Universidade do Minho
Escola de Medicina

Tiago Pacheco Teixeira Monteiro

INTRASTROMAL CORNEAL RING SEGMENT IMPLANTATION FOR KERATOCONUS TREATMENT: MANUAL TECHNIQUE VERSUS FEMTOSECOND LASER ASSISTED TECHNIQUE

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INTRASTROMAL CORNEAL RING SEGMENT IMPLANTATION FOR KERATOCONUS TREATMENT: MANUAL TECHNIQUE VERSUS FEMTOSECOND LASER ASSISTED TECHNIQUE

Tese de Doutoramento em Medicina

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Declaração

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Assinatura

CARTÃO DE CIDADÃO

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Aos meus colegas de serviço e técnicos de ortóptica no Hospital de Braga e Hospital CUF Porto

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A toda a minha família pelo apoio incondicional

STATEMENT OF INTEGRITY

I hereby declare having conducted my thesis with integrity. I confirm that I have not used plagiarism or any form of falsification of results in the process of the thesis elaboration.

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CARTÃO DE CIDADÃO

TÍTULO: IMPLANTE INTRAESTROMAL DE SEGMENTOS DE ANEL NO TRATAMENTO DO QUERATOCONE: TÉCNICA MANUAL *VERSUS* TÉCNICA ASSISTIDA POR LASER FEMTOSEGUNDO

RESUMO

O queratocone é uma doença ectásica não inflamatória da córnea, que se torna mais curva e fina, induzindo miopia e astigmatismo irregular. A visão torna-se progressivamente desfocada e distorcida e a doença progride durante alguns anos até estabilizar. Durante a progressão, o astigmatismo irregular aumenta e o queratocone é a indicação mais frequente de transplante de córnea na população adulta jovem. Os segmentos de anel intraestromais são implantes de polimetilmetacrilato, inseridos no interior do estroma corneano periférico, reduzem o encurvamento corneano e o astigmatismo irregular, melhorando a acuidade visual. Relativamente à cirurgia manual, os resultados visuais são satisfatórios, mas está associada a uma alta taxa de complicações e a uma previsibilidade visual e refractiva baixas. Na última década, foi introduzido na cirurgia oftalmológica um aparelho de laser femtosegundo, capaz de realizar de forma automática uma parte deste procedimento. Este trabalho de investigação visa comparar a eficácia e a segurança da correção do queratocone com implante de segmentos por duas técnicas cirúrgicas: manual ou assistida por laser femtosegundo. Ainda que os resultados visuais e refractivos obtidos sejam semelhantes, a cirurgia assistida por femtosegundo demonstrou ser mais precisa e previsível em termos da profundidade atingida pelo túnel intraestromal e ter uma taxa de complicações intra- e pós-operatórias menor, diminuindo a incidência de perda visual e evitando a necessidade de um procedimento cirúrgico complementar. A melhor previsibilidade e segurança obtidas com a cirurgia assistida por femtosegundo permitem indicar a sua aplicação a grupos de maior risco (como a idade pediátrica), e a possibilidade de desenvolvimento de novos modelos de implantes, cuja aplicação poderá alargar o leque de indicações da cirurgia. Em resumo, o implante de segmentos de anel intraestromais assistido por laser de femtosegundo é um procedimento mais seguro e eficaz quando comparado com a técnica mecânica manual.

Palavras-chave: Queratocone, Segmentos de anel intraestromal, Cirurgia manual, Cirurgia femtosegundo.

TITLE: INTRASTROMAL CORNEAL RING SEGMENT IMPLANTATION FOR KERATOCONUS TREATMENT: MANUAL TECHNIQUE VERSUS FEMTOSECOND LASER ASSISTED TECHNIQUE

ABSTRACT

Keratoconus is a noninflammatory ectatic disorder of the cornea, which becomes steepened and thinned, thereby inducing myopia and irregular astigmatism. Vision becomes progressively more blurred and distorted and the disease normally progresses for several years before stabilizing. As the disease progresses, the amount of irregular astigmatism increases, being the most frequent indication for corneal transplantation in the young adult population. Intrastromal corneal ring segments are polymethylmethacrylate implants that are inserted into the midpheripheral corneal stroma, reducing corneal steepening and irregular astigmatism, and improving visual acuity. During two decades, the surgery was performed manually, visual acuity results were satisfactory but a high rate of complications and a low visual and refractive predictability were reported. In the last decade, a femtosecond laser device was introduced to ophthalmic surgery, being able to perform automatically part of this procedure. This clinical research thesis aims to compare the efficacy and safety of keratoconus correction with intrastromal ring implantation by two different techniques: a manual or a femtosecond laser-assisted procedure. Our results have demonstrated that even though the major visual and refractive results of both procedures are equal, femtosecond-laser surgery is more precise and predictable in terms of achieved tunnel depth inside the corneal stroma and has a significantly lower rate of intra and postoperative complications, decreasing the visual acuity loss rates and avoiding a second surgical procedure. The better predictability and safety of the femtosecond-assisted surgery allows its indication in higher-risk patients (like the paediatric population), and the possibility to develop new implant designs, whose application could widen the list of indications of the surgery. In summary, intrastromal corneal ring segment implantation assisted by a femtosecond laser is a safer and more predictable procedure, when compared to manual mechanical surgery.

Key-Words: Keratoconus, Intrastromal ring segments, Manual surgery, Femtosecond surgery.

INDEX

ABBREVIATION LIST

ART – Ambrósio's Relational Thickness Index

AS-OCT – Anterior Segment Optical Coherence Tomography

BAD-D – Belin/Ambrósio Enhanced Ectasia Display

CDVA – Corrected Distance Visual Acuity

CH – Corneal Hysteresis

CRF – Corneal Resistance Factor

DALK – Deep Anterior Lamellar Keratoplasty

DM – Descemet Membrane

FS – Femtosecond

HOA – Higher Order Aberrations

ICAM-1 – Intercellular Adhesion Molecule 1

ICRS – Intrastromal Corneal Ring Segments

IL-a – Interleukin-A

IL-1 – Interleukin-1

IL-6 – Interleukin-6

IL-10 – Interleukin-10

I-S – Inferior to Superior Dioptric Asymmetry

KISA% - Keratoconus Percentage Index

MMP-9 – Metalloproteinase 9

MMP-13 – Matrix Metalloproteinase 13

OCT – Optical Coherence Tomography

OR – Odds Ratio

PAS – Periodic Acid Schiff

PK – Penetrating Keratoplasty

PTI – Percentage of Thickness Increase

RMS – Root Mean Square

SOD1 – Superoxide Dismutase 1

SP-A1 – Stiffness Parameter A1

SRAX – Skewed Radial Axes

TCT – Total Corneal Thickness

TNF-alfa – Tumor Necrosis Factor

μm – Micrometer

VCAM1 – Vascular Cell Adhesion Molecule 1

VSX1 – Visual System Homeobox 1

FIGURE LIST

CHAPTER I - INVESTIGATION QUESTION AND MOTIVATION

1. Investigation Question

The current doctoral thesis arises as a consequence of a primary investigation question:

Is the efficacy and safety of intrastromal corneal ring segments implantation for the treatment of keratoconus the same, whether the surgery is performed manually or assisted by a femtosecond laser?

2. Motivation

Keratoconus is a degenerative condition of the cornea that profoundly affects vision and vision-specific quality of life. The cornea thins and protrudes, resulting in irregularity and, eventually, scarring of the central visual axis. There are multiple options available for treating keratoconus, medical or surgical treatment is mandatory. In the late stages of the disease, a corneal keratoplasty procedure could be necessary; however, there are currently other treatments available for the initial or moderate stages of the disease like corneal collagen crosslinking or intrastromal corneal ring segments implantation.

This doctoral thesis is based on the experience earned in the last decade by our Cornea Department at the Hospital de Braga and Hospital CUF Porto with the treatment of keratoconus patients and from the knowledge that I personally acquired from the mentoring of Prof. José Alfonso, during the multiple clinical visits to the *Instituto Oftalmológico Fernandez-Vega*. Intrastromal corneal ring segments are small, crescent-shaped plastic ring segments that are placed in the deep, peripheral corneal stroma in order to flatten the cornea. The implants are placed inside the cornea using two different surgical methods, one available at a public institution and the other available at a private practice hospital. There is currently limited scientific knowledge about the two surgical procedures, and the medical community widely accepts some empirical assumptions.

This Doctoral Thesis proposes to distinguish the results of the two surgical procedures in terms of anatomical outcomes, visual and refractive results, and also complications incidence and management. The results will also elucidate the applicability of such a procedure in public care institutions, where manual procedures are the only surgical treatment available, about the applicability in high-risk patients such as paediatric patients, patients after a previous complication, or patients classically indicated for a corneal keratoplasty procedure.

CHAPTER II - INTRODUCTION

1. Essential aspects of the cornea

1.1 Anatomy of the cornea

The cornea is the transparent and avascular front part of the eye playing a central role in light refraction and providing a physical barrier to the external environment. It consists of 5 layers: the epithelium, Bowman's layer, stroma, Descemet membrane, and endothelium (figure 1).

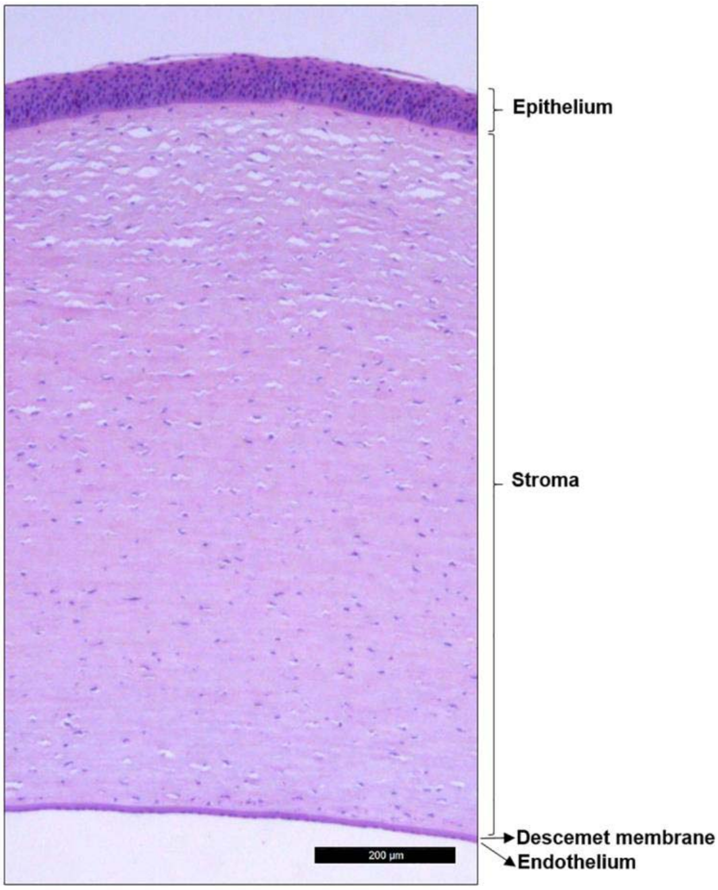

Figure 1. Corneal histology (image adapted from epomedicine.com)

The outermost layer of the cornea, the epithelium, comprises of 5-6 layers of stratified non-keratinized cells measuring approximately 50 μm in humans. The cells in the uppermost layers form intercellular tight junctions that prevent the invasion of microorganisms and other potentially harmful exogenous factors. The corneal epithelium is maintained by a population of stem cells residing at the basal layers of the vascularized junction between the cornea and the conjunctiva, namely the limbus. The highly (lymph)vascularized Palisades of Vogt are stromal invaginations located in the limbus and are considered a putative limbal epithelial stem cell niche. The limbus is the border between the physiologically avascular cornea and the heavily hem- and lymph vascularized conjunctiva.

The corneal basal epithelial cell layer rests on the acellular Bowman's layer, which is a strong membrane consisting of randomly oriented collagen fibrils. Contrary, the corneal stroma features a highly organized structure consisting of highly organized collagen type I and V fibers to which the cornea owes its transparency and biomechanical strength. The corneal keratocytes, mainly localized in the anterior stroma, produce these collagen fibrils while remaining relatively sparse within the stromal tissue.

The Descemet membrane underlies the corneal stroma and consists mainly of collagen type IV, which is produced by a monolayer of quiescent endothelial cells that perform the critical function of keeping the cornea dehydrated by continuously pumping fluid out of the stroma and into the aqueous humour.

In addition to the previously described structures, the cornea contains numerous nerves, immune cells, putative mesenchymal stem cells, and hem- and lymph- vascular sprouts close to the limbus. If corneal transparency, integrity or function are compromised, visual acuity loss may occur.

The cornea serves as the transparent "window" of the eye that allows the entry of light. The smooth surface of the cornea contributes to visual clarity. The regular arrangement of collagen fibers in the corneal stroma accounts for the transparency of this tissue[1]. Maintenance of corneal shape and transparency is critical for light refraction, with the cornea accounting for more than two-thirds of the total refractive power of the eye. A functionally intact corneal endothelium is essential for the maintenance of stromal transparency as a result of the regulation of corneal hydration exerted by the endothelium.

The anterior corneal surface is covered by the tear film, whereas the posterior surface is bathed directly by the aqueous humour. The highly vascularized limbus, which is thought to contain a reservoir of pluripotent stem cells, constitutes the transition zone between the cornea and the sclera. The anterior corneal surface is convex and aspheric, and it is transversely oval as a result of scleralization superiorly and inferiorly.

The adult human cornea measures 11 to 12 mm horizontally and 9 to 11 mm vertically; it is approximately 0.5 mm thick in the center, with thickness increasing gradually toward the periphery, where it is about 0.7 mm thick[2]. The curvature of the corneal surface is not constant, being highest at the center and smallest at the periphery. The radius of curvature is between 7.5 and 8.0 mm at the 3-mm central optical zone of the cornea, where the surface is almost spherical. The refractive power of the cornea is 40 to 44 diopters, constituting about two-thirds of the total refractive power of the eye.

1.2 Optical properties

The optical properties of the cornea are determined by its transparency, surface smoothness, contour, and refractive index of the tissue[3]. If the diameter of (or the distance between) the collagen fibers in the corneal stroma becomes heterogeneous (as occurs in fibrosis or edema), incident light rays are scattered randomly, and the cornea loses its transparency. Given that the spherocylindrical surface of the cornea has both minor and major axes, changes in corneal contour caused either by pathological conditions such as scarring, thinning, keratoconus, or by refractive surgery render the surface regularly or irregularly astigmatic.

The total refractive index of the cornea is determined by the sum of refraction at the anterior and posterior interfaces together with the tissular transmission properties. The refractive indexes of air, tear fluid, corneal tissue, and aqueous humour are 1.000, 1.336, 1.376, and 1.336, respectively. The refractive power of a curved surface is determined by the refractive index and the radius of curvature. The refractive power of the central cornea is about +43 diopters, being the sum of that at the air-tear fluid (+44 diopters), tear fluid-cornea (+5 diopters), and cornea-aqueous humour (-6 diopters) interfaces. Most keratometry and topography measurements assume a standard refractive index of 1.3375.

1.3 Innervation

Innervation of the cornea is required for pain sensation as well as for tissue repair. In addition, the autonomic innervation of the scleral spur and blood vessels in the episclera, the surface of the sclera immediately beneath the subconjunctival connective tissue, plays an essential role in the regulation of intraocular pressure.

The cornea is one of the most densely innervated and most sensitive tissues in the body. The density of nerve endings in the cornea is thus about 300 to 400 times greater than that in the skin[4]. Most of the sensory nerves in the cornea are derived from the ciliary nerves of the ophthalmic branch of the trigeminal nerve. The long ciliary nerves provide the perilimbal nerve ring. Nerve fibers penetrate the cornea in the deep peripheral stroma radially and then course anteriorly, forming a terminal subepithelial plexus. The nerve fibers lose their myelination within a short distance of their point of entry into the cornea, penetrate Bowman's layer, and terminate at the wing cell level of the epithelium. Histochemical studies have revealed the presence of various neurotransmitters, including substance P, calcitonin gene-related peptide, neuropeptide Y, vasoactive intestinal peptide, galanin, methionine-enkephalin, catecholamines, and acetylcholine, in the cornea[(4)]. The cornea thus contains peptidergic, sympathetic, and parasympathetic nerve fibers.

1.4 Vascular system

The cornea is one of the few avascular tissues in the body. Although the normal cornea does not contain blood vessels, factors derived from the blood play important roles in corneal metabolism and wound healing. The anterior ciliary artery, which is derived from the ophthalmic artery, forms a vascular arcade in the limbal region that anastomoses with vessels derived from the facial branch of the external carotid artery. The cornea is thus supplied with blood components by both internal and external carotid arteries. In certain pathological conditions, new vessels enter the transparent corneal stroma from the limbus and result in a loss of corneal transparency.

1.5 Oxygen and nutrient supply

Corneal epithelial and endothelial cells are metabolically active. Cellular activities require adenosine triphosphate (ATP) as an energy source, with catabolism of glucose by glycolysis and the citric acid cycle generating ATP under aerobic conditions. A supply of glucose and oxygen is thus essential to maintain the normal metabolic functions of the cornea[(5, 6)]. The cornea is supplied with glucose by diffusion from the aqueous humour. In contrast, oxygen is supplied to the cornea primarily by diffusion from the tear fluid, which absorbs oxygen from the air. Direct exposure of tear fluid to the atmosphere is thus essential for oxygenation of the cornea. Disruption of the oxygen supply to the cornea, such as that resulting from the wearing of contact lenses with less gas permeability, can lead to corneal hypoxia and consequent stromal edema[(7, 8)]. Closure of the eyelids during sleep also reduces the amount of oxygen that reaches the cornea. Corneal metabolism, therefore, changes from aerobic to anaerobic (with consequent accumulation of lactate) during sleep[(9)].

