect might affect the final visual outcomes. Another explication is the possible increased postoperative rotation. Zhu and coworkers[106] reported that postoperative toric IOL rotation was positively correlated with AL myopia and capsular bag size. We suggest capsular tension ring placement whenever a toric IOL is to be implanted in a KC eye; optic capture might represent an option. Another relevant consideration is the asphericity of the IOL. As many KC eyes have a steep cornea with a large negative preoperative anterior surface Q value, adding an IOL with a zero or even positive Q value may lead to a better visual outcome.[92]

In case of progression and/or keratoplasty, mixed implant techniques like power split approaches are an alternative option: the surgeon may implant an initial nontoric, monofocal IOL to correct the majority of the refractive error and then utilize a subsequent procedure such as a secondary sulcus-supported IOL (piggyback IOL) to correct the residual refractive error.[62]

In cases of eyes with KC, piggyback IOLs may rotate significantly and in these cases a sulcus suture might be utilized to improve stability.[63]

Also, multicomponent IOL technologies are available having a basic power and a toric IOL attached like the new PreciSight IOL (InfiniteVision Optics, Strasbourg, France). This compact IOL is composed of a hydrophobic base lens that serves as a docking station and an exchangeable hydrophilic front lens that is connected to the base lens by bilateral bridge openings.[102] Moreover, in situations like potential progression, expected corneal decompensation or need for keratoplasty is recommended to implant a “space holder” in the bag like a capsular bending ring in order to ease IOL exchange.

Other interesting commercially available IOLs are coming onto the market that might be good options/alternatives given the potential deviation from target refraction in a KCN patients.[87] A small-aperture IOL (IC-8, AcuFocus, Inc.) is one of such alternatives that improves vision in eyes with severe corneal irregularities (e.g., in advanced KC) using the pinhole effect.[89] Selected cases of KC could be treated by a new intraocular pinhole device (XtraFocus Morcher), which can be safely implanted either in the sulcus or in the bag.[84,85]

Finally, light adjustable lens (RxSight Inc., Aliso Viejo, CA) is a foldable, PC three-piece silicone lens that has been explored as a potential advancement in improving postoperative visual outcomes after lens surgery, being able to adjust spherical power from – 2.00 to + 2.00D and cylindrical power from – 0.75 to – 2.00D by 0.25D increments.[64]

KC patients, even with a *form fruste* of KC, represent an important contraindication to multifocal IOL, given the high amount of high-order aberration (especially coma) and the consequent poor visual outcomes if an IOL with an advanced multifocal optic is implanted.

6. Summary

ICRS implantation represents a minimally invasive, high-precision - with the advent of modern femtosecond lasers - surgical option for visual improvement in patients with KC. ICRS modify the corneal geometry in a manner that enhances its refractive properties and thereby, they improve visual acuity. Success rate after ICRS implantation is high and, most importantly, the overall complication rate is low. In the crosslinking plus panorama the CAIRS consists of ring segments derived from allogenic eye-bank processed donor corneas that can be combined simultaneously or sequentially with CXL procedure in KC patients intolerant to RGP contact lenses who need a conservative improvement of spectacle CDVA. The advantage of CAIRS consists in avoiding the major part of complications reported with synthetic ICRS, maintaining the advantage of additive treatment with reshaping ability, improving the refractive power of the cornea also in a customized fashion. CAIRS, being allogenic and less rigid, may be implanted into thinner corneas, so is implantable in more advanced cases. Limitation can be possible in consequence of poorly predictable refractive outcomes despite less invasiveness and higher integration into the host corneal stroma are a must for allogenic corneal tissue.

Selective topography-guided sequential and simultaneous excimer laser t-PRK or t-PTK combined with conventional and accelerated CXL is another way in selected cases to improve spectacles CDVA of KCs. Long-term 10-year follow-up data reported gain in UCVA and CDVA in absence of adverse events despite a small amount of tissue ablation. The micro-photo-ablative remodeling of the central corneal profile is generally planned by using topo-guided excimer laser software, optimizing the optical zones, minimizing tissue consumption to a maximum 55 μm of corneal stroma, and taking into account the contribution of the epithelium and posterior corneal surface thank to ray-tracing software, thus avoiding overcorrections. Despite the optimal results reported in the literature, the protocols require a standardization and global consensus both for laser planning and CXL-associated protocols. PIOLs represent an important reversible option in the KC eye as cornea biomechanics remain unaltered, thus not interfering with the natural evolution of the disease. Their implant is considered in patients with stable disease, acceptable CDVA and with acceptable anatomical requirements. In these KC patients, since the cornea and the crystalline lens remain unchanged, IOL power calculation is based on the subjective preoperative refraction according to the specific IOL calculation nomogram provided from the different pIOL companies. The 2 types of pIOLs, depending on their implantation inside the eye, are AC-pIOLs, with Artilens (Ophtec BV) representing the only commercially available model today, which fixate to the anterior surface of the iris by using a PMMA claw at the 2 haptics, and PC-pIOLs, with ICL (Staar) constitute almost all available scientific evidence about the use of PC-pIOL in KC. Scientific evidences demonstrated that both implants provided equivalent results, with no statistically significant differences between them in terms of efficacy, safety and stability of the refractive result. Patients with both cataract and KC present unique challenges for the surgeon, given the peculiar optical characteristics of the ectatic corneas. In the preoperative evaluation, the correct IOL power is difficult to obtain due to the irregular corneal shape and K values, which vary significantly between those at the cone apex and those from the remaining cornea. Intraoperatively, the planning of the wound creation is important to avoid area of CT and if possible, to be performed at the steep axis to reduce astigmatism. IOL selection is another crucial moment in the surgery. Toric IOLs are recommended, but require carefully judging the topography and the possible need of subsequent keratoplasties.