2. Basic aspects of keratoconus

2.1 Definition

Keratoconus is a clinical term used to describe a condition in which the cornea assumes a conical shape because of thinning and protrusion (figure 2). The process is classically defined as noninflammatory. Cellular infiltration and vascularization do not occur. The disease is bilateral but asymmetric and progressive; the disease process results in mild to marked impairment of visual function[10]. The anterior cornea is the primary refractive surface of the eye, responsible for over two-thirds of its total dioptric power. Therefore, minimal changes in corneal shape can have a dramatic effect on the clarity with which an image is focused on the retina. In keratoconus, the cornea thins, steepens, and protrudes, and its outer surface becomes irregular, distorted, and sometimes even scarred, resulting in blurry vision, even with visual optical correction. Recently, this definition has suffered a substantial modification, as the disease is now thought of as a pathology with inflammatory[11-15] and neurotrophic[16] components; it should be otherwise considered as a neuro-inflammatory disease of the cornea.

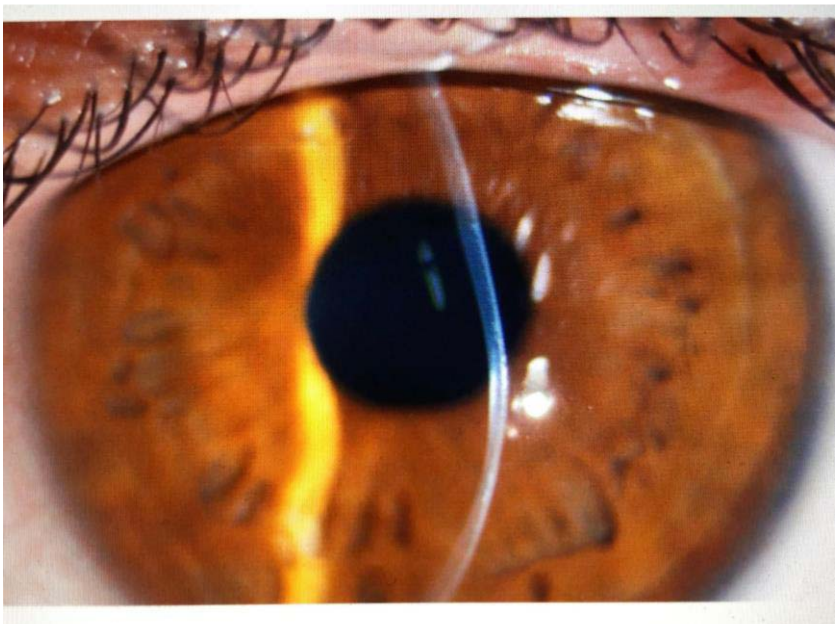

Figure 2. Slit-lamp image of a patient with keratoconus (HB 40176972)

2.2 Pathophysiology and histopathology

Although much research has been done, the cause of keratoconus remains unknown; recent advances have pointed out that the disease is multifactorial, with genetic and environmental influences[17, 18]. It has been proposed that the corneal tissue of individuals with a genetic predisposition is more easily weakened by oxidative stress than those without a genetic factor[19, 20]. If the weakened corneal tissue is exposed to sustained mechanical trauma, corneal ectasia or keratoconus may eventually be induced[21]. To date, several associated factors for keratoconus have been reported, including minor ocular trauma, eye rubbing, ocular allergy, a poorly fitted contact lens, and some connective tissue disorders such as Ehlers-Danlos syndrome[21-23]. However, except for eye rubbing, there has been controversy around these risk factors. A recent meta-analysis has demonstrated a clear relationship between keratoconus and eye rubbing (OR 3.09), family history of keratoconus (OR 6.42), allergy (OR 1.42), asthma (OR 1.94), and eczema (OR 2.95)[24].

Every layer and tissue of the cornea can potentially be involved in the pathologic process of keratoconus. The classic triad of histopathologic findings includes corneal stromal thinning, Bowman's layer ruptures, and iron deposits at the basal layers of the corneal epithelium[10, 25].

Central epithelial thinning has been found with variable frequency. Specular microscopy of the corneal epithelium has revealed enlargements of the superficial cells and prominence of elongated cells, findings not observed in long-term hard contact lens wearers. Early degeneration of the basal epithelial cells can be followed by disruption of the epithelial basement membrane. Breaks in the epithelial layer can be associated with epithelium growing posteriorly into Bowman's layer and collagen growing anteriorly into the epithelium, forming Z-shaped interruptions at the level of Bowman's layer[10, 25].

A hallmark of keratoconus is the Fleischer ring found at the base of the cone; the brown iron ring can be seen histopathologically. Light and electron microscopy reveal that ferritin particles accumulate within and between the epithelial cells, particularly in the basal epithelium. At the level of the Bowman's layer, the changes detected include several ruptures filled with stromal collagen fibers, nodules staining positive for PAS, and interruptions with a Z-shape, secondary to the separation of the collagen strands. The consolidation of these fine scars may result in the reticular branching opacities often seen at this level.

At the level of the stroma, there is a closer packing of the collagen fibrils and a significant alteration of the usual orthogonal arrangement of the collagen fibrils; the number of collagen lamellae is abnormally low and stromal thinning occurs. It has been suggested that collagen lamellae are released from their interlamellar attachments or their attachments to Bowman's layer and become free to slide. This lamellar disorganization results in thinning without collagenolysis, leading to biomechanical instability.

The Descemet membrane is normal except in cases after acute hydrops, where ruptures are found. The endothelium cell morphology and density are generally normal, except in cases where endothelial cell pleomorphism and polymegathism occur, after a long-term contact lens use.

2.3 Prevalence and course

Keratoconus is the most common corneal ectasia. According to some series, the estimated prevalence of the disease has ranged from 37 to 2300 cases per 100.000(10, 26-28) and the incidence of 2-4.4 cases per 100.000(26,29); the prevalence is reported to be higher in Asian people versus other ethnic groups(28, 30, 31). The reason for the differences in these rates between studies is related to differences in the ethnic groups included, the age of the enrolled patients, and the inclusion diagnostic criteria, especially for early keratoconus. The reported incidence could be higher if we included cases like forme-fruste keratoconus, subclinical keratoconus, keratoconus suspects, and even if routine corneal topographies were performed on a random young population. Because the disease is rare, other worldwide incidence and prevalence rates have never been rigorously assessed. The great discrepancy observed in the prevalence of the disease is due to a genetic predisposition, the geographic localization, the exposure to different risk factors and certainly to different diagnostic criteria, especially after the advent of corneal topography.

Keratoconus usually occurs bilaterally. Unilateral cases occur. However, it has been convincingly shown that when diagnostic criteria and topographical analysis allow the detection of very early keratoconus in the fellow eye, the incidence of unilateral involvement is probably in the range of 2-4%(32, 33). The onset of keratoconus occurs at about the age of puberty. The cornea begins to thin and protrude, resulting in irregular astigmatism usually associated with a steep curvature. Typically, over a period of 10 to 20 years, the process continues until the progression gradually stops. The rate of progression is variable. The severity of the disorder at the time progression stops can range from very mild irregular astigmatism to severe thinning, protrusion, and scarring requiring keratoplasty.

2.4 Genetic studies

Previous studies performed before the advent of corneal topography have concluded that around 6-8% of subjects with a close family history of keratoconus would develop keratoconus, these findings suggest an autosomal dominant inheritance pattern with complete penetrance but variable expression[(34)]; family history was recently pointed out as the strongest risk factor for the disease, with an OR of 6.42[(24)]. Recent publications with corneal topography have shown that family-related individuals of keratoconus patients have a 15-67 higher risk to develop the disease when compared to individuals related to normal patients[(35)], and the disease prevalence in the general population is much higher than expected.

It is of high clinical interest to study the genetics of keratoconus disease to identify common chromosomic regions and new disease-associated genes at those loci. A family history of keratoconus can arise from the environment or genetic factors; sometimes, it is unclear whether one factor was determinant; however, recent information about consanguinity and keratoconus suggests an important contribution of genetic factors to the development of the disease[(36)]. In recent epidemiological studies, the percentage of family-related individuals affected by keratoconus does not vary significantly, from 13.5% in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) to 17.8% in other publications[(37)]. In the Dundee University Scottish Keratoconus Study (DUSKS)[(38)], it was detected a higher incidence of keratoconus in Asiatic patients (25%) than in Caucasian patients (5%). This evidence could be explained by the fact that it is normal to detect a higher incidence of family disease in areas where the prevalence of the disease is also higher; several publications have reported a higher prevalence of keratoconus in certain geographic areas, with prevalence higher than 20%[(39, 40)]. The first study to establish a significant genetic relationship was published in Israel, the authors have demonstrated that when both parents were first-grade cousins, there was a four times higher risk to develop keratoconus, the parents could be carriers of the same mutation in a specific locus, and the transmission would be autosomal recessive[(40)]. The percentage of affected individuals is even higher in countries where consanguineous marriages are a tradition[(41-43)]; on the other side, there are some forms of keratoconus with an extensive family history, suggesting an autosomal dominant inheritance pattern[(44)]. Although environmental factors have been involved in keratoconus pathogenesis, strong underlining genetic susceptibility has been proven. The lack of consistent findings among early genetic studies suggested an heterogeneous and complex nature of the genetic contribution to the development of keratoconus.

One of the most significant and recent developments in the field of keratoconus genetics is the identification of polymorphisms in the *LOX* (collagen crosslinking enzyme lysyl oxidase) gene that is potentially responsible for a linkage signal at the 5q32-q33 chromosomal region identified by two-stage genome-wide linkage studies using hundreds of polymorphic microsatellite markers and the nonparametric method of analysis(45). After looking at the biological functions of the hundreds of known or predicted genes in five linkage regions, *LOX* was found to be the most promising candidate among plausible keratoconus candidate genes(46). There are many other genes associated with keratoconus, but the *VSX1* gene and the *SOD1* gene are two of the most important and relevant. The *VSX1* gene belongs to a family of homeodomain transcription factors that are thought to control cell differentiation in craniofacial and ocular development, making it a promising functional candidate gene for keratoconus pathogenesis of various corneal dystrophies(47). The *SOD1* gene has been proposed and repeatedly investigated as a candidate for keratoconus with published data supporting its involvement(48, 49). The increased levels of oxidative stress markers sometimes identified in corneas from patients with keratoconus suggest that defects in the *SOD1* gene, encoding a major cytoplasmic antioxidant enzyme that metabolizes superoxide radicals, might be involved in the development of this disease(19).

The discovery of new genes is essential for a better understanding of the disease; it will enable the establishment of a relationship between the genotype and the phenotype of the disease, new diagnostic criteria, innovative and very early genetic therapy.

2.5 Biochemical Studies

Over the past decades, biochemistry has provided an essential line of research into the etiology of keratoconus. Since much of the work has been done on host corneas following penetrating keratoplasty, it is crucial to keep in mind that the results of many of these studies relate more to advanced keratoconus rather than early disease. Several biochemical theories have been proposed to support the hypothesis that corneal thinning occurs as a result or a combination of one of two biochemical processes: a defect in the collagen stromal synthesis process and/or an excessive metabolic degradation.

Even though some studies about corneal collagen composition in keratoconus have not found differences to normal corneas(50), some have shown a heterogeneous reduction in the synthesis of collagen type I(51), and a change in the expression of collagen type VI. It was also demonstrated that the keratocytes in the previous cases have a four times higher number of IL-1 when compared to healthy subjects[52]. As the IL-1 has been suggested as a modulator of proliferation, differentiation, and death of the keratocytes, it was thought that the loss of stromal keratocytes could be due to an excessive level of cellular apoptosis driven by IL-1[53]. A higher liberation of IL-1 also occurs after minor epithelial trauma; this could explain the disease progression that sometimes occurs after the chronic use of contact lenses, eye rubbing, or uncontrolled atopia[54]. Some pro-inflammatory markers like IL-6, ICAM-1, and V-CAM-1 are overexpressed, while some anti-inflammatory markers like IL-10 are underexpressed in patients with keratoconus who wear contact lenses when compared to myopic patients with normal corneas who also wear contact lenses[55]. These findings suggest that the use of contact lenses could be a precursor of disease development.

On the other side, the excessive degradation of the corneal stroma could be a consequence of the intense proteolytic activity of proteases and other catabolic enzymes[56], or because of the reduction of the levels of the proteinase inhibitors, like the alfa-2 macroglobulin and the alfa-1 anti-protease[57, 58]. The tear film is also a vehicle for cytokines and enzymes responsible for extracellular matrix degradation. Recent studies have demonstrated a higher expression of pro-inflammatory factors like IL-6, TNF-alfa, and MMP-9[14, 15] with a reduction of anti-inflammatory factors like IL-10, supporting the theories that advocate the existence of chronic inflammatory processes implicated in the pathogenesis of keratoconus.

In conclusion, local chronic inflammatory stimuli like eye rubbing, allergic conjunctivitis, ocular rosacea, or the floppy eyelid syndrome could trigger the production of inflammatory cytokines and catabolic enzymes; these would generate tissue damage and a consecutive corneal thinning. However, it remains a lack of concordance between the elevated levels of inflammatory markers and the pathologic and histologic findings demonstrating a complete lack of inflammation in the corneal tissue in some patients with keratoconus.

2.6 Biomechanical Studies

The objective of corneal biomechanical studies is to explore the function and structure of the cornea as a physical element; the cornea has a viscoelastic property, non-linear and anisotropic, with different physical properties when submitted to diverse applied stress forces[59]. Biomechanical studies have two variants: one is related to the diagnosis and the description of several pathologies, aims to describe the normal and the diseased cornea; the other variant is related to the creation of theoretical biomechanical models to predict the functional response of the cornea as a tissue after several surgical procedures[60].

The different distribution and the lower number of stromal lamella in keratoconus patients when compared to healthy individuals have been proposed as the precursor of the corneal thinning and weakening process. The stromal layer of the cornea is the main responsible for the corneal integrity; it is composed of the keratocytes, the collagen, and the polysaccharide-rich extracellular matrix. In keratoconus, the collagen fibbers tend to diminish its structural rigidity, leaving the cornea more susceptible to structural damage caused by external factors like intraocular pressure, eye rubbing, inflammation, or previous surgery. There are fewer bridges between the collagen fibers, and this fact causes a direct compromise of the structural integrity of the stromal lamellae. This compromise favours the slippage of the collagen fibers, generating a progressive thinning at the level of the corneal apex[61].

The Ocular Response Analyser (ORA®; Reichert Inc, Depew, NY, United States) was introduced as the first device for evaluating corneal biomechanical parameters *in vivo*. It monitors the corneal deformation response to an air pulse and provides biomechanical related parameters, including corneal hysteresis and corneal resistance factor. Although studies have shown that CH and CRF in keratoconus eyes are significantly lower than in healthy eyes, the specificity and sensitivity of both values are not sufficiently high to diagnose keratoconus[62, 63].

The corneal visualization Scheimpflug tonometer (Corvis® ST, Oculus Optikgeräte GmbH; Wetzlar, Germany) is an even newer instrument, which also enables the assessment of the biomechanical parameters. It uses an ultra-high-speed Scheimpflug camera that enables direct visualization of corneal movement during the measurements and provides several corneal deformation parameters. The main advantage versus the ORA® device is that it shows qualitative monitoring of the corneal morphology simultaneous to the acquisition of the numeric biomechanical parameters[64, 65]. The Corvis® ST has been shown to be an effective instrument aiding in the diagnosis of sub-clinic keratoconus, to monitor the disease progression and to evaluate the results obtained after specific surgical procedures[60, 66, 67]. Recently, a stiffness parameter A1 was introduced as a new parameter for corneal stiffness[68]. It is generated from the initial data acquired by the Corvis® ST and calculated using a particular equation. SP-A1, the first corneal stiffness value recorded *in vivo* by the Corvis® ST, was developed by using the displacement of the apex from the non-deformed state to the first applanation in the deformation process. It takes into account confounding factors such as intraocular pressure and whole eye motion. In a recent study, a decrease of SP-A1 in keratoconus compared with controls was demonstrated; a statistically significant difference between various levels of severity of keratoconus was presented as well. Additionally, a statistically positive correlation was revealed between SP-A1 and TCT in all keratoconus groups, and the relative index increased with the severity of keratoconus[69].

2.7 Associated Systemic Diseases

Even though multiple associations with systemic diseases have been described in keratoconus, the most frequent clinical form of the disease is idiopathic, sporadic, and isolated. Some of the rare clinical associations are just coincidence; they could be more relevant if they were to be originated from close genetic defects, affected in conjunction by a single translocation or a chromosomal change. Nowadays, it is still challenging to know whether these associated morbidities favour the development of keratoconus as in a normal genetic susceptible individual or if they act directly in the disease pathology.

The most frequent clinical associations are Down's syndrome (0.5-20% have keratoconus, a 10-400 times higher incidence than the general population), and Leber's congenital amaurosis (up to 30% above 15 years of age also have keratoconus). The clear relationship between these diseases has driven several genetic studies regarding the implicated genes. However, the increase in the incidence of keratoconus in patients with Down's syndrome and Leber's congenital amaurosis is, in fact, related to the frequent eye rubbing and not the systemic disease itself, even though some controversy remains[30].

Several different mechanisms have been proposed to explain how the ocular eye rubbing can induce the development of keratoconus:

- In animal studies, the conjunctival mastocyte cells activation leads to degranulation and the liberation of histamine along with prostaglandins; allergic molecules derived from eosinophils were detected in the tear film, and they have a direct cytotoxic effect in vitro in the corneal epithelial cells.
- The increase of intraocular pressure: the combination of ocular occlusion and scleral indentation due to eye rubbing can increase the intraocular pressure value to higher than average values.
- The corneal epithelial trauma can induce biochemical and biomechanical changes. There is an increase in the levels of IL-a, which is a modulator of keratocyte proliferation, differentiation, and death; it was suggested that the loss of keratocytes could be explained by the imbalance between their proliferation and their apoptosis.

- The liberation of proteases and inflammatory mediators such as MMP-13, IL-6, and TNF-alfa can contribute to disease development. A study has shown a significant increase in the concentration levels of several proteases in the tear film of healthy individuals just after a short period (60 seconds) of ocular eye rubbing.