7. Method of literature search

An extensive literature search published in the MEDLINE/PubMed and EMBASE database was performed to identify relevant articles (with no time restrictions) using the search terms: “refractive surgery,” “photorefractive keratectomy,” “phototherapeutic keratectomy,” “intracorneal ring segment,” “corneal cross linking,” “phakic intraocular lens,” “toric intraocular lens,” “intraocular lens” and “keratoconus.” Emphasis was given to RCTs, meta-analysis, original research, and prospective studies that focused on the different surgical options to manage the refractive error of keratoconic patients. Review articles were also included if they added new data. Articles published in English with an available abstract were included in the literature search; non-English articles were included only if they include an English abstract that provide adequate information. All publications were screened by two authors (F. D. and S. A. B.) and any disagreement was discussed by the two authors and resolved.

8. Disclosures

The authors have no financial disclosure to make with any of the companies involved in the manuscript.

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Declaration of Competing Interest

None.

REFERENCES

1. Abdelmassih Y, El-Khoury S, Chelala E, Slim E, Cherfan CG, Jarade E. Toric ICL implantation after sequential intracorneal ring segments implantation and corneal cross-linking in keratoconus: 2-year follow-up. J Refract Surg. 2017;33(9):610–6. https://doi.org/10.3928/1081597X-20170621-02.
2. Alhamzah A, Alharbi SS, Alfardan F, Aldebasi T, Almudhaiyan T. Indications for exchange or explantation of phakic implantable collamer lens with central port in patients with and without keratoconus. Int J Ophthalmol. 2021;14(11):1714–20. https://doi.org/10.18240/ijo.2021.11.10.
3. Ali M, Kamiya K, Shimizu K, Igarashi A, Ishii R. Clinical evaluation of corneal biomechanical parameters after posterior chamber phakic intraocular lens implantation. Cornea. 2014;33(5):470–4. https://doi.org/10.1097/ICO.0000000000000088.
4. Alió JL, Peña-García P, Abdulla GF, Zein G, Abu-Mustafa SK. Comparison of iris-claw and posterior chamber collagen copolymer phakic intraocular lenses in keratoconus. J Cataract Refract Surg. 2014;40(3):383–94. https://doi.org/10.1016/j.jcrs.2013.07.052.
5. Alió JL, Peña-García P, Abdulla Guliyeva F, Soria FA, Zein G, Abu-Mustafa SK. MICS with toric intraocular lenses in keratoconus: outcomes and predictability analysis of