A recent study, based on a Korean population, has reported that only allergic conjunctivitis significantly increased the risk of a positive keratoconus diagnosis. On the other hand, systemic atopy and eczema did not show a significant association with keratoconus. One possible explanation suggested by the authors might be that systemic atopy and eczema would not always result in eye rubbing severe enough to develop keratoconus, compared with allergic conjunctivitis. Unlike with ocular allergy, there has been some debate around whether other allergic diseases might promote the development or progression of keratoconus. Besides, although some medical conditions were related to keratoconus, no conclusions have been established because large-scale studies are lacking. Recently, however, a large-scale study involving 16.053 patients with keratoconus was conducted in the United States of America to determine the risk factors for keratoconus using a national health care claims database[70]. In their study, sleep apnea and asthma showed increased odds for the development of keratoconus, whereas uncomplicated or complicated Diabetes Mellitus and collagen vascular disease showed low odds; allergic rhinitis did not show a significant difference. Especially in the previously published articles, allergic rhinitis had consistently increased odds in the keratoconus group versus the control group[70, 71].

3. Diagnosis of keratoconus

The diagnosis of keratoconus depends on clinical suspicion; it can be confirmed by several available diagnostic tools, including biomicroscopy, keratometry, pachymetry, tomography, aberrometry, and epithelial mapping.

3.1 Clinical examination

Keratoconus typically presents in the late teens or early adulthood. It is usually sporadic, although 6-8% of cases have a family history. The condition is almost always bilateral but can be very asymmetric. It tends to progress slowly over many years but it may advance rapidly in some cases. In the past, the diagnosis relied upon the clinical history and the subjective assessment of clinical signs. Patients often present with symptoms of progressive visual blurring or distortion. Photophobia, glare, monocular diplopia, and ocular irritation are also presenting symptoms. Early in the course of the disease, visual acuity might be normal, even in symptomatic patients. The morphologic changes in the cornea induce refractive changes, the initial increase in mean corneal power induces a myopic shift; the initial refractive error is usually low myopia and myopic astigmatism; as soon as the disease progresses, so does astigmatism, becoming irregular. A clinical history of frequent changes in refraction in a young patient should make us think about the possibility of an underlying corneal disease like keratoconus. High, irregular myopic astigmatism with a scissoring reflex on retinoscopy is typical in established keratoconus. In advanced keratoconus, the corneal protrusion may cause angulation of the lower lid on downgaze. This nonspecific finding has been referred to as Munson's sign. Usually, the diagnosis of the disease is made long before Munson's sign is evident.

The slit-lamp examination reveals characteristic findings. An eccentrically located ectatic protrusion of the cornea is noted. While the apex is usually inferior to an imaginary horizontal line drawn through the pupillary axis, it can be located in the central cornea. Vogt's striae occur in the posterior stroma, just anterior to Descemet's membrane (vertical stress lines, figure 3). When the intraocular pressure is transiently raised, by applying external pressure to the globe, the folds disappear. The fine parallel striae described are to be distinguished from the superficial linear scars seen at the corneal apex. These result from ruptures of the Bowman's layer. In more advanced cases, deeper opacities can be seen at the apex of the cone resulting from ruptures of the Descemet's membrane.

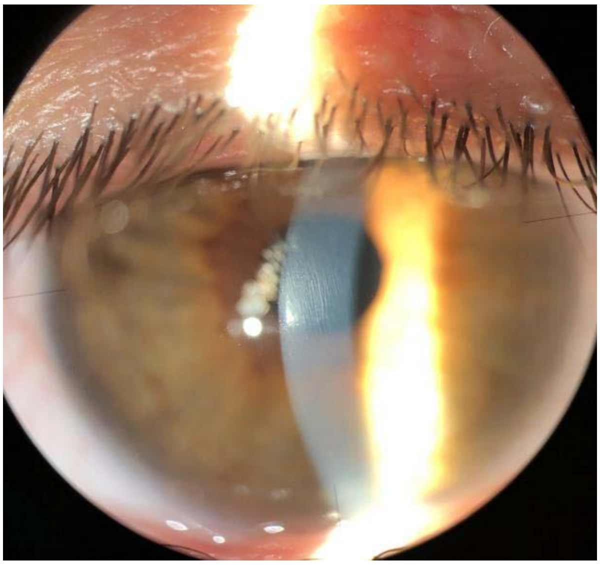

Figure 3. Vogt's striae (Oftalconde 37670)

Acute keratoconus or corneal hydrops results from stromal imbibition of aqueous through these defects. The edema may persist for weeks or months, usually diminishing gradually. Eventually, it is replaced by scarring, which in some cases may result in flattening of the conical contour. The Fleischer's ring (epithelial iron deposition line) is a partial or complete annular line commonly seen at the base of the cone. When identified, it provides a landmark for the peripheral edge of the cone. As the ectasia progresses, the ring tends to become more densely pigmented and narrower, and it may completely encircle the cone at its base.

3.2 Corneal imaging

3.2.1 Topography

In 1619, Scheiner made the first measurements of the corneal shape; in the 1820s, Cuignet developed a keratoscope through which he observed the reflected image of an illuminated target held in front of the patient's cornea; in 1882 Placido placed an observation hole in the center of the target, overcoming the difficulties of alignment associated to Cuignet's device. The target developed by Placido was a disc bearing alternating black and white concentric rings, and this pattern still forms the basis of many topography systems today. The quantification of the corneal curvature became possible in 1854 with the development of the keratometer (ophthalmometer) by von Helmholtz. The distance between two pairs of reflected points gave the spherocylindrical curvature of the central 3,0 mm of the cornea, in two meridians. In order to increase the area of cornea analysed, Javal (1889) attached a Placido-type disc to the keratometer; later in 1896, Gullstrand applied photography to keratoscopy (photokeratoscopy). Photokeratoscopy provided qualitative information about a large area of the cornea, but it was only as a result of developments in computing that quantitative analysis of these images could be performed using videokeratoscopy. The majority of topography systems in clinical use today are based on the Placido principle of reflection. They measure the slope of the corneal surface and can use this information to calculate the radius of curvature and power. However, corneal elevation cannot be calculated from measurements of corneal slope alone. The slope provides information about the gradient of a particular point at location (x, y), but it does not determine the elevation of that point in the z-axis. Therefore, the real corneal shape cannot be reconstructed from measurements obtained by reflection alone, without making many assumptions.

Corneal topography has been used to quantify the shape of the normal cornea and improve our understanding of the relationships between anatomy and visual function. The technique is sufficiently sensitive to diagnose corneal shape anomalies, such as keratoconus, at an early stage. Corneal topography is helpful in the management and treatment of patients, the identification of affected family members for genetic studies, and screening before corneal refractive surgery. Corneal disease processes can be monitored by comparison of serial measurements, and their effects on vision can be better understood.

In keratoconus, videokeratoscopy mires are distorted (figure 4). They lie closest together in the inferior-central region, where the cornea is steepest, and furthest apart superiorly, where the cornea is flattest. Inferior corneal steepening is the earliest sign of keratoconus in classic Placido-disk topography (figure 5). In early keratoconus, a focal area of increased corneal curvature appears as an isolated area of smaller ring spacing and distortion. As the condition progresses, the ring spacing decreases overall and becomes increasingly irregular. Placido-disk topography is based on the principle of reflection; thus, it only offers information about the anterior surface of the cornea, it takes into account neither the posterior surface nor the relationship between them. Poor patient fixation, misalignment of the keratometry, dry spots in the cornea, inferior eyelid compression, and contact lens-related warpage can all result in a pseudo-keratoconus appearance on a curvature map of a Placido-disk topography.

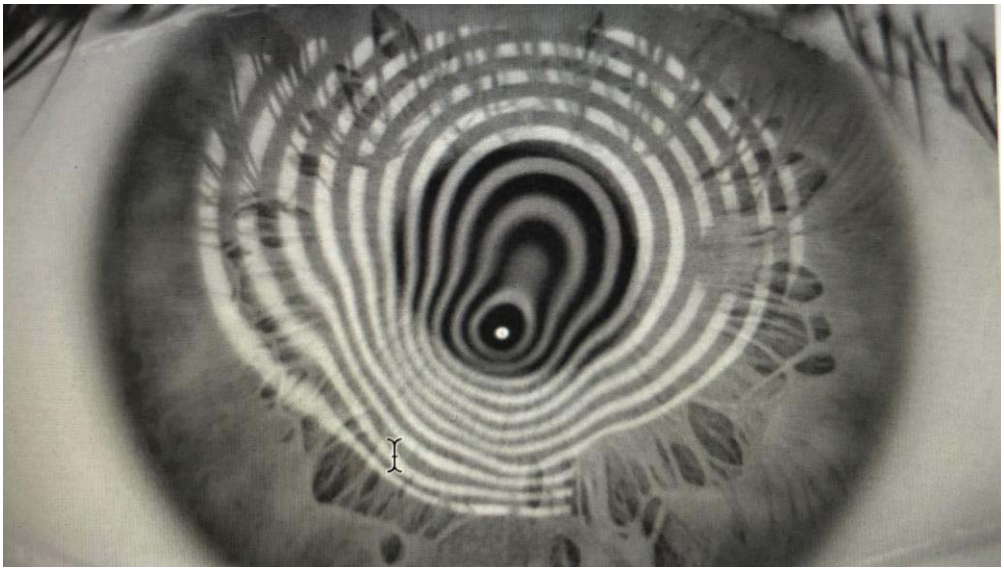

Figure 4. Placido disk (adapted from *"Corrección del queratocono com segmentos intracorneales tipo Ferrara: Estrategia personalizada para su implante"*. Carlos Lisa Fernández, 2017)

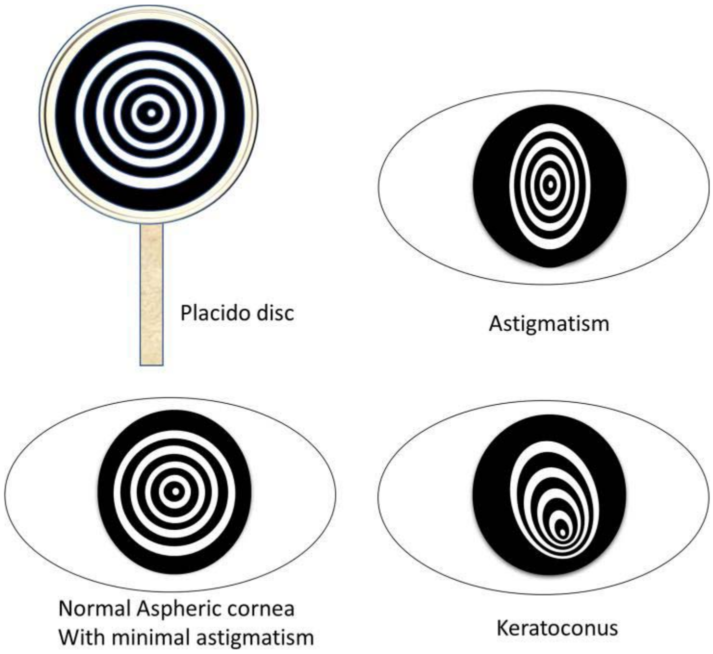

Figure 5. Placido disk and representative patterns of corneal shape (adapted from researchgate.net)

Color-coded curvature or power maps of an eye with keratoconus show an asymmetric bow-tie corresponding to the exaggerated prolate shape and irregular astigmatism of the corneal surface (figure 6). Although the topography in moderate and severe cases of keratoconus is usually recognized as such, the diagnosis can be more difficult in subtle cases or in those with an atypical shape. Uncertainty arises for two main reasons. First, controversy still exists regarding the minimum topographic criteria for the diagnosis of keratoconus. Second, there is variation in the topographic patterns seen in this condition; the interpretation of the images requires detailed knowledge and clinical experience of the subtle and complex patterns contained in them, both in normality and disease. In order to remove the subjectivity of the assessment and the need for expertise, several authors have developed specific corneal indices and detection programs designed to aid the topographic diagnosis of keratoconus. Rabinowitz has suggested four quantitative video keratographic indices as a tool for screening patients for keratoconus[72]. These indices include central corneal power value greater than 47.2 D, inferior-superior dioptric asymmetry (I-S value) over 1.2, Sim-k astigmatism greater than 1.5 D, and skewed radial axes greater than 21 degrees. These indices were used to distinguish keratoconus from normal corneas and were most effective when astigmatism was greater than 1.5 diopters. Maeda et al.[73, 74] developed an expert classification system using eight topographic indices; it was found to be significantly better than keratometry for identifying keratoconus or the Rabinowitz-McDonnel test, which is based on central corneal power and I-S value.

Evolution in keratoconus detection has resulted in continued refinement of the neural network approach by Smolek and Klyce[75] and the KISA% index described by Rabinowitz and Rasheed[76]. The KISA%, proposed by Rabinowitz, is calculated from four different variables: K-central, AST (Sim K astigmatism), I-S value, and the SRAX.

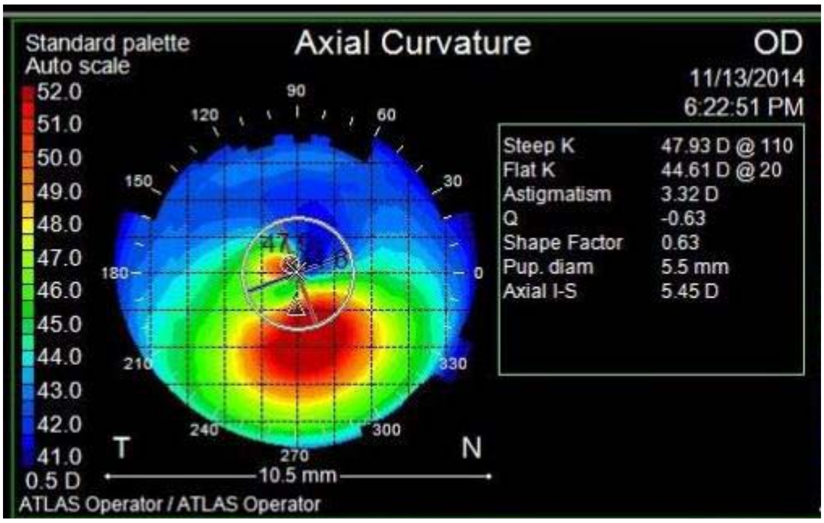

Figure 6. Color-coded curvature axial map (CUF 755079)

3.2.2 Tomography

Topography is considered an essential part of every refractive and corneal diagnostic or therapeutic evaluation. Original topography systems were based on reflective technology and determined slope as the basic unit of measure. The topographic data was presented as the first derivative of slope (curvature), which was initially more intuitive; however, it had a significant limitation: Placido-based systems rely on the analysis of a reflected image, this precludes obtaining data from the posterior corneal surface. Additionally, without information about the posterior corneal surface, complete pachymetric evaluation is not possible. While ultrasonic pachymetry can give central or isolated readings, a full pachymetric map requires accurate data from both the anterior and posterior corneal surfaces. Moreover, the posterior corneal surface started to be appreciated as a sensitive indicator of corneal disease (ectasia) and can often be abnormal despite a normal anterior corneal surface. When tomography was created, it started to be recognized that while the refractive power of the cornea is determined in large part by the anterior surface, the anatomical or mechanical properties of the cornea are at least equally dependent upon a thorough understanding of both anterior and posterior surfaces.

With the advent of tomography, associating the anterior corneal imaging of Placido topography with slit-scan Scheimpflug imaging enabled the clinical diagnosis of ectatic disorders to suffer a small revolution: clinicians were now able to correlate the data of the anterior curvature maps with an anterior elevation map (anterior float) based on a best-fit sphere, a posterior elevation map of the back surface of the cornea, and a full pachymetry map (figure 7). With the advent of Scheimpflug photography of the cornea, there were a more descriptive and accurate means of measuring corneal thickness and elevation. The Scheimpflug camera is a rotating camera that provides 25 to 50 cross-sectional corneal images during a single scan; each image typically contains 500 to 2750 elevation points (depending on the camera's resolution); the cross-sectional images generated are used to locate the anterior and the posterior corneal surfaces as well as the iris and the anterior lens surface.

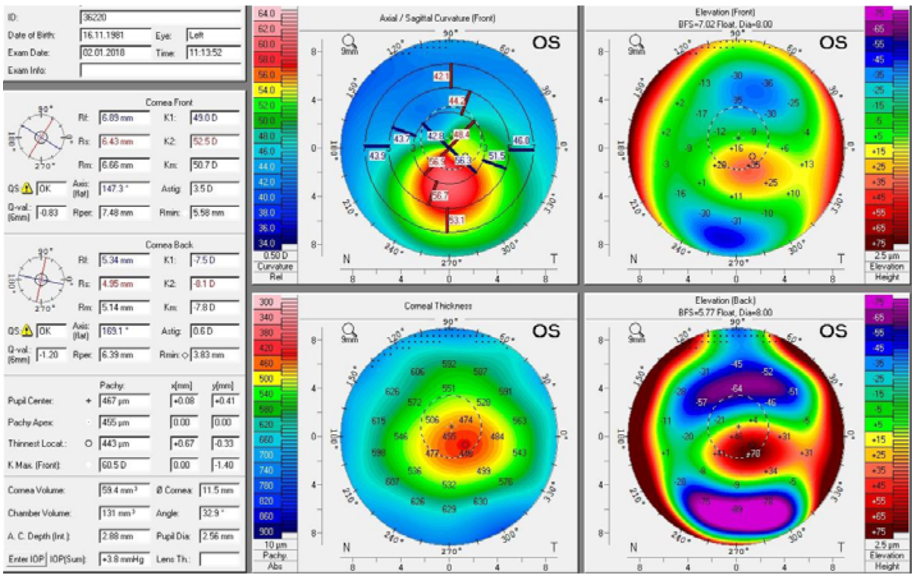

Figure 7. Scheimpflug tomography (Oftalconde 36220)

There are currently three types of tomographers, according to the technology used to capture the cross-sectional images of the cornea:

- Slit-scan
  - Orsbcan II® (Bausch & Lomb)
- Scheimpflug:
  - Sirius® (Contruzione Strumenti Oftalmici, CSO)
  - Pentacam® (Oculus)
  - Galilei® (Ziemer Ophthalmic Systems)

- Optical coherence
  - Omni® system (Zeiss)

The importance of studying the posterior surface of the cornea is something that at that time begun to be emphasized, as well as the idea that the ectatic process starts at the posterior surface of the cornea(77). A virgin cornea with an isolated island of anterior elevation higher than 11 μm as detected by the Pentacam®, and a posterior elevation greater than 20 μm is suspicious for an ectatic corneal contour. The exclusive study of the anterior surface of the cornea can lead to false-negative diagnosis due to the phenomenon of epithelial masking (figure 8). Epithelial masking can hide a posterior subclinical keratoconus(78). Above the area of corneal steepening, there is a local thinning of the corneal epithelial layer, and this phenomenon enables the anterior corneal surface to remain relatively regular during the early stages of the disease. Apart from these details, corneal tomography also enables clinicians to monitor the disease progression and to analyse diagnostic indexes with a predictive prognosis(79, 80).