postoperative refraction. Br J Ophthalmol. 2014;98(3):365–70. https://doi.org/10.1136/bjophthalmol-2013-303765.
6. Alió JL, Piñero DP, Sögütlü E, Kubaloglu A. Implantation of new intracorneal ring segments after segment explantation for unsuccessful outcomes in eyes with keratoconus. J Cataract Refract Surg. 2010;36(8):1303–10. https://doi.org/10.1016/j.jcrs.2010.02.017.
7. Alio J.L., D'Oria F. Cataract Surgery in Keratoconus. In: Alio JL, Burkhard D, eds. *Cataract Surgery - Advanced Techniques for Complex and Complicated Cases. Essentials in Ophthalmology*, vol. 1. Cham: Springer; 2022.
8. Alió JL, Shabayek MH, Belda JI, Correas P, Feijoo ED. Analysis of results related to good and bad outcomes of Intacs implantation for keratoconus correction. J Cataract Refract Surg. 2006;32(5):756–61. https://doi.org/10.1016/j.jcrs.2006.02.012.
9. Al-Torbak A, Al-Amri A, Wagoner MD. Deep corneal neovascularization after implantation with intrastromal corneal ring segments. Am J Ophthalmol. 2005;140(5):926–7. https://doi.org/10.1016/j.ajo.2005.05.020.
10. Antonios R, Dirani A, Fadlallah A, et al. Safety and visual outcome of visian toric ICL implantation after corneal collagen cross-linking in keratoconus: up to 2 years of follow-up. J Ophthalmol. 2015;2015:514834https://doi.org/10.1155/2015/514834.
11. Asbell PA, Uçakhan OO, Odrich M. Photorefractive keratectomy after intrastromal corneal ring segment explantation. Am J Ophthalmol. 1999;128(6):755–6. https://doi.org/10.1016/S0002-9394(99)00248-2.
12. Bali SJ, Chan C, Hodge C, Sutton G. Intracorneal ring segment reimplantation in keratectasia. Asia Pac J Ophthalmol. 2012;1(6):327–30. https://doi.org/10.1097/APO.0b013e31826e1d30.
13. Balparda K, Vanegas-Ramírez CM, Herrera-Chalarca T, Silva-Quintero LA. Early results with the EyeCryl Phakic Toric intraocular lens implantation in keratoconus patients. Rom J Ophthalmol. 2021;65(2):163–70. https://doi.org/10.22336/rjo.2021.32.
14. Bourcier T, Borderie V, Laroche L. Late bacterial keratitis after implantation of intrastromal corneal ring segments. J Cataract Refract Surg. 2003;29(2):407–9. https://doi.org/10.1016/S0886-3350(02)01484-0.
15. Bourges J-L, Trong TT, Ellies P, Briat B, Renard G. Intrastromal corneal ring segments and corneal anterior stromal necrosis. J Cataract Refract Surg. 2003;29(6):1228–30. https://doi.org/10.1016/S0886-3350(02)02036-9.
16. Camellin M, Guidotti JM, Arba Mosquera S. Corneal-wavefront guided transepithelial photorefractive keratectomy after corneal collagen cross linking in keratoconus. J Optom. 2017;10(1):52–62. https://doi.org/10.1016/j.optom.2016.02.001.
17. Chan K, Hersh PS. Removal and repositioning of intracorneal ring segments: improving corneal topography and clinical outcomes in keratoconus and ectasia. Cornea. 2017;36(2):244–8. https://doi.org/10.1097/ICO.0000000000001075.
18. Chhadva P, Yesilirmak N, Cabot F, Yoo SH. Intrastromal corneal ring segment explantation in patients with keratoconus: causes, technique, and outcomes. J Refract Surg. 2015;31(6):392–7. https://doi.org/10.3928/1081597X-20150521-05.
19. Colin J, Cochener B, Savary G, Malet F. Correcting keratoconus with intracorneal rings. J Cataract Refract Surg. 2000;26(8):1117–22. https://doi.org/10.1016/s0886-3350(00)00451-x.
20. Cosar CB, Sridhar MS, Sener B. Late onset of deep corneal vascularization: a rare complication of intrastromal corneal ring segments for keratoconus. Eur J Ophthalmol. 2009;19(2):298–300. https://doi.org/10.1177/112067210901900222.