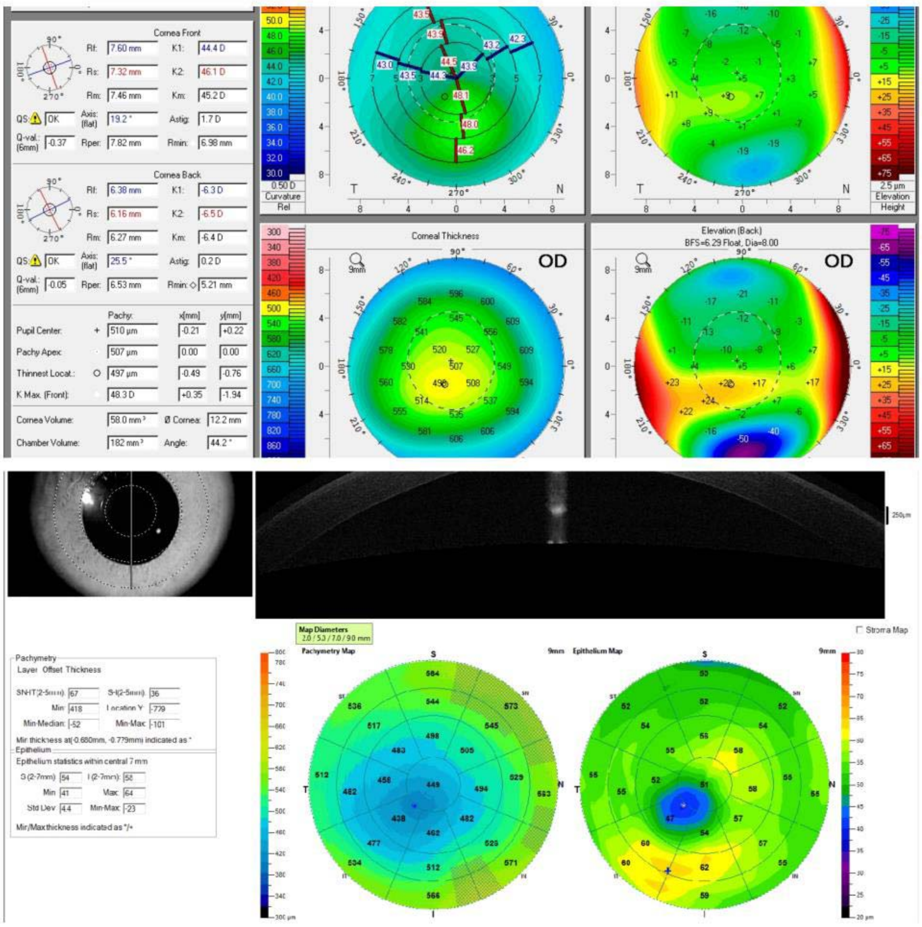

Figure 8. Epithelial mapping (Oftalconde 36746)

3.2.3 Pachymetry

Li Lim et al. and Pflugfelder et al. have demonstrated that corneal thinning is a hallmark of keratoconus[81, 82]; however, the disease can appear in thicker corneas or a thin cornea can be considered normal[83]. During decades, only the ultrasonic pachymetry was available to measure corneal thickness; the measurement was made as an isolated point centrally or peripherally (operator dependant), but it was of great utility to diagnose or discard the diagnosis of keratoconus, and to classify the ectasia in terms of severity[83]. Nowadays, with the use of tomography or OCT (figure 9), we can obtain a global pachymetric map of the cornea, describing with greater accuracy the location and absolute value of the thinnest point, and be able to correlate it with the different sectors of the cornea[84]. We were offered the possibility to plot the change in corneal thickness from the thinnest point spot outward toward the periphery and to analyse the rate of thickness change compared to normative data (Figure 10).

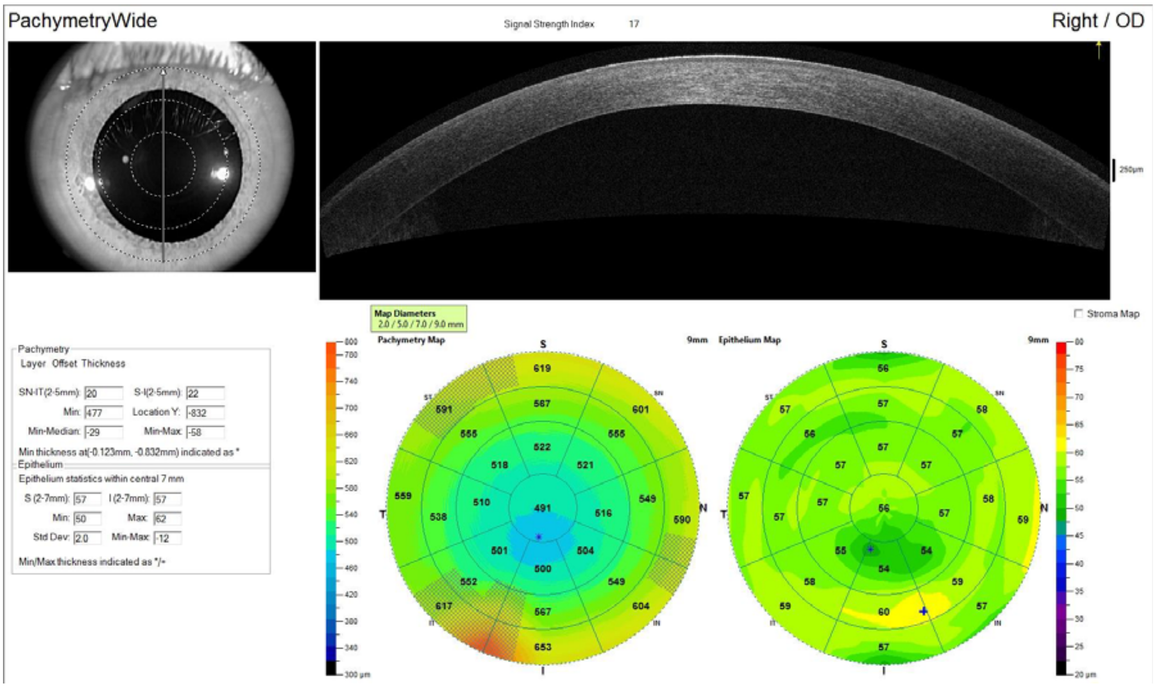

Figure 9. Corneal thickness map (Oftalconde 36746)

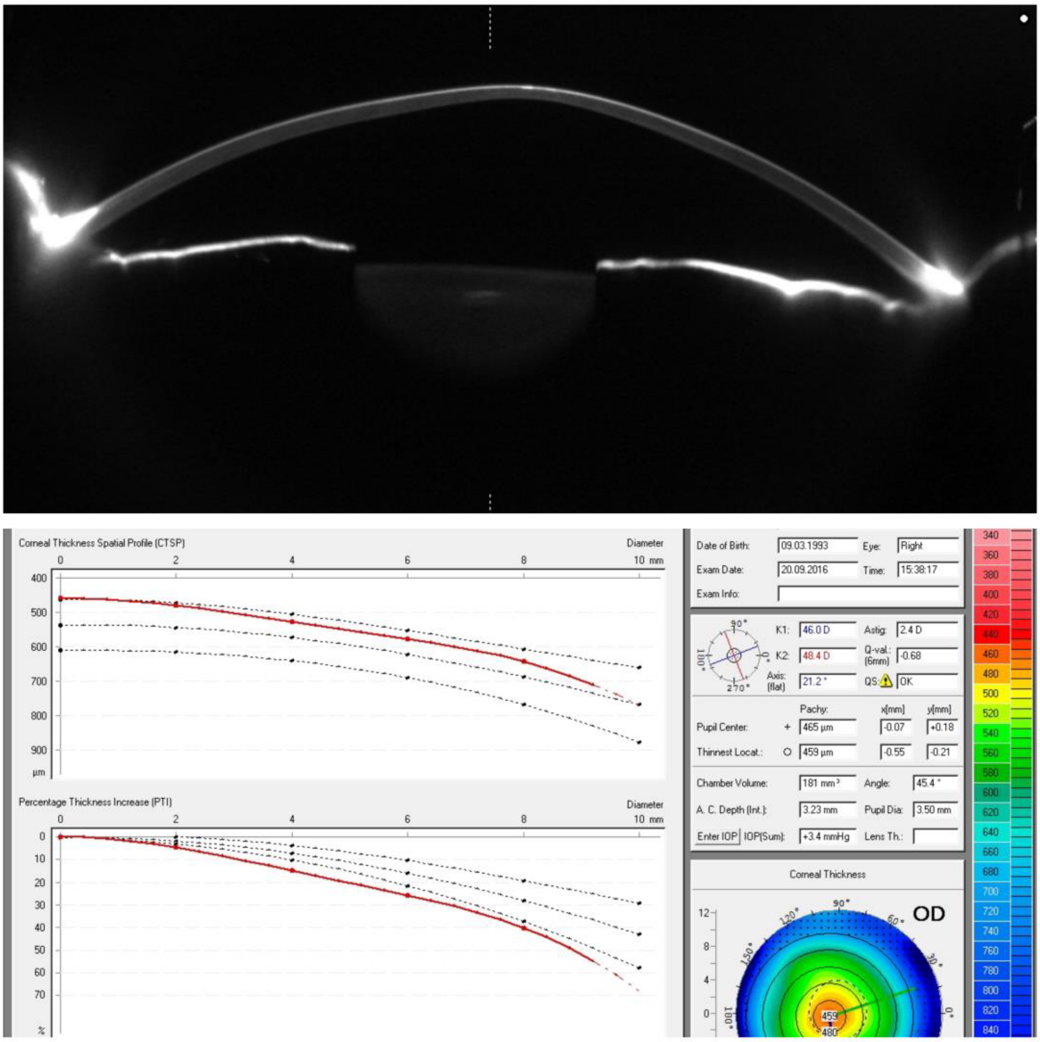

Figure 10. CTSP and PTI graphs (Oftalconde 32404)

The identification of the thinnest point location with respect to the center of the cornea has a great interest in the maintenance of the healthy structure and morphology of the cornea; this is the point of highest dynamic stress and the place where the ectatic process could begin. Ambrósio et al. have demonstrated that the PTI index from the thinnest point towards the periphery is distinct in keratoconus and normal corneas: keratoconus corneas are thinner, have less tissue volume and have more significant changes in the PTI value[85]. The BAD-D index, also incorporated in the Pentacam®, is very useful to the diagnosis of subclinical keratoconus; it takes into consideration the relationship between the elevation maps and the pachymetric maps (Figure 11). The pachymetric map represents the distribution of the corneal thickness across the corneal diameter; a significant change in the PTI is very suggestive of corneal ectasia. Other authors have employed the PTI value to better diagnose cases of subclinical keratoconus[86].

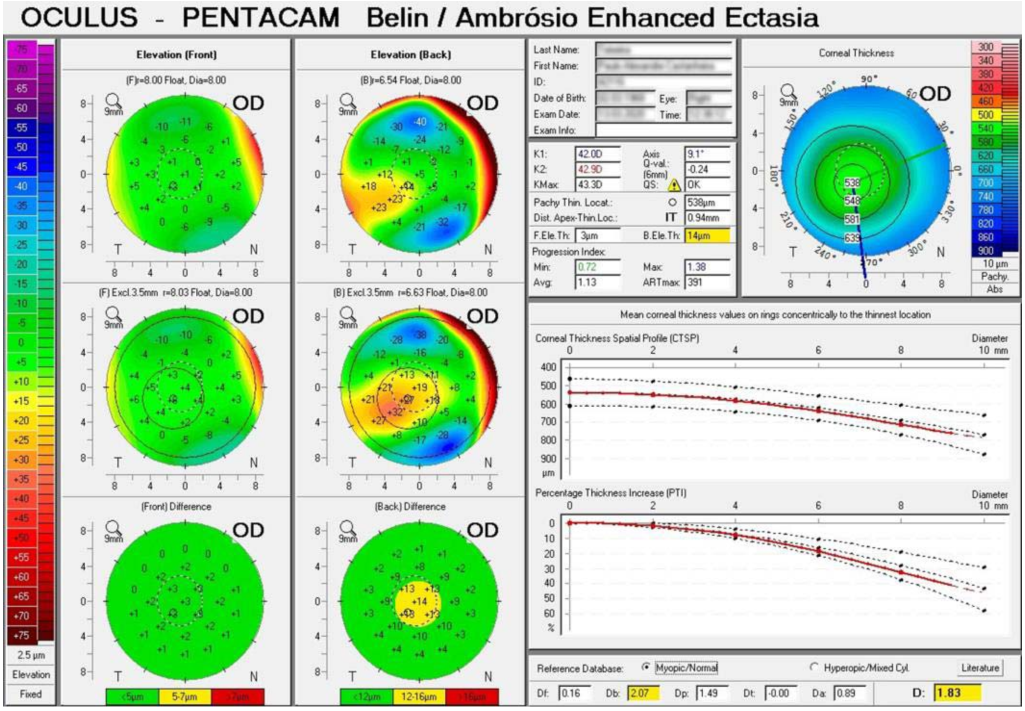

Figure 11. Belin/Ambrósio Enhanced Ectasia Display (Oftalconde 42116)

Recently, it has been established a new correlation between the thinnest point, the central corneal thickness and the PPI values (pachymetric progression indices), which is called the ART index, having a sensitivity of 100 % and a specificity of 96.5% to the diagnosis of sub-clinical or early keratoconus[(61)]. Using the Orbscan II®, Prakash et al. measured the central corneal thickness (ECC), the minimum corneal thickness (MEC) and the difference between both (ECC-MEC); and have established cut-off values of corneal thickness for the diagnosis of keratoconus and correlated them with the keratometry values and the diagnostic indexes of KISA% and the Massachusetts Eye and Ear Infirmary (MEEI criteria). The authors propose that a cornea with a MEC of 461 µm and ECC of less than 476 µm only has a 2.5% possibility of being normal. At the same time, a cornea with a MEC lower than 444 µm and an ECC lower than 425 µm and a difference between both higher than 27-32 µm has very high probabilities of being classified as keratoconus[(87)].

The corneal thickness measurement performed by OCT has also been demonstrated to be as sensitive and specific as the KISA topographic index for the diagnosis of keratoconus[(88)]. The diagnosis of clinical or subclinical keratoconus based on the corneal thickness map is also an important diagnostic tool; several values have been suggested to define the existence of the disease:

- Central corneal thickness lower than 475 µm[(87)].
- Corneal thickness point 27 µm thinner than the central corneal thickness[(87)].

- Thinnest point location farther than 0.7 mm from the center[88].
- Thinnest point location in the inferior temporal direction[89, 90].
- Central corneal thickness difference between both eyes higher than 20-25 μm[91].

The previous studies reinforce the importance of the pachymetric map study to diagnose and differentiate between healthy and affected corneas and also to monitor the disease progression[92].

3.2.4 Asphericity (Q)

Asphericity describes the geometric shape of the cornea and how the curvature changes from the center to the periphery. In the context of corneal ectasia, it is currently used to establish the stage of the disease and to define the treatment strategy[93]. The asphericity value changes according to the optical zone diameter used; this fact should be taken into consideration[94]. The asphericity value (Q value) is generally obtained from the anterior elevation map. An average human cornea is a prolate ellipse, with a mean Q value of -0.20 ± 0.12[94, 95]; a normal cornea is more curved at the center than at the periphery (prolate), the opposite of patients previously treated with excimer laser ablation for myopia, which have a flatter cornea in the center than at the periphery (oblate shape). In the case of keratoconus patients, Savini et al. have observed a mean value of asphericity at the 8.00 mm of -0.84 for the anterior surface and -1.10 for the posterior surface[96]. Another study has demonstrated similar results, from -0.65 to -1.18 for the anterior surface and -0.66 to -1.17 for the posterior surface[97], depending on the keratoconus severity grade according to the Amsler-Krumeich classification[98]. However, as the asphericity value is normally measured at the central cornea (4-6 mm), if the ectasia is very peripheral, we might obtain asphericity values near the normal range[99].

3.2.5 Aberrometry

Considering the light as a wave, all the points having the same energy as they reach the surface of an optical system constitute a wavefront. If the wavefront crosses an ideal optical system, no change of configuration will occur; however, if the optical system is not perfect, like the human eye, the wavefront loses its homogeneity and becomes irregular. These changes are the wavefront aberrations and are responsible for the degradation of the quality of the retinal image. The refractive errors (myopia, hyperopia, and astigmatism) generate low order aberrations, which can be fully compensated with the use of spectacles or soft contact lenses (figure 12). However, there are specific higher-order aberrations, like those present in patients with keratoconus, which degrade the quality of the retinal image and could be used as diagnostic parameters to identify the disease (figure 13). The clinical study of the corneal wavefront is critical in ectatic corneal diseases:

- The higher-order aberrations allow us to correlate the shape of the cornea with the optical image quality and to quantity this relationship in an objective manner[91], offering a complimentary analysis to the information obtained from the corneal topography.
- If we analyze the total aberrations and the corneal aberrations, there is a good correlation between them; in healthy eyes, most of the total ocular aberrations originate from the cornea, and the same happens in patients with keratoconus. The relationship between them is an essential factor to consider when deciding which type of medical or surgical treatment to apply.
- The analysis of corneal aberrometry is a significant parameter to consider in the evaluation of the efficacy of a given treatment.
- Several publications establish diagnostic indices of keratoconus based on the analysis of the Zernicke polynomials, these type of aberrometry quantification enables us to individually analyze each type of ocular aberration, to quantify its value in terms of root mean square[100] and to correlate them with the visual symptoms. This quantification of the HOA helps to differentiate between normal corneas and subclinical keratoconus[101]. Corneal wavefront analysis is an important adjuvant for the diagnosis of forme-fruste or mild keratoconus.

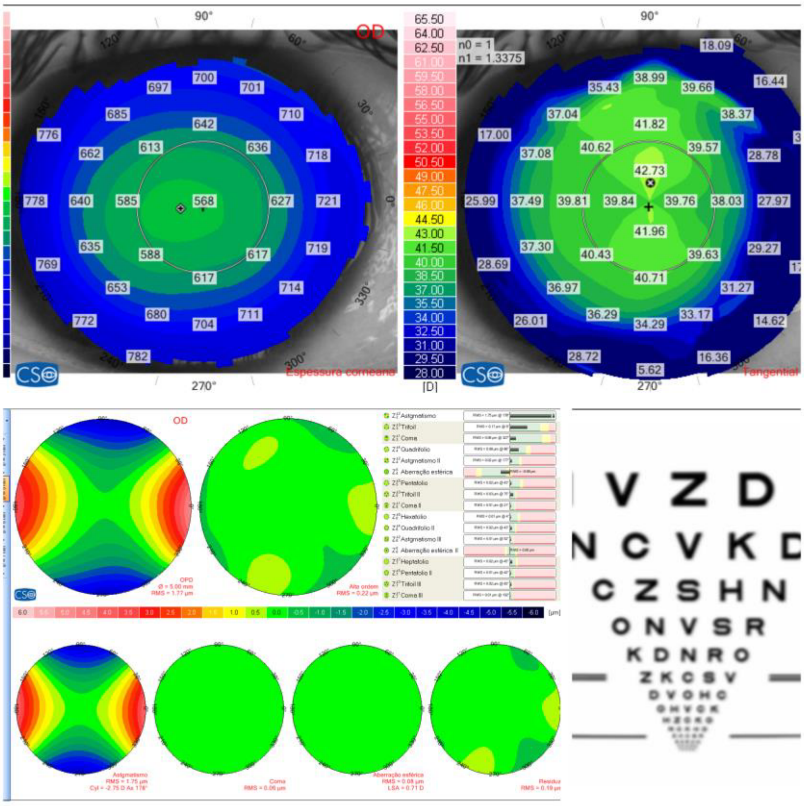

Figure 12. Corneal wavefront analysis of a normal patient (adapted from CSO.com)

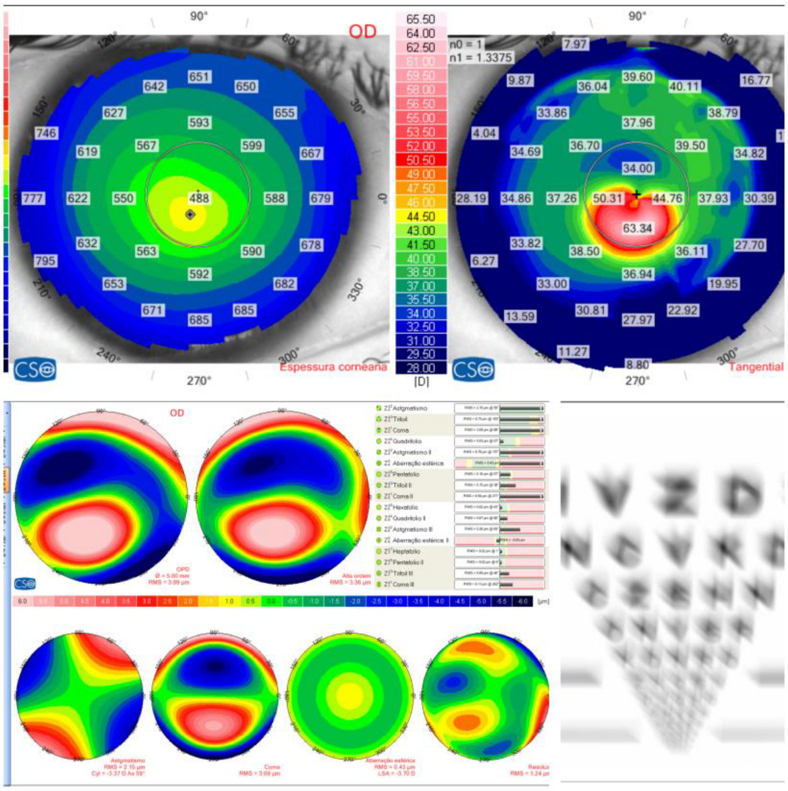

Figure 13. Corneal wavefront analysis of keratoconus (adapted from CSO.com)

In a healthy cornea, the corneal HOA represent 1% of the total ocular aberrations; Salmon et al. observed that in 2560 normal eyes, the RMS for total HOA was 0.33 ± 0.33 µm for a pupil diameter of 5 mm and the RMS for coma was 0.112 ± 0.068 µm[102]. When we observe HOA values higher than two standard deviations of the previously mentioned, we must carefully analyse the corneal topography in order to exclude a corneal ectasia; coma RMS values higher than 0.24 µm are suspicious of keratoconus[103].

A published work by Torres-Soriano et al. highlights the fact that the most important HOAs in keratoconus are the vertical coma (mean -1.215 µm) and the spherical aberration (mean -0.463 µm) for a 6.5 mm pupil diameter[104]. These results are similar to the values obtained by Maeda et al.; using a wavefront sensor Hartmann-Shack, they have demonstrated more prevalence of vertical coma and spherical aberration in eyes with keratoconus when compared to normal eyes[105]. Pantanelli et al. have demonstrated that HOAs are 5.5 times higher in patients with keratoconus or previous penetrating keratoplasty when compared to normal eyes, the vertical coma was predominant in keratoconus and trefoil in eyes with a previous corneal transplant[106]. These findings are coincident with other studies that have demonstrated that coma is the highest HOA in patients with keratoconus and that the increase in HOA in keratoconus is mainly due to the vertical coma[105, 107]. The CLEK study (Collaborative Longitudinal Evaluation of Keratoconus) takes into consideration the RMS value of HOA (6 mm) to classify the grade of severity of keratoconus[108].

3.2.5 a) Coma Aberration

The $Z3^{-1}$ and $Z5^{-1}$ are the coefficients that represent vertical coma in the Zernike polynomials diagram, they usually stand out from the others in patients in keratoconus, and they have the highest discriminative capacity between normal and keratoconus eyes[109, 110]; these findings suggest that the earliest manifestation of the corneal asymmetry is the vertical asymmetry, more than the toricity increase (figure 13). Alió et al. consider that the vertical coma HOA should be taken into consideration to classify the keratoconus in different grades of severity, they have found a significant correlation between the RMS value for coma (6.0 mm) and the mean keratometry of the different keratoconus grades according to the Amsler-Krumeich classification[107]. Gobbe et al. consider a suspicious value whenever the vertical coma RMS is higher than -0.116 µm and a confirmatory value if higher than -0.301 µm. The authors also analysed the RMS for total coma value; they consider it to be diagnostic of keratoconus if the value is above 0.512 µm. These cut-off values used to differentiate healthy eyes from keratoconus also positively correlate with the loss of visual acuity; they can also be used to classify and describe the loss of visual quality[109]. In a study by Buhren et al., vertical coma ($Z3^{-1}$) showed a sensitivity of 100% and a specificity of 93.8% for the diagnosis of keratoconus from values worse than -0.385 µm and a total coma RMS of 0.555 µm for a pupil of 6.0 mm[101].

3.2.5 b) Spherical Aberration

Spherical aberration can be described as the image degradation produced by a different refractive power between the center and the periphery of the cornea. When the peripheral rays converge behind the retina, spherical aberration is positive; when they converge in front of the retina, the spherical aberration is negative. In an average eye, to compensate for the ocular aberrations and improve the optical quality, it is necessary to have an optimal prolate shape cornea. If the cornea loses its natural prolate shape and its negative asphericity, it becomes oblate shape, and an increment of spherical aberration will occur, leading to the degradation of the optical quality of the image. The value of the Q factor varies according to the spherical aberration; when the Q value is more positive, the spherical aberration increases, on the other hand, when it becomes more negative the value of spherical aberration decreases. The increase in spherical aberration will clinically translate into the presence of halos and glare, which will be more intense in higher pupil diameters. This significant correlation between corneal asphericity and spherical aberration makes asphericity an essential parameter for keratoconus diagnosis and treatment planning[93]. However, as proposed by Maeda et al., the coma HOAs are 3.26 times higher than the spherical aberration in keratoconus and Pantanelli et al. suggest the same: vertical and horizontal coma are responsible for 62% of all HOA in keratoconus, trefoil 18% and the spherical aberration just 6%. The finding previously described is highly dependent on the location of the keratoconus apex; since in central keratoconus the spherical aberration is highly increased into the negative values and consistent with the increase of the central corneal curvature; while in keratoconus where the apex is displaced inferiorly, the vertical coma aberration and the astigmatism are predominant[111]. Depending on the location of the ectasia, one must consider a specific type of HOA, the optical properties of the cornea will vary in each of these clinical situations as well as the type of treatment to be considered[91].

3.3 Classifications of Keratoconus

Until today, there is no widely accepted universal classification of the disease grade of keratoconus. There are a wide variety of scales of disease, using a combination of objective and subjective parameters. Their primary role is to describe the disease in terms of severity, to allow an objective follow-up of patients in terms of eventual disease progression, and to indicate which cases should not be susceptible to any kind of surgical treatment rather than a penetrating keratoplasty. The main inconvenience is that they all assume that all parameters individually worsen as the disease progress, which is not always real.

3.3.1 Rabinowitz Classification

Rabinowitz was the first author to correlate topographic and clinical data to establish a simple classification(72):

- Keratoconus suspect: suspicious topographic data;
- Forme-fruste keratoconus: typical topographic data without other findings;
- Early keratoconus: typical topographic data with scissoring reflex on retinoscopy;
- Clinical keratoconus: typical topographic data, scissoring reflex, and clinical findings at the slit-lamp examination.

3.3.2 Amsler-Krumeich Classification

The Amsler-Krumeich classification is the most widely used classification, establishes four grades of disease severity, combining refraction, sagittal map keratometry, pachymetry, and clinical findings(98, 112):

- Grade 1: eccentric corneal steepening; myopia and/or astigmatism < 5 D; mean central keratometry readings < 48.00 D;
- Grade 2: myopia and astigmatism from 5.00 to 8.00 D; mean central keratometry readings < 53.00 D; absence of scarring, minimum corneal thickness > 400 μm;
- Grade 3: Myopia and astigmatism from 8.00 to 10.00 D; mean central keratometry readings > 53.00 D, absence of scarring, minimum corneal thickness from 300 to 400 μm;

- Grade 4: refraction not measurable, mean central keratometry readings > 55.00D, central corneal scarring, minimum corneal thickness from 200 to 300 μm.

While the Amsler-Krumeich scale is still the most widely used for staging purposes, two obstacles stand in the way of its current universal acceptance. First, it is increasingly being viewed as antiquated or outdated since it relies on relatively “old” indices (corneal steepness, refractive change, the presence of scarring). Second, newer grading schemes employ a variety of detailed metrics of corneal structure provided by AS-OCT or Scheimpflug tomography(108, 113, 114). Additionally, Amsler-Krumeich grades do not always correlate well with the disease impact; not uncommonly, an eye with low scores (indicating milder disease) may develop contact lens intolerance, resulting in reduced functional vision and significant disability. On the other hand, some eyes with high scores (indicating severe disease) may nevertheless remain contact lens tolerant and thereby continue to enjoy a relatively good functional vision with few complaints(115). These two factors combined – first, the growing number of alternative grading classifications; and second, the Amsler-Krumeich’s uncertain ability to predict the actual burden of the disease, have made the objective scoring of disease severity controversial, especially in moderate and advanced cases.

3.3.3 Amsler-Krumeich-Alió Classification

Corneal higher-order aberrations are the main responsible for the quality of vision degradation observed in keratoconus patients; the most important aberrations in keratoconus are irregular astigmatism, coma, and spherical aberration. The study of the total aberrations of the optical system is not easy in keratoconus, because most of the topography and aberrometry devices are not efficient and reproducible for these types of measurements.

Previously, it was possible to correlate the information obtained from the curvature map, the corneal elevation and the corneal power maps obtained by a corneal topographer, and to obtain the information about the magnitude of corneal higher-order aberrations of normal and irregular corneas of patients with keratoconus(116). Alió et al. found that the RMS for the coma and spherical aberration (at a 6.00 mm corneal diameter) constitutes an excellent clinical parameter to monitor and grade the severity of the disease, since the HOAs of the corneal surface were significantly higher in keratoconus than in normal individuals, especially the coma aberration, like previously mentioned by Maeda(105). The value of the RMS for coma increases as the disease progresses, and the RMS value of coma has a high positive correlation with the anterior curvature values and the stage of the ectasia according to the Amsler-Krumeich classification system. The authors have not found a good correlation between the coma and the pachymetry values, although they included the corneal thickness values in their final classification system[107].

- Grade I: central mean keratometry ≤ 48 D, RMS corneal coma between 1.5 and 2.0 μm, and absence of corneal scarring.
- Grade II: central pachymetry > 400 μm, mean central keratometry between 48 D and 53 D, RMS corneal coma between 2.5 and 3.5 μm, and absence of corneal scarring.
- Grade III: central pachymetry between 300 and 400 μm, mean central keratometry between 53 D and 55 D, RMS corneal coma between 3.5 and 4.5 μm, and absence of corneal scarring.
- Grade IV: central pachymetry ≤ 200 μm, mean central keratometry > 55 D, RMS corneal coma > 4.5 μm, and presence of corneal scarring.

3.3.4 CLEK study group classification

The CLEK study group classification is based on clinical biomicroscopic findings, the morphologic characteristics of the corneal topography map, and two topographic indices: the mean central corneal power (ACP: average corneal power) and the RMS value for total HOA[108]. The clinical signs detected at the slit-lamp examination are also taken into consideration for the classification of the disease; it considers the existence of Fleischer's ring, Vogt's striae, and corneal apex scars. In terms of topographic map analysis, the classification considers three patterns: normal, atypical (not keratoconus), and localized steepening (compatible with keratoconus).

The evaluation of the parameters described allows a classification based on five subgroups, based on the KSS index (Keratoconus Severity Score):

- KSS = 0 (no disease): normal axial topographic map, no slit-lamp findings, ACP < 47.75 D and RMS-HOA < 0.65 μm.
- KSS = 1 (atypical case): abnormal topographic map (irregular, asymmetric bow-tie, increased curvature < 3.0 D from the ACP value), no slit-lamp findings, ACP < 48.00 D and RMS-HOA < 1.00 μm.

- KSS = 2 (keratoconus suspect): inferior or central isolated corneal steepening, no slit-lamp findings, ACP < 49.00 D, and RMS-HOA between 1.00 and 1.50 μm.
- KSS = 3 (light): axial topographic map compatible, slit-lamp findings without corneal scarring, ACP < 52.00 D and RMS-HOA between 1.50 and 3.50 μm.
- KSS = 4 (moderate): axial topographic map compatible, slit-lamp findings with corneal scarring, ACP between 52.00 – 56.00 D and RMS-HOA between 3.50 and 5.75 μm.
- KSS = 5 (severe): axial topographic map compatible, slit-lamp findings with corneal scarring, ACP > 56.00 D and RMS-HOA > 5.75 μm.

There are some limitations to the current use of this classification, mainly the fact that it did not use modern corneal imaging methodology and does not take into account the posterior corneal surface data or corneal thickness map analysis, which are essential in detecting early or subclinical keratoconus(92).

3.3.5 ABCD Classification

Recently, a grading system known as *"Belin ABCD keratoconus Staging"* (Topometric/KC-Staging) has been presented based on the tomographic data and visual acuity to better describe both anatomical and functional changes seen in keratoconus(79, 80). The ABCD classification score developed by Michael Belin is based on Pentacam Scheimpflug tomographic data and clinical data (spectacle-corrected visual acuity.)

In this system "A", "B", "C", and "D", respectively, stand for the anterior radius of curvature in the 3.0 mm zone centered on the thinnest point (TP), the posterior radius of curvature in the 3.0 mm zone centered on the TP, corneal thickness at the TP, and the DCVA. It also has another variable that shows the presence or absence of corneal scarring. This system consists of 5 stages (stages 0-4), and each component is independently graded. For anterior corneal curvature, stages 1 to 4 are closely in agreement with the Amsler-Krumeich classification. The 3.0 mm zone used in this staging system corresponds to the exclusion zone used in the *"Belin-Ambrósio Enhanced Ectasia Display"* screening program for keratoconus and other corneal ectatic disorders. The reason for the choice of this region is that this zone contains the most ectatic areas compared with a single parameter, such as the point with the highest elevation or the point with the maximum curvature value(117). This new classification conveys both the anatomical and the functional data that is missing from the Amsler-Krumeich classification. It includes information on both anterior and posterior corneal surfaces, is centered on the thinnest point, which is typically the region of the cone and adds a visual acuity measurement as well as an indication of corneal scarring. It also may allow for more tailored treatment plans as different surfaces of the cornea may be more amenable to different medical or surgical intervention. Finally, another significant advance of this new classification system is that it was designed to study the progression of the disease based on several indexes generally accepted as crucial to evaluate the disease progression[92] (figure 14).