21. Coskunseven E, Kymionis GD, Tsiklis NS, et al. Complications of intrastromal corneal ring segment implantation using a femtosecond laser for channel creation: a survey of 850 eyes with keratoconus. Acta Ophthalmol. 2011;89(1):54–7. https://doi.org/10.1111/j.1755-3768.2009.01605.x.
22. Coskunseven E, Sharma DP, Grentzelos MA, Sahin O, Kymionis GD, Pallikaris I. Four-stage procedure for keratoconus: ICRS implantation, corneal cross-linking, toric phakic intraocular lens implantation, and topography-guided photorefractive keratectomy. J Refract Surg. 2017;33(10):683–9. https://doi.org/10.3928/1081597X-20170807-01.
23. Dapena I, Parker JS, Melles GRJ. Potential benefits of modified corneal tissue grafts for keratoconus: Bowman layer 'inlay' and 'onlay' transplantation, and allogenic tissue ring segments. Curr Opin Ophthalmol. 2020;31(4):276–83. https://doi.org/10.1097/ICU.0000000000000665.
24. Darcy K, Gunn D, Tavassoli S, Sparrow J, Kane JX. Assessment of the accuracy of new and updated intraocular lens power calculation formulas in 10 930 eyes from the UK National Health Service. J Cataract Refract Surg. 2020;46(1):2–7. https://doi.org/10.1016/j.jcrs.2019.08.014.
25. D'Oria F, Abdelghany A, Ledo N, Barraquer RI, Alio JL. Incidence and reason for intrastromal corneal ring segment explantation. Am J Ophthalm. 2021;222:351–8. https://doi.org/10.1016/j.ajo.2020.09.041.
26. D'Oria F, Alio JL, Martinez-Abad A, Izquierdo Jr L, Larco Jr P, Abdelghany AA. Astigmatic change as a predictor of intrastromal corneal ring segment late extrusion. J Cataract Refract Surg. 2022;48(4):401–7. https://doi.org/10.1097/j.jcrs.0000000000000774.
27. D'Oria F, Palazon A, Alio JL. Corneal collagen cross-linking epithelium-on vs epithelium-off: a systematic review and meta-analysis. Eye Vis. 2021;8(1):34https://doi.org/10.1186/s40662-021-00256-0.
28. Emerah SH, Sabry MM, Saad HA, Ghobashy WA. Visual and refractive outcomes of posterior chamber phakic IOL in stable keratoconus. Int J Ophthalmol. 2019;12(5):840–3. https://doi.org/10.18240/ijo.2019.05.22.
29. Fairaq R, Almutlak M, Almazyad E, Badawi AH, Ahad MA. Outcomes and complications of implantable collamer lens for mild to advance keratoconus. Int Ophthalmol. 2021;41(7):2609–18. https://doi.org/10.1007/s10792-021-01820-2.
30. Fadlallah A, Dirani A, El Rami H, Cherfane G, Jarade E. Safety and visual outcome of Visian toric ICL implantation after corneal collagen cross-linking in keratoconus. J Refract Surg. 2013;29(2):84–9. https://doi.org/10.3928/1081597X-20130117-01.
31. Ferrer C, Alió JL, Montañés AU, et al. Causes of intrastromal corneal ring segment explantation: clinicopathologic correlation analysis. J Cataract Refract Surg. 2010;36(6):970–7. https://doi.org/10.1016/j.jcrs.2009.12.042.
32. Ferreira TB, Güell JL, Manero F. Combined intracorneal ring segments and iris-fixated phakic intraocular lens for keratoconus refractive and visual improvement. J Refract Surg. 2014;30(5):336–41. https://doi.org/10.3928/1081597X-20140319-01.
33. Fischinger IR, Wendelstein J, Tetz K, Bolz M, Tetz MR. Toric phakic IOLs in keratoconus-evaluation of preoperative parameters on the outcome of phakic anterior chamber lens implantation in patients with keratoconus. Graefes Arch Clin Exp Ophthalmol. 2021;259(6):1643–9. https://doi.org/10.1007/s00417-020-05041-8.
34. Ganesh S, Shetty R, D'Souza S, Ramachandran S, Kurian M. Intrastromal corneal ring segments for management of keratoconus. Indian J Ophthalmol. 2013;61(8):451–5. https://doi.org/10.4103/0301-4738.116065.

35. Grentzelos MA, Liakopoulos DA, Siganos CS, Tsilimbaris MK, Pallikaris IG, Kymionis GD. Long-term comparison of combined t-PTK and CXL (Cretan Protocol) versus CXL with mechanical epithelial debridement for keratoconus. J Refract Surg. 2019;35(10):650–5. https://doi.org/10.3928/1081597X-20190917-01.
36. Güell JL, Morral M, Malecaze F, Gris O, Elies D, Manero F. Collagen crosslinking and toric iris-claw phakic intraocular lens for myopic astigmatism in progressive mild to moderate keratoconus. J Cataract Refract Surg. 2012;38(3):475–84. https://doi.org/10.1016/j.jcrs.2011.10.031.
37. Hashemian SJ, Soleimani M, Foroutan A, Joshaghani M, Ghaempanah J, Jafari ME. Toric implantable collamer lens for high myopic astigmatism in keratoconic patients after six months. Clin Exp Optom. 2013;96(2):225–32. https://doi.org/10.1111/j.1444-0938.2012.00800.x.
38. Hashemi H, Heidarian S, Seyedian MA, Yekta A, Khabazkhoob M. Evaluation of the results of using toric IOL in the cataract surgery of keratoconus patients. Eye Contact Lens. 2015;41(6):354–8. https://doi.org/10.1097/ICL.0000000000000136.
39. Hashemi H, Yekta A, Khabazkhoob M. Effect of keratoconus grades on repeatability of keratometry readings: comparison of 5 devices. J Cataract Refract Surg. 2015;41(5):1065–72. https://doi.org/10.1016/j.jcrs.2014.08.043.
40. He C, Joergensen JS, Knorz MC, McKay KN, Zhang F. Three-step treatment of keratoconus and post-LASIK ectasia: implantation of ICRS, corneal cross-linking, and implantation of toric posterior chamber phakic IOLs. J Refract Surg. 2020;36(2):104–9. https://doi.org/10.3928/1081597X-20191217-01.
41. Hoffer KJ. The Hoffer Q formula: a comparison of theoretic and regression formulas. J Cataract Refract Surg. 1993;19(6):700–12. https://doi.org/10.1016/s0886-3350(13)80338-0.
42. Hofling-Lima AL, Branco BC, Romano AC, et al. Corneal infections after implantation of intracorneal ring segments. Cornea. 2004;23(6):547–9. https://doi.org/10.1097/01.ico.0000126434.95325.24.
43. Jacob S, Patel SR, Agarwal A, Ramalingam A, Saijimol AI, Raj JM. Corneal Allogenic Intrastromal Ring Segments (CAIRS) combined with corneal cross-linking for keratoconus. J Refract Surg. 2018;34(5):296–303. https://doi.org/10.3928/1081597X-20180223-01.
44. Kanellopoulos AJ, Asimellis G. Keratoconus management: long-term stability of topography-guided normalization combined with high-fluence CXL stabilization (the Athens Protocol). J Refract Surg. 2014;30(2):88–93. https://doi.org/10.3928/1081597X-20140120-03.
45. Kanellopoulos AJ, Binder PS. Collagen cross-linking (CCL) with sequential topography-guided PRK: a temporizing alternative for keratoconus to penetrating keratoplasty. Cornea. 2007;26(7):891–5. https://doi.org/10.1097/ICO.0b013e318074e424.
46. Kanellopoulos AJ, Pe LH, Perry HD, Donnenfeld ED. Modified intracorneal ring segment implantations (INTACS) for the management of moderate to advanced keratoconus: efficacy and complications. Cornea. 2006;25(1):29–33. https://doi.org/10.1097/01.ico.0000167883.63266.60.
47. Kanellopoulos AJ. Comparison of sequential vs same-day simultaneous collagen cross-linking and topography-guided PRK for treatment of keratoconus. J Refract Surg. 2009;25(9):S812–8. https://doi.org/10.3928/1081597X-20090813-10.
48. Kanellopoulos AJ. The management of cornea blindness from severe corneal scarring, with the Athens Protocol (transepithelial topography-guided PRK therapeutic remodeling, combined with same-day, collagen cross-linking). Clin Ophthalmol. 2012;6:87–90. https://doi.org/10.2147/OPTH.S27175.