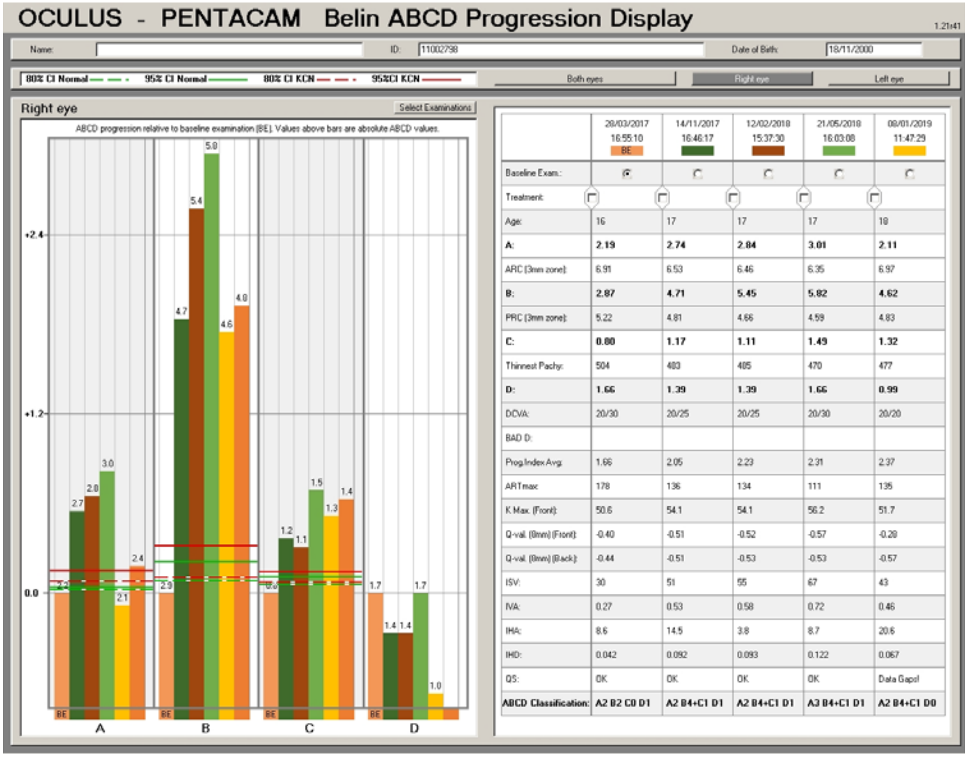

Figure 14. ABCD classification (clinical example of progression analysis, HB 92079674)

4. Keratoconus Treatment

4.1 Prevention and Medical Treatment

There is currently no medical treatment available capable of improving the shape of the cornea permanently; it is only possible to control and treat the clinical factors responsible for the development and progression of the disease. The objective of the medical treatment of keratoconus is to diminish the ocular surface inflammation through controlling allergy and dry eye; treating this inflammatory status enables the patient to avoid frequent eye rubbing. The current medical treatment available was developed for allergic patients; however, there is no clinical study published to prove its efficacy. The disease develops earlier in patients with allergy, and its progression is also more aggressive, with a higher risk of developing corneal hydrops[39]. Because of this background, it is important to investigate the clinical history of allergies, to treat them aggressively and fully avoid eye rubbing. Medical treatment includes ocular surface lubrication and the elimination of different allergens with the use of unpreserved cold artificial tears. Also recommended is the use of topical anti-allergic medications (mainly anti-histamine eye drops), which are the mainstay of allergy treatment. Recently, it has been proposed that the use of topical calcineurin inhibitors (like cyclosporine or tacrolimus) could have an important role in controlling the ocular surface inflammation and in improving the corneal innervation. A recent work published about the tears and the corneal epithelium of keratoconus patients has demonstrated a decrease of the inflammatory marker MMP-9 after the topical use of cyclosporine[118]. The author also demonstrates that the application of topical cyclosporine-A could, apart from controlling the inflammatory markers, improve the corneal topographic indexes of patients with keratoconus, promoting a decrease in the values of maximum keratometry observed in the anterior axial curvature map. Patients with uncontrolled systemic allergy should consult with a general physician in order to improve the systemic disease, to consider the use of oral anti-histamine medication and to suggest hygiene protocols that could minimize or eradicate the episodes of allergy. It is also advisable to use topical steroid medication for short periods of time to eradicate the inflammation associated with allergy; the use of steroids is helpful to improve the efficacy of allergy treatment but should be limited in time because of their local side effects. It has been previously published that the use of topical corticosteroids in rabbits produces a reduction of 34% in corneal rigidity[119], this should alert the clinician for the chronic use of these medications in keratoconus patients.

The use of contact lenses in keratoconus is a good option for their visual rehabilitation, especially in situations where the use of rigid lenses enables the correction of irregular astigmatism and corneal HOA, which is not possible with standard spectacle use. As progressive keratoconus is characterised by increasing degrees of higher-order optical aberrations, in particular the vertical coma, the major shortcoming of traditional soft contact lens correction is the limited capacity to mask irregular astigmatism. Given such limitations, traditional soft contact lenses are only regarded as a relevant potential mode of visual correction for forme-fruste and early forms of keratoconus[120, 121]. Rigid contact lenses, both before and since the availability of gas-permeable materials, have been the major refractive non-surgical correction modality of keratoconus[122, 123]. Through maintaining their conformation on the eye, rigid contact lenses create a thin lacrimal lens between the irregular anterior corneal surface and the posterior lens surface that neutralises most of the corneal astigmatic error and will necessarily normalise most of the higher-order corneal aberrations[124, 125]. Rigid lens classification is usually based upon differences in total diameter, although the terminology can vary: corneal lenses are defined as having a diameter of 7.0 to 12.0 mm, corneoscleral lenses with a diameter of 12.1 to 15.0 mm, mini-scleral lenses with a diameter of 15.1 to 18.0 mm and scleral lenses with a diameter over 18.0 mm. As recently as ten years ago, corneal lenses were the most common form of rigid lens used for keratoconus. Although the use of scleral lenses was becoming highly infrequent, continuing the trend of the previous 20 to 30 years, contact lens practice witnessed the re-emergence of the larger diameter rigid lens modalities, in the form of corneo-scleral and mini-scleral lenses. Over the last decade, the use of these alternative shape rigid lenses for the contact lens management of keratoconus has increased significantly due to associated advantages of larger diameter contact lenses, which include decreased lens awareness, more patient comfort, and enhanced on-eye stability[47].

However, the use of soft or rigid contact lenses does not slow or stop the eventual progression of the disease; and in some cases, the ocular surface inflammation elicited by an improperly fitted lens can induce clinical progression of the disease. Several biomarkers of inflammation have been previously correlated with the use of contact lenses in normal and keratoconus patients. The corneal epithelial trauma generates the production and liberation of interleukins; this could elicit a progression of the disease in patients with contact lens use, uncontrolled allergy, or eye rubbing[54]. Pro-inflammatory markers like IL-6, ICAM-1, and V-CAM 1 were found to be over-expressed, while the anti-inflammatory marker IL-10 was under-expressed in patients with keratoconus that normally use contact lenses when compared to normal myopic patients[55]. This finding suggests that the use of contact lenses could be a precursor of the disease development; patients who wear contact lenses could be more vulnerable to the previously mentioned corneal epithelial micro-trauma or to eye rubbing episodes.

In summary, keratoconus corneas have increased oxidative damage compared to normal or other corneal diseases. Therefore, with keratoconus patients, it may be prudent to minimize the trauma and insults to their corneas. Sources of reactive oxygen species include ultraviolet light (UV), mechanical trauma (vigorous eye rubbing, poorly fit contact lenses), and atopy/allergies. Efforts should be made to improve patient comfort in order to minimize eye rubbing; it should be mandatory to regularly use preservative-free artificial tears, allergy medications, and limited periods of steroidal anti-inflammatory drugs. While the CLEK study has explored many aspects of the natural history of the disease[126] and continues to investigate the fitting of contact lenses in these patients, it should be advisable to make an effort to minimize trauma to the corneas of keratoconus patients; so, proper contact lens fitting with a trained and experienced ophthalmologist or optical technician is mandatory.

4.2 Corneal Collagen Cross-Linking

In recent years, corneal collagen crosslinking (CXL) treatment has been introduced as a minimally invasive treatment option to stop the progression of keratectasia, and it has revolutionized the treatment of keratoconus and other corneal ectasias including pellucid marginal degeneration (PMD) and iatrogenic ectasia. Crosslinking is the process of formation of chemical bridges following chemical reactions between proteins and other molecules[(127)]. Crosslinking occurs naturally within corneas during the aging process, the collagen fibrillary diameter increases by 4.5 % over a person's lifetime due to age-related glycosylated crosslinking[(128, 129)]. Strengthening of the corneal collagen by crosslinking was initially described in the 1990s by researchers at the University of Dresden, Germany. After extensive investigations, collagen CXL with riboflavin and UVA light was introduced as an effective treatment mode for keratoconus[(130, 131)]. CXL treatment is the only minimally invasive surgical procedure in current practice that has been proposed to halt the progression of keratoconus and is considered the "gold standard" procedure to halt the progression of keratoconus[(132-134)]. Several techniques have been developed in the past decade to increase the efficacy of CXL. The conventional Dresden protocol (C-CXL), accelerated corneal crosslinking (A-CXL), corneal epithelium-on/transepithelial (T-CXL) techniques using chemical enhancers, and iontophoresis crosslinking techniques (I-CXL) are some of the commonly used and currently investigated procedures in clinical practice. Wollensak et al. introduced the Dresden protocol in 2003 as a treatment option for keratoconus[(131)]. The classical technique involves the removal of the corneal epithelium followed by the application of riboflavin solution (0,1 % riboflavin in 20 % dextran solution) to the deepithelized cornea for 30 minutes; the cornea is then UVA irradiated (wavelength 370 nm and power 3mW/cm^2 or 5,4 J/cm^2) for another 30 minutes (figure 15). The riboflavin solution is applied every 3-5 minutes during the irradiation process.

All the new techniques of CXL try to overcome some of the limitations of the classical C-CXL, such as the prolonged treatment time, and the complications associated with corneal deepithelization techniques like postoperative pain, corneal scarring, infectious keratitis and corneal melt or perforation[(135-137)].

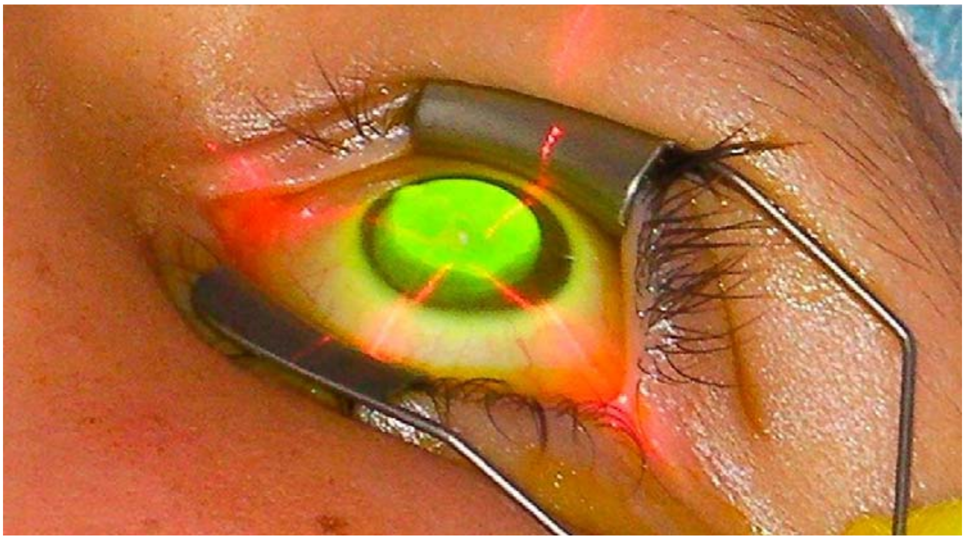

Figure 15. Collagen cross-linking (adapted from keratoconuscenter.com

Corneal collagen crosslinking appears to be capable of arresting the progression of ectatic corneal disorders, with most studies reporting significant improvements of visual, keratometric, and topographic measurements. The current follow-up is limited to 5-10 years but suggests sustained stability and enhancement in corneal shape with time[138-140]. Nearly all published long-term data, and comparative studies are with epithelium-off techniques. Epithelium-on investigations suggest some efficacy, but less than with epithelium-off treatments and long-term data are so far unavailable[141].

Even though the efficacy of CXL to arrest the disease progression is very high, it is also evident that the corneal topography regularization obtained in the majority of patients is insufficient to promote an effective visual rehabilitation[133, 142]. A significant limitation of corneal collagen crosslinking, when compared with other surgical treatments of keratoconus, is the limited visual acuity improvement observed in most long-term studies. Most of the authors report on a mean gain of 0.10 to 0.15 logMAR corrected visual acuity[143-145], which can be a limitation, especially in terms of binocular visual rehabilitation of the patient, and even more critical if the technique is applied to moderate cases of keratoconus, where spectacle visual acuity is already very low before treatment. The limited visual acuity improvement associated with CXL is the reason why in recent years, several authors have reported the outcomes of combining CXL as a stabilizing treatment with intracorneal ring segments (ICRS) implantation or photorefractive keratectomy (PRK) treatments as a refractive enhancement of the technique. Currently, the most widely used combination protocol associates CXL with PRK: the application of a topography-guided corneal ablation profile decreases the irregular corneal astigmatism and the HOAs, while at the same time the CXL strengthens the corneal tissue[146-148]. Most authors perform both procedures simultaneously: first perform a partial PRK ablation (limited to 70% of astigmatism and sphere, with a maximum of 50 μm of tissue ablation), immediately followed by the CXL procedure. The possibility to associate CXL with ICRS implantation has also been previously published; visual acuity results are better than CXL alone; the question remains about the correct timing and sequence of both procedures[149, 150]. The most logical sequence would be to first implant the ICRS, regularize the cornea, and in a second procedure, apply the CXL procedure to offer stability to the previous treatment. However, there is no consensus about the correct sequence of treatment in the most recent published papers[151-153]; a recent meta-analysis has published relatively similar results with this combination, regardless of the sequence of treatments used[153].

In summary, CXL is the most effective surgical treatment to halt the progression of the disease; however, due to its limited capacity to improve the corneal HOA and the visual acuity, its main indication should be younger patients with a recently diagnosed keratoconus and good visual acuity with spectacle correction. Its application in moderate or advanced disease has a very limited utility since the recovery of the visual function will be null, and because in such cases, there is a higher incidence of postoperative complications related to the procedure[154].

4.3 Intrastromal corneal ring segments

4.3.1 Historical Evolution: from complete rings to segments of a ring

The implantation of ICRS is included in the category of corneal additive surgery; the objective is to restore the regular geometry of the cornea and correct irregular astigmatism associated with certain corneal diseases. This statement was made based on the *"Barraquer Law of Thickness"*; which proposes that when a material is added to the periphery of the cornea or the same amount of material is removed from the center of the cornea, a flattening of the central cornea is achieved[155]. Initially, in 1953, Stone et al. published the first results about the use and biocompatibility of the PMMA material inside the corneal stroma[156]; posteriorly, Belau et al. have confirmed their long-term biocompatibility[157]. The idea of implanting a ring segment inside the corneal stroma in order to change the corneal curvature was from Blavatskaia in 1966; he reported on the first implants of peripheral intracorneal rings in humans, targeting potential changes in refraction[158]; the results with a complete 360° ring were not satisfactory, mainly due to postoperative healing complications. Later, further improvements included changes in geometry (different arc lengths and heights, adjustable rings) and materials (synthetic gels or rigid materials)[159]. The first implants made of PMMA were published by Reynolds and later by Fleming in 1987[159], with the objective of myopia correction. The unsatisfactory results with the complete 360° ring led to the creation of the ring segment of 150° with a hexagonal morphology. In 1987, intrastromal corneal ring segments were proposed to achieve refractive adjustment by flattening the cornea. At the same time, in Brazil, Paulo Ferrara creates a similar ring but with a pyramidal shape, with an idea of better correcting astigmatism. In 1986, Ferrara initiated the first implants of the modified ring of PMMA produced by Mediphacos®, in rabbit corneas. In 1991, Ferrara implanted the first 360° degree triangular shape ring in an unsighted human eye, through a lamellar cut performed by a microkeratome. In the same year (1991), Nosé et al.[160] published his first experiences with the PMMA implants in human corneas. Due to the high rates of extrusions related to the lamellar pocket, Ferrara decides to divide the complete ring into two 160° segments and develops a new technique for the implantation of the segments inside a stromal tunnel, avoiding the mechanical complications associated to the microkeratome pocket. In 1995, he reported on the first results of the 160° arc length ICRS, which he used in patients with keratoconus that were on the waiting list for a corneal penetrating keratoplasty. The ICRS implanted at that time had an apical diameter of 5.0 mm (4.4 mm internal diameter, 5.6 mm external diameter), 160° arc, triangular transversal shape, and a base of 600 μm. These two Brazilian doctors were the main developers of this type of surgical technique in the decade of the 90's[161, 162].

Intrastromal corneal ring segments were lately developed and FDA-approved in 1999 for the treatment of low myopia but were quickly overshadowed by laser refractive procedures. Interest in ICRS resurfaced in Europe when Prof. Joseph Colin reported their usefulness in treating mild to moderate keratoconus in 2000[163]. Currently, all the implanted ring models are made of polymethylmethacrylate (PMMA), have a triangular or hexagonal shape, and are available in several dimensions[164].

4.3.2 ICRS models

a) ICRS Hexagonal shape

The ICRS of hexagonal shape was the first to be developed, in 1990. They are represented by the Intacs® (Addition Technology, USA), and their first approved indication was the surgical treatment of low myopia(165). They are made of PMMA, have two different models regarding the diameter and transversal section (figure 16).