49. Kim TI, Alió Del Barrio JL, Wilkins M, Cochener B, Ang M. Refractive surgery. Lancet. 2019;393(10185):2085–98. https://doi.org/10.1016/S0140-6736(18)33209-4.
50. Kontadakis GA, Kankariya VP, Tsoulnaras K, Pallikaris AI, Plaka A, Kymionis GD. Long-term comparison of simultaneous topography-guided photorefractive keratectomy followed by corneal cross-linking versus corneal cross-linking alone. Ophthalmology. 2016;123(5):974–83. https://doi.org/10.1016/j.ophtha.2016.01.010.
51. Kubaloglu A, Sari ES, Cinar Y, et al. Comparison of mechanical and femtosecond laser tunnel creation for intrastromal corneal ring segment implantation in keratoconus: prospective randomized clinical trial. J Cataract Refract Surg. 2010;36(9):1556–61. https://doi.org/10.1016/j.jcrs.2010.04.028.
52. Kymionis GD, Grentzelos MA, Kankariya VP, Pallikaris IG. Combined transepithelial phototherapeutic keratectomy and corneal collagen crosslinking for ectatic disorders: cretan protocol. J Cataract Refract Surg. 2013;39(12):1939. https://doi.org/10.1016/j.jcrs.2013.10.003.
53. Kymionis GD, Grentzelos MA, Kankariya VP, et al. Long-term results of combined transepithelial phototherapeutic keratectomy and corneal collagen crosslinking for keratoconus: Cretan protocol. J Cataract Refract Surg. 2014;40(9):1439–45. https://doi.org/10.1016/j.jcrs.2014.01.040.
54. Li K, Wang Z, Zhang D, et al. Visual outcomes and corneal biomechanics after V4c implantable collamer lens implantation in subclinical keratoconus. J Cataract Refract Surg. 2020;46(10):1339–45. https://doi.org/10.1097/j.jcrs.0000000000000262.
55. Kamiya K, Kono Y, Takahashi M, Shoji N. Comparison of simulated keratometry and total refractive power for keratoconus according to the stage of Amsler-Krumeich classification. Sci Rep. 2018;8(1):12436https://doi.org/10.1038/s41598-018-31008-1.
56. Kamiya K, Shimizu K, Kobashi H, et al. Three-year follow-up of posterior chamber toric phakic intraocular lens implantation for the correction of high myopic astigmatism in eyes with keratoconus. Br J Ophthalmol. 2015;99(2):177–83. https://doi.org/10.1136/bjophthalmol-2014-305612.
57. Kymionis GD, Grentzelos MA, Kounis GA, Diakonis VF, Limnopoulou AN, Panagopoulou SI. Combined transepithelial phototherapeutic keratectomy and corneal collagen cross-linking for progressive keratoconus. Ophthalmology. 2012;119(9):1777–84. https://doi.org/10.1016/j.ophtha.2012.03.038.
58. Kymionis GD, Kontadakis GA, Kounis GA, et al. Simultaneous topography-guided PRK followed by corneal collagen cross-linking for keratoconus. J Refract Surg. 2009;25(9):S807–11. https://doi.org/10.3928/1081597X-20090813-09.
59. Mazzotta C, Jacob S, Agarwal A, Kumar DA. In vivo confocal microscopy after contact lens-assisted corneal collagen cross-linking for thin keratoconic corneas. J Refract Surg. 2016;32(5):326–31. https://doi.org/10.3928/1081597X-20160225-04.
60. Mazzotta C, Raiskup F, Hafezi F, et al. Long term results of accelerated 9 mW corneal crosslinking for early progressive keratoconus: the Siena Eye-Cross Study 2. Eye Vis. 2021;8(1):16https://doi.org/10.1186/s40662-021-00240-8.
61. Melles RB, Holladay JT, Chang WJ. Accuracy of intraocular lens calculation formulas. Ophthalmology. 2018;125(2):169–78. https://doi.org/10.1016/j.ophtha.2017.08.027.
62. Meyer JJ, McGhee CN. Supplementary, sulcus-fixated intraocular lens in the treatment of spherical and astigmatic refractive errors in pseudophakic eyes after keratoplasty.