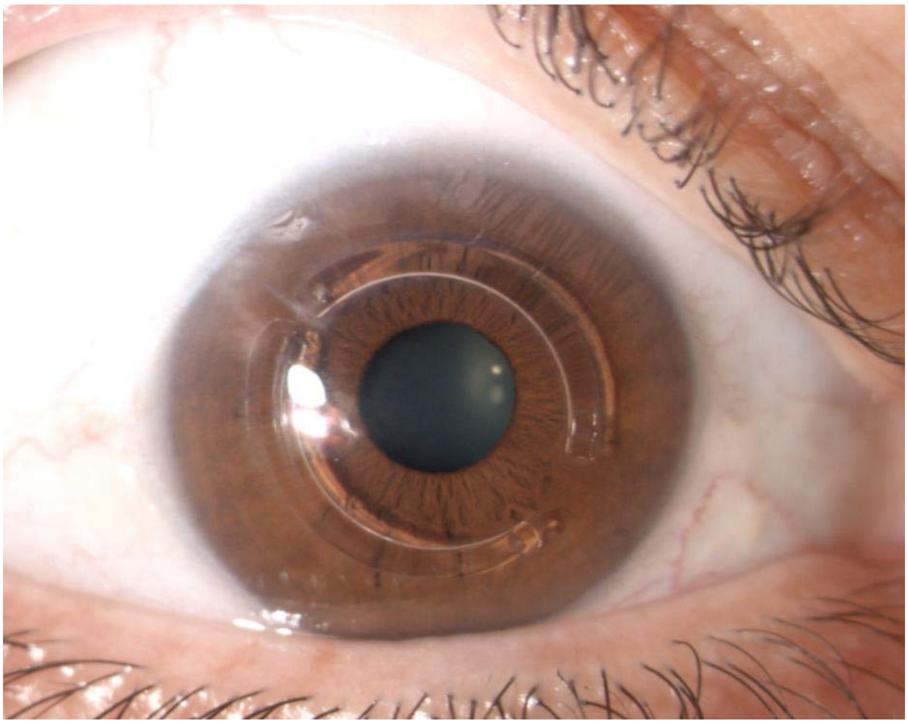

Figure 16. Intacs ICRS, slit-lamp image of a patient (HB 1101702)

Intacs® Optical Zone 7,0 mm

Represent the original model, have an internal diameter of 6,80 mm and an external diameter of 8,10 mm, they occupy an optical zone between 7,0 and 8,0 mm. The arc lengths available are 150° and 210°, thickness models of 250, 300, 350, 400 and 450 μm. Their lateral profile resembles the corneal shape, having an angulation of 25 degrees.

Intacs® SK (Severe Keratoconus) Optical Zone 6,0 mm

In 2007, a new Intacs model was presented, designated as SK from “severe keratoconus”. These ICRS have a new elliptical/oval section, arc lengths of 90°, 130°, and 150°; thickness models of 250, 300, 350, 400, 450, and 500 μm.

b) ICRS Triangular Shape

The ICRS of triangular section is generally known as Ferrara ICRS (figure 17). Several companies produce this type of ICRS; the most significant are FerraraRing® from AJL (Spain) and Keraring® from Mediphacos (Brazil).

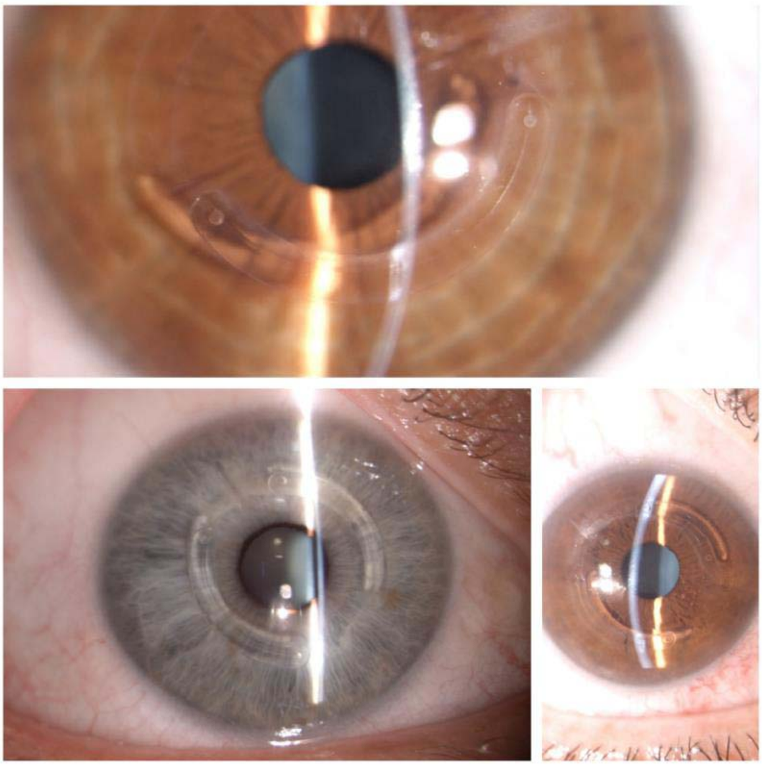

Figure 17. Ferrara ICRS, slit-lamp clinical examples (HB 29004615, HB 654345719)

FerraraRing® (AJL, Spain)

Ferrara ICRS is made of PMMA; they have the option of being made with a yellow filter. These ICRS have two different diameters; and a prismatic profile to help reducing the mesopic halos and glare reported by some patients:

- 5,0 mm diameter: isosceles morphology, base of 600 μm and a truncated apex.
- 6,0 mm diameter: scalene morphology, base of 800 μm and a truncated apex.
- The arc length varies from 90° to 300°, thickness profile ranging from 150 to 300 μm (50 μm steps).

Keraring® (Mediphacos, Brazil)

Made of PMMA, no yellow filter available. Also two optical zone models:

- Model SI-5: optical zone 5,0 mm.
- Model SI-6: optical zone 6,0 mm.

The arc lengths available for the SI-5 model are 90°, 120°, 160°, and 210°; for the SI-6 model 90°, 120°, 150°, and 210°. For all models, thickness ranges from 150 to 350 μm in 50 μm steps. Recently, two new models were made available: one with an arc length of 355° for an optical zone of 5,00 mm (thickness from 150 to 350 μm) and another with a 340° arc length for an optical zone of 5,0 mm (thickness of 200 or 300 μm).

c) ICRS Convex-Concave Shape

The Myoring® is also made of PMMA but has a complete ring design; it is inserted in a corneal pocket inside the corneal stroma (figure 18). The ring arc varies from 5,0 to 8,0 mm, and the thickness ranges from 200 to 400 μm. The anterior surface is convex, and the posterior surface is concave; this morphology allows its manipulation with forceps in order to implant it inside the corneal pocket. The surgical technique, named CISIS, consists of the creation of an intrastromal pocket of 9,0 mm diameter and 300 μm of depth, it can be obtained manually with a diamond blade *"PocketMaker Ultrakeratome"* (DIOPTEX GmbH, Austria) or assisted with a femtosecond laser.

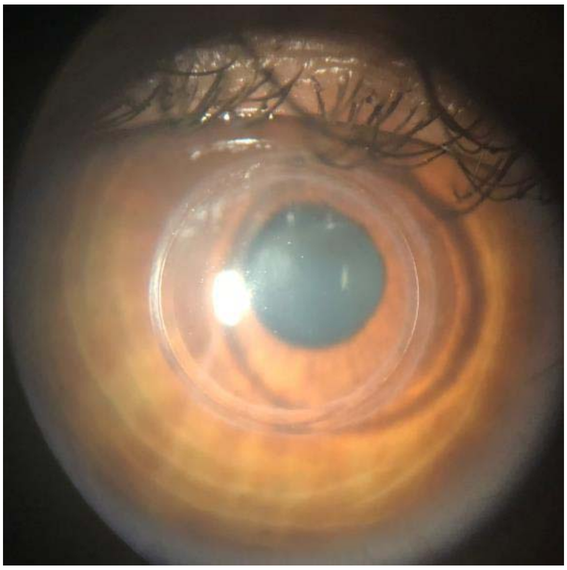

Figure 18. Myoring implant, slit-lamp clinical example (HB 11458675)

Mahmood et al. and Daxer et al. published the earlier results obtained with this type of implant in patients with keratoconus[166, 167]; lately, Alió et al. have reported on the outcomes of the same implant but using a surgical technique assisted by a femtosecond laser, confirming a significant reduction in the central mean keratometry and mean corneal asphericity values[168].

4.3.3 ICRS mechanism of action

a) Theoretical proposition

Currently, it is accepted that the tension originated in the corneal stroma by the volume occupied by the implant and its profile, induces the correction of the corneal irregularity and astigmatism. The tension produced at the implant extremities induces the flattening of the adjacent corneal meridian and an increase in corneal curvature in the opposite corneal meridian, the one that is parallel to the center of the implant. Because of this physical action on the cornea, the center of the ICRS should be implanted in the flattest corneal axis, inducing the applanation of the steepest corneal axis. This concept, applied to the correction of keratoconus, enables the ICRS to flatten the central cornea, decrease corneal astigmatism and reduce the corneal HOA, namely the coma. There are other factors responsible for the mechanism of action of the ICRS. Published evidence indicates that the transversal design of the implant influences the clinical result[169]; the higher the ICRS thickness or, the lower the arc length, a higher tension will be exerted on the corneal stroma, producing more effect in the astigmatism correction; the lower optical zone (5,0 mm) also results in a higher effect of the implant in the central cornea[170].

Intrastromal corneal ring segments act as passive spacing elements that shorten the arc length of the anterior corneal surface and cause displacement of the collagen fibers, resulting in flattening of the cornea in myopic eyes. Working at a deeper corneal depth, the ICRS presents no anterior lamellar effect and causes a steepening of the meridian of implantation and flattening of the perpendicular one. The primary explanation for this differential response is associated with mechanical action. The ICRS acts by pushing and redistributing the corneal tissue, forcing the lamellae to detour around the ring and causing a small local bump (Figure 19). As a consequence of this effect, the central portion of the anterior corneal surface tends to flatten, and the peripheral area adjacent to the ring is displaced forward[159, 171]. The *"Barraquer Thickness Law"*[155] can roughly predict the induced change in corneal shape after the additive device implantation, whereby the outcome achieved is directly proportional to the thickness of the ICRS and inversely proportional to the diameter[165, 172, 173]. When a comparable amount of material or tissue is either added to the periphery of the cornea or removed from the central cornea, a resultant flattening effect is achieved.

Figure 19. High-resolution OCT image of a cornea with two symmetric ICRS (HB 40369658)

Although the mechanism of action of ICRS is well documented in myopic eyes, the structural alterations responsible for topographic homogenization of ectatic corneas after ICRS implantation are not fully understood[174]. The response of the ectatic cornea to a prosthesis appears to be more complex, and this variable response is hypothesized to be due to the non-orthogonal lamellar architecture of these corneas[175, 176]. The refractive results achieved with ICRS implantation in ectatic eyes are independent of patient age[177]. They are thought to be due to a reduction in HOAs[178, 179], central and peripheral corneal flattening, anterior chamber depth shortening, and corneal apex displacement to a more physiologic location via a reduction in paracentral ectasia[174]. Intrastromal corneal ring segments do not appear to alter the corneal viscoelastic biomechanical properties[180, 181].

b) Clinical evidence

b.1) Transversal section

The ICRS of triangular shape and flat base produce a higher effect on the correction of astigmatism when compared to the hexagonal shape ICRS[169]; this is probably explained by the fact that the triangular shape ICRS exert more tension on the corneal stroma because their morphology does not follow the natural shape of the cornea. Following this conclusion, a similar refractive effect can be accomplished with triangular shape ICRS using thinner implants.

The hexagonal shape ICRS correlate better than the triangular shape ICRS with the *"Barraquer Thickness Law"*, and they accomplish a better result in terms of myopia correction. It can also be observed; using high-resolution OCT images, that the triangular shape ICRS produces a higher effect of torsion in the posterior surface of the cornea when compared to the hexagonal implants (figure 20).

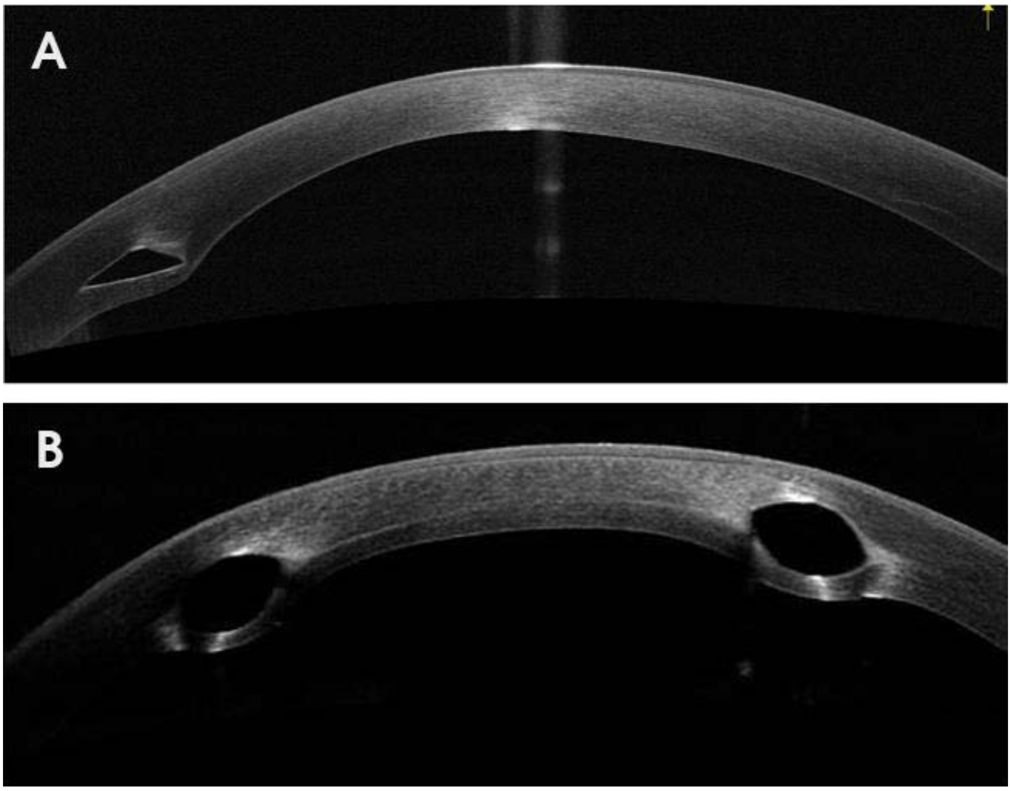

Figure 20. Transverse OCT images of ICRS; top image with a triangular shape ICRS (HB 40160908); bottom image with an hexagonal ICRS (HB 29004615)

b.2) Thickness

It is necessary to understand that the biomechanical theory applied to the ectatic corneas does not correlate perfectly with the effect produced by the same implants in normal corneas for the correction of myopia.

Barraquer has defined the *"Barraquer Thickness Law"* based on the relationship between thickness and corneal curvature: when one modifies the corneal thickness at the anterior two thirds, the anterior surface steepens if tissue is added in the center or removed from the periphery; on the opposite, the cornea flattens if tissue is subtracted from the center or added at the periphery[182]. Blavatskaia[158], in a study based on intralamellar ring-shaped homotransplants, confirmed the idea that as higher the amount of tissue added to the periphery of the cornea, the higher the applanation created in the center of the cornea. Burris et al.[173] confirmed in an eye-bank study that the previous clinical evidence could be applied to intracorneal ring segments. The previous findings explain the correction of higher degrees of myopia obtained with the implant of two symmetric ICRS of higher thickness in normal corneas, and also the higher astigmatism correction obtained in keratoconus corneas if a thicker ICRS is used.

b.3) Arc length

The clinical evidence available about this topic is sole that the smaller the arc length in degrees, the higher the correction of astigmatism. From a biomechanical point of view, the tension produced in the corneal stroma is higher if the two extremities of the implant are close to each other. The higher arc lengths of 210º or above have a higher impact on mean central keratometry and asphericity and a lower impact on the corneal asymmetry, coma, or astigmatism[170, 183].

b.4) Diameter (optical zone)

In general, the lower the ICRS diameter or optical zone, the more the applanation effect will be concentrated in the central cornea; this is the explanation to use ICRS of 5,0 mm optical zone in central keratoconus cases. This theory was previously proved by Blavatskaia[158]: a lower implant optical diameter produces a higher refractive correction. In general, smaller optical zones (5,0 mm) produce a higher incidence of dysphotopic phenomena, while larger optical zones (7,0 mm) originate inflammatory reactions at the corneoscleral limbus. It is because of these clinical side effects that most of the surgeons choose the 6,0 mm optical zone as the preferred diameter of implantation for most of the clinical situations.

b.5) Depth of implantation

The intrastromal corneal depth for ICRS implantation was empirically established to be around 70 to 80% of the minimum corneal thickness measured at the optical zone of the implant; however, no other options were studied or published. In manual mechanical dissection, the corneal depth is calculated for 80% while in the femtosecond laser-assisted surgery, the treatment is programmed for 70%. The rationale behind it is based on the fact that most of the mechanical complications related to intrastromal implants are associated with shallow implantation near the superficial stroma; in theory, the objective is to achieve the posterior third of the corneal depth in order to place the intrastromal segment safely.

In cases of shallower intrastromal tunnels, the refractive clinical effect can be higher, but a higher risk of spontaneous implant extrusion is also associated. The corneal epithelium above the area of the ICRS thins after surgery, and the adjacent epithelium thickens, in an attempt to compensate for the stromal torsional effect of the implant and the subsequent change in the corneal curvature in the anterior surface. (figure 21). This fact is also the motive for the epithelial keratitis and melting that ultimately leads to spontaneous extrusion in cases of shallow implants[184].