Cornea. 2015;34(9):1052–6. https://doi.org/10.1097/ICO.0000000000000506.
63. Meyer JJ, Kim BZ, Ziaei M, McGhee CN. Postoperative rotation of supplementary sulcus-supported toric intraocular lenses. J Cataract Refract Surg. 2017;43(2):285–8. https://doi.org/10.1016/j.jcrs.2016.12.014.
64. Moshirfar M, Wagner WD, Linn SH, et al. Astigmatic correction with implantation of a light adjustable vs monofocal lens: a single site analysis of a randomized controlled trial. Int J Ophthalmol. 2019;12(7):1101–7. https://doi.org/10.18240/ijo.2019.07.08.
65. Mounir A, Radwan G, Farouk MM, Mostafa EM. Femto second assisted intracorneal ring segment complications in keratoconus: from novelty to expertise. Clin Ophthalmol. 2018;12:957–64. https://doi.org/10.2147/OPTH.S166538.
66. Morral M, Güell JL, El Husseiny MA, Elies D, Gris O, Manero F. Paired-eye comparison of corneal endothelial cell counts after unilateral iris-claw phakic intraocular lens implantation. J Cataract Refract Surg. 2016;42(1):117–26. https://doi.org/10.1016/j.jcrs.2015.08.018.
67. Mulè G, Chen S, Zhang J, et al. Central corneal regularization (CCR): an alternative approach in keratoconus treatment. Eye Vis. 2019;6:40https://doi.org/10.1186/s40662-019-0165-y.
68. Nacaroglu SA, Yesilkaya EC, Perk FFNK, Tanriverdi C, Taneri S, Kilic A. Efficacy and safety of intracorneal allogenic ring segment implantation in keratoconus: 1-year results. Eye. 2023. https://doi.org/10.1038/s41433-023-02618-5 Epub ahead of print.
69. Nanavaty MA, Lake DB, Daya SM. Outcomes of pseudophakic toric intraocular lens implantation in keratoconic eyes with cataract. J Refract Surg. 2012;28(12):884–9. https://doi.org/10.3928/1081597X-20121106-02.
70. Nattis AS, Rosenberg ED, Donnenfeld ED. One-year visual and astigmatic outcomes of keratoconus patients following sequential crosslinking and topography-guided surface ablation: the TOPOLINK study. J Cataract Refract Surg. 2020;46(4):507–16. https://doi.org/10.1097/j.jcrs.0000000000000110.
71. Oatts JT, Savar L, Hwang DG. Late extrusion of intrastromal corneal ring segments: a report of two cases. Am J Ophthalmol Case Rep. 2017;8:67–70. https://doi.org/10.1016/j.ajoc.2017.10.004.
72. Olsen T, Funding M. Ray-tracing analysis of intraocular lens power in situ. J Cataract Refract Surg. 2012;38(4):641–7. https://doi.org/10.1016/j.jcrs.2011.10.035.
73. Packer M. The Implantable Collamer Lens with a central port: review of the literature. Clin Ophthalmol. 2018;12:2427–38. https://doi.org/10.2147/OPTH.S188785.
74. Parker JS, Dockery PW, Parker JS. Flattening the curve: manual method for corneal allogenic intrastromal ring segment implantation. J Cataract Refract Surg. 2021;47(11):e31–3. https://doi.org/10.1097/j.jcrs.0000000000000555.
75. Parker JS, Dockery PW, Parker JS. Trypan blue-assisted corneal allogenic intrastromal ring segment implantation. J Cataract Refract Surg. 2021;47(1):127. https://doi.org/10.1097/j.jcrs.0000000000000316.
76. Park J, Gritz DC. Evolution in the use of intrastromal corneal ring segments for corneal ectasia. Curr Opin Ophthalmol. 2013;24(4):296–301. https://doi.org/10.1097/ICU.0b013e3283622a2c.
77. Packer M. Meta-analysis and review: effectiveness, safety, and central port design of the intraocular collamer lens. Clin Ophthalmol. 2016;10:1059–77. https://doi.org/10.2147/OPTH.S111620.
78. Piñero DP, Alio JL. Intracorneal ring segments in ectatic corneal disease - a review. Clin Exp Ophthalmol. 2010;38(2):154–67. https://doi.org/10.1111/j.1442-9071.2010.02197.x.
79. Piñero DP, Camps VJ, Caravaca-Arens E, Pérez-Cambrodí RJ, Artola A. Estimation of the central corneal power in keratoconus: theoretical and clinical assessment of the error of the keratometric approach. Cornea. 2014;33(3):274–9. https://doi.org/10.1097/ICO.0000000000000048.
80. Rabinowitz YS, Li X, Ignacio TS, Maguen E. Intacs inserts using the femtosecond laser compared to the mechanical spreader in the treatment of keratoconus. J Refract Surg. 2006;22(8):764–71. https://doi.org/10.3928/1081-597X-20061001-06.
81. Rabina G, Mimouni M, Kaiserman I. Epithelial photorefractive keratectomy vs mechanical epithelial removal followed by corneal crosslinking for keratoconus: the Tel-Aviv Protocol. J Cataract Refract Surg. 2020;46(5):749–55. https://doi.org/10.1097/j.jcrs.0000000000000122.
82. Rechichi M, Mazzotta C, Oliverio GW, et al. Selective transepithelial ablation with simultaneous accelerated corneal crosslinking for corneal regularization of keratoconus: STARE-X protocol. J Cataract Refract Surg. 2021;47(11):1403–10. https://doi.org/10.1097/j.jcrs.0000000000000640.
83. Reitblat O, Levy A, Kleinmann G, Lerman TT, Assia EI. Intraocular lens power calculation for eyes with high and low average keratometry readings: comparison between various formulas. J Cataract Refract Surg. 2017;43(9):1149–56. https://doi.org/10.1016/j.jcrs.2017.06.036.
84. Trindade BLC, Trindade FC, Werner L, Trindade CLC. Long-term safety of in-the-bag implantation of a supplementary intraocular pinhole. J Cataract Refract Surg. 2020;46(6):888–92. https://doi.org/10.1097/j.jcrs.0000000000000163.
85. Trindade BLC, Trindade FC, Trindade CLC. Toric intraocular lens combined with a supplementary pinhole implant to treat irregular corneal astigmatism. J Cataract Refract Surg. 2020;46(12):e22–6. https://doi.org/10.1097/j.jcrs.0000000000000356.
86. Sadoughi MM, Einollahi B, Veisi AR, et al. Femtosecond laser implantation of a 340-degree intrastromal corneal ring segment in keratoconus: short-term outcomes. J Cataract Refract Surg. 2017;43(10):1251–6. https://doi.org/10.1016/j.jcrs.2017.07.026.
87. Shajari M, Mackert MJ, Langer J, et al. Safety and efficacy of a small-aperture capsular bag-fixated intraocular lens in eyes with severe corneal irregularities. J Cataract Refract Surg. 2020;46(2):188–92. https://doi.org/10.1097/j.jcrs.0000000000000045.
88. Sakellaris D, Balidis M, Gorou O, Szentmary N, Alexoudis A, Grieshaber MC, Sagri D, Scholl H, Gatzioufas Z. Intracorneal ring segment implantation in the management of keratoconus: an evidence-based approach. Ophthalmol Ther. 2019;8(Suppl 1):5–14. https://doi.org/10.1007/s40123-019-00211-2.
89. Sakla HF, Altroudi W, Sakla YFR, Muñoz G, Pineza C. Visual and refractive outcomes of toric implantable collamer lens implantation in stable keratoconus after combined topography-guided PRK and CXL. J Refract Surg. 2021;37(12):824–9. https://doi.org/10.3928/1081597X-20210920-02.
90. Sakla H, Altroudi W, Muñoz G, Albarrán-Diego C. Simultaneous topography-guided partial photorefractive keratectomy and corneal collagen crosslinking for keratoconus. J Cataract Refract Surg. 2014;40(9):1430–8. https://doi.org/10.1016/j.jcrs.2013.12.017.

91. Savini G, Abbate R, Hoffer KJ, et al. Intraocular lens power calculation in eyes with keratoconus. J Cataract Refract Surg. 2019;45(5):576–81. https://doi.org/10.1016/j.jcrs.2018.11.029.
92. Savini G, Hoffer KJ, Barboni P. Influence of corneal asphericity on the refractive outcome of intraocular lens implantation in cataract surgery. J Cataract Refract Surg. 2015;41(4):785–9. https://doi.org/10.1016/j.jcrs.2014.07.035.
93. Schanzlin DJ, Abbott RL, Asbell PA, et al. Two-year outcomes of intrastromal corneal ring segments for the correction of myopia. Ophthalmology. 2001;108(9):1688–94. https://doi.org/10.1016/S0161-6420(01)00692-3.
94. Shafik Shaheen M, El-Kateb M, El-Samadouny MA, Zaghloul H. Evaluation of a toric implantable collamer lens after corneal collagen crosslinking in treatment of early-stage keratoconus: 3-year follow-up. Cornea. 2014;33(5):475–80. https://doi.org/10.1097/ICO.0000000000000094.
95. Shehadeh-Masha'our R, Modi N, Barbara A, Garzozi HJ. Keratitis after implantation of intrastromal corneal ring segments. J Cataract Refract Surg. 2004;30(8):1802–4. https://doi.org/10.1016/j.jcrs.2004.01.034.
96. Shaheen MS, Shalaby Bardan A, Piñero DP, et al. Wave front-guided photorefractive keratectomy using a high-resolution aberrometer after corneal collagen cross-linking in keratoconus. Cornea. 2016;35(7):946–53. https://doi.org/10.1097/ICO.0000000000000888.
97. Shetty R, Nuijts RM, Nicholson M, Sargod K, Jayadev C, Veluri H, Sinha Roy A. Cone location-dependent outcomes after combined topography-guided photorefractive keratectomy and collagen cross-linking. Am J Ophthalmol. 2015;159(3):419–25.
98. Srivatsa S, Jacob S, Agarwal A. Contact lens assisted corneal cross linking in thin ectatic corneas - a review. Indian J Ophthalmol. 2020;68(12):2773–8. https://doi.org/10.4103/ijo.IJO_2138_20.
99. Stojanovic A, Zhang J, Chen X, Nitter TA, Chen S, Wang Q. Topography-guided transepithelial surface ablation followed by corneal collagen cross-linking performed in a single combined procedure for the treatment of keratoconus and pellucid marginal degeneration. J Refract Surg. 2010;26(2):145–52. https://doi.org/10.3928/1081597X-20100121-10.
100. Torquetti L, Ferrara G, Almeida F, et al. Intrastromal corneal ring segments implantation in patients with keratoconus: 10-year follow-up. J Refract Surg. 2014;30(1):22–6. https://doi.org/10.3928/1081597X-20131217-02.
101. Uy HS, Tesone-Coelho C, Ginis H. Enhancement-procedure outcomes in patients implanted with the precisight multicomponent intraocular lens. Clin Ophthalmol. 2019;13:107–14. https://doi.org/10.2147/OPTH.S188383.
102. Vargas V, Marinho A, El Sayyad F, Alio Del Barrio JL, Alio JL. Safety and visual outcomes following Iris-claw phakic intraocular lens bilensectomy. Eur J Ophthalmol. 2021;31(4):1795–801. https://doi.org/10.1177/1120672120944033.
103. Vega-Estrada A, Alio JL, Brenner LF, et al. Outcome analysis of intracorneal ring segments for the treatment of keratoconus based on visual, refractive, and aberrometric impairment. Am J Ophthalmol. 2013;155(3):575–584.e1. https://doi.org/10.1016/j.ajo.2012.08.020.
104. Xia T, Martinez CE, Tsai LM. Update on intraocular lens formulas and calculations. Asia Pac J Ophthalmol. 2020;9(3):186–93. https://doi.org/10.1097/APO.0000000000000293.
105. Yeung SN, Lichtinger A, Ku JYF, Kim P, Low SAW, Rootman DS. Intracorneal ring segment explantation after intracorneal ring segment implantation combined with same-day corneal collagen crosslinking in keratoconus. Cornea. 2013;32(12):1617–20. https://doi.org/10.1097/ICO.0b013e3182a738ba.
106. Zhu X, He W, Zhang K, Lu Y. Factors influencing 1-year rotational stability of AcrySof Toric intraocular lenses. Br J Ophthalmol. 2016;100(2):263–8. https://doi.org/10.1136/bjophthalmol-2015-306656.