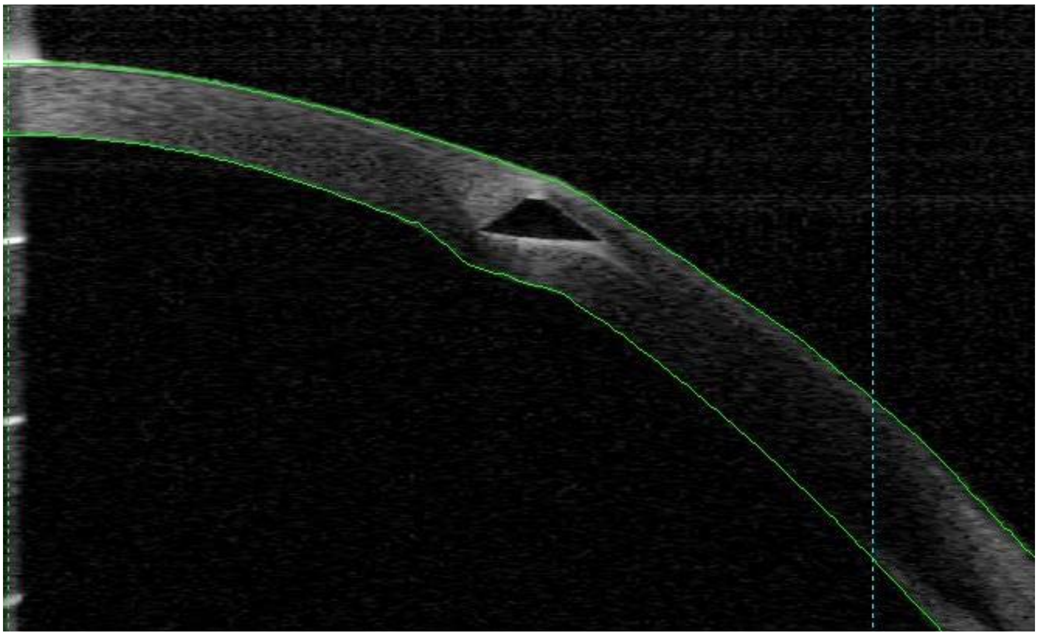

Figure 21. High-resolution OCT image of a shallow ICRS (clinical example, HB 40022449)

b.6) Intrastromal tunnel width

As the tunnel depth influences the clinical results, the width of the tunnel might also impact on the mechanical effect of the implant inside the corneal stroma. It could be predicted that a wider tunnel could induce a weaker effect of the ICRS in the stroma; and that a narrow tunnel would help the implant to exert a higher tension force in the corneal stroma, and subsequently, a higher clinical effect. The width of the tunnel is always the same in the manual mechanical technique; it can only be programmed and changed in the surgical cases assisted by a femtosecond-laser device. However, the clinical evidence published about this aspect is neither clear nor indicative of a clinical benefit of this type of personalization of the tunnel width[179, 185].

b.7) Stromal reaction

The ICRS produces a scarring reaction in the corneal stroma; this reaction helps to stabilize the initial tensional effect in the long-term. After the initial biomechanical effect, there occurs a biological effect secondary to scarring processes, and these phenomena maintain the corneal shape stable after surgery during a long-term period[186, 187]. It has been demonstrated the transformation of the keratocytes into fibroblasts and myofibroblasts, which help in anchoring and fixating the implant inside the cornea (figure 22).

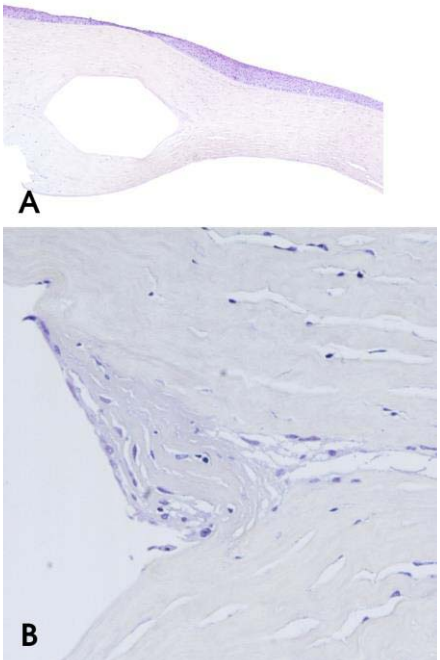

Figure 22. Histopathology of a cornea after ICRS (adapted from: Samimi, S., et al. (2007). "Histopathological findings after intracorneal ring segment implantation in keratoconic human corneas." J Cataract Refract Surg 33(2): 247-253.)

Intrastromal corneal ring segments appear to be highly biocompatible[188], with confocal studies showing typically normal corneal images from all corneal layers including healthy epithelial cells, an intact corneal nerve plexus, normal keratocyte distribution, and an undisturbed endothelial morphology in most individuals[189, 190]. A recent study[191], analysing explanted ICRS with scanning electron microscopy has revealed that, in cases of ICRS explantation for refractive failure, the surfaces of all ICRS were clean; that is, there was no cell debris or exopolysaccharide on either end of or along the segment (figure 23.1). Scanning electron microscopy analysis of ICRS provides information on the biocompatibility of the ICRS material in the stroma. The results of the above-mentioned study found no inflammatory material on the surface of any ICRS explanted for refractive failure, showing the biocompatibility of the PMMA in the area of ICRS implantation. However, in the case of ICRS extruded due to mechanical complications, the same study has found the presence of cell debris and cells on the surface of the ICRS (figure 23.2).

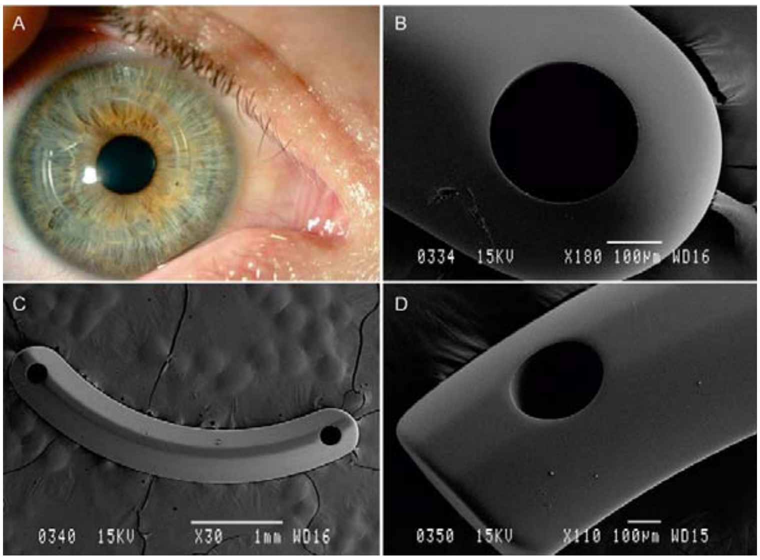

Figure 23.1. Histopathology findings after ICRS explantation for refractive failure (adapted from: Ferrer, C., et al. (2010). "Causes of intrastromal corneal ring segment explantation: clinicopathologic correlation analysis." J Cataract Refract Surg 36(6): 970-977.)

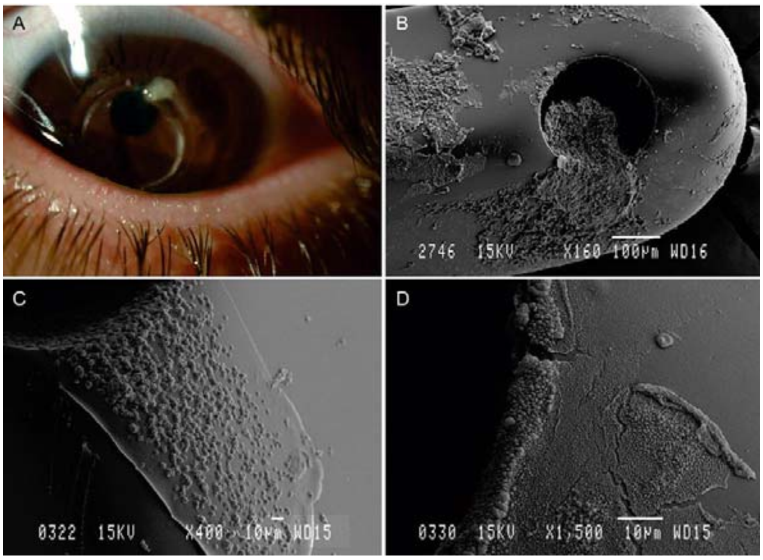

Figure 23.2. Histopathology findings after spontaneous ICRS extrusion (adapted from: Ferrer, C., et al. (2010). "Causes of intrastromal corneal ring segment explantation: clinicopathologic correlation analysis." J Cataract Refract Surg 36(6): 970-977.)

b.8) Surgical technique

Both the safety and the refractive efficacy of the surgical procedure depend on the correct selection of the implant features and a precise intrastromal surgical implantation. Shallower intrastromal tunnels are associated with complications such as implant exposure due to corneal thinning over the implant, segment migration, and extrusion (figure 24.1 and 24.2), astigmatism overcorrection, or corneal melting(192-194).

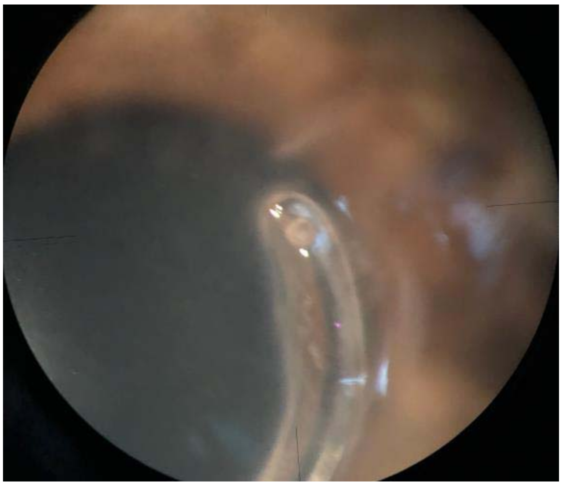

Figure 24.1 ICRS extrusion, slit-lamp clinical example (HB 29012580)

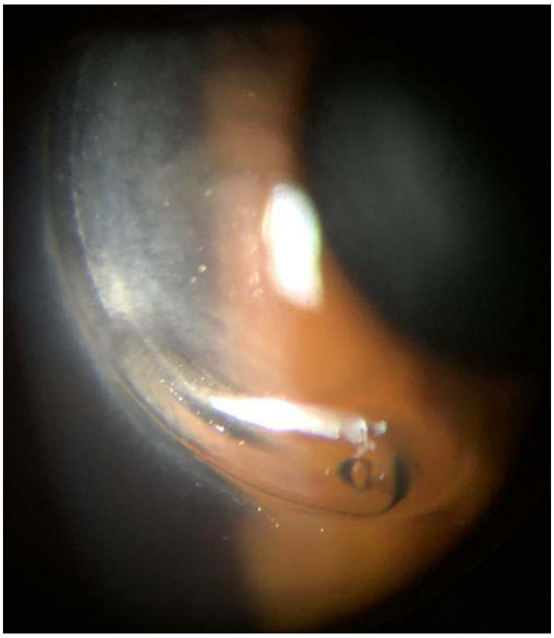

Figure 24.2. ICRS extrusion, slit-lamp clinical example (HB 40035056)

Deeper tunnels can be associated with posterior corneal perforation (figure 25.1 and 25.2) or endothelial cell damage and a minor refractive and topographic effect on the cornea[195]. Therefore, a precise and predictable tunnel depth creation is crucial for this surgical procedure. Currently, there are two types of surgical techniques in order to implant the ICRS inside the corneal stroma: a manual mechanical technique and a femtosecond-laser assisted technique.

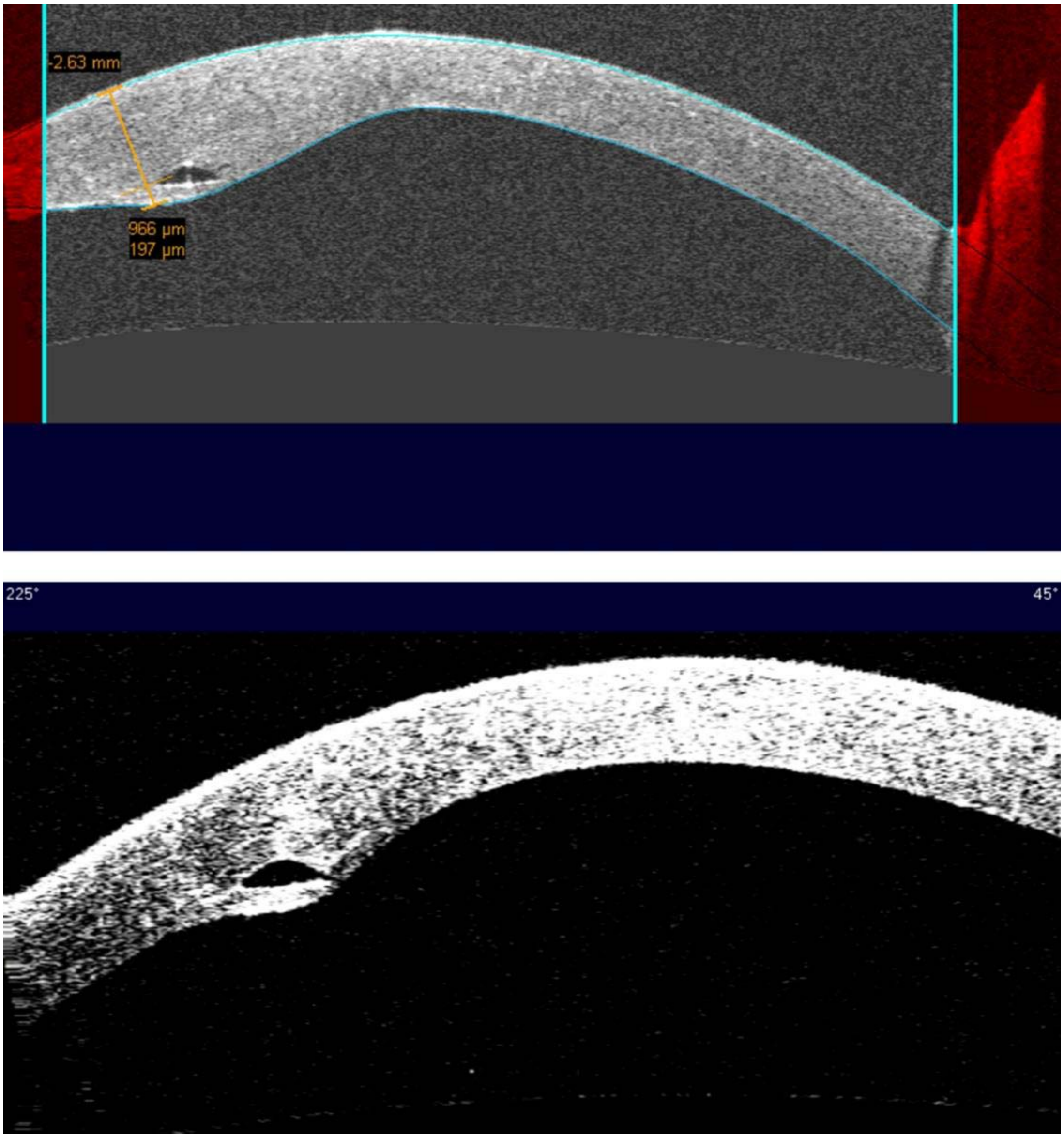

Figure 25.1. OCT image of a posterior corneal rupture, clinical example (CUFP 380337)

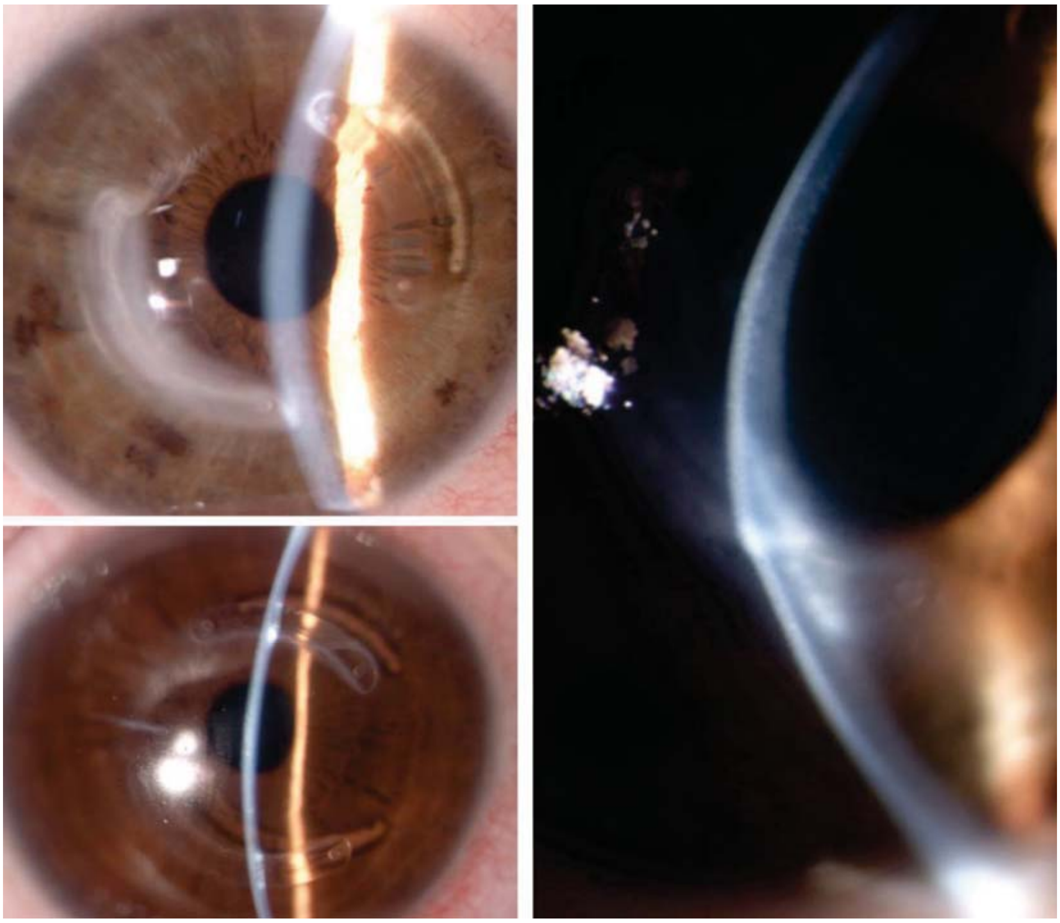

Figure 25.2. Endothelial rupture after ICRS, slit-lamp clinical examples (HB 434652, HB 227932)

In the manual mechanical technique, the visual axis is marked by pressing the Sinskey hook on the central corneal epithelium while asking the patient to fixate on the corneal light reflex of the microscope light. Using a marker tinted with gentian violet, a 5.00 or 6.00 mm optical zone is chosen, and the incision site is aligned to the desired axis in which the incision will be made. The incision site is normally performed at the steepest topographic axis of the cornea given by the topographer. A square diamond blade is set at 80% of the thinnest point along the implantation optical zone track; this blade is used to make the incision. Corneal thickness is measured intraoperatively with ultrasonic pachymetry. Using a "stromal spreader", a pocket is formed on each side of the incision. Two (clockwise and counter-clockwise) 270° semi-circular dissecting spatulas are consecutively inserted through the incision and gently pushed with some quick, rotary "back and forth" tunnelling movements. Following channel creation, the ring segments are inserted using a modified McPherson forceps. The rings are then adequately positioned with the aid of a Sinskey hook.

In femtosecond laser-assisted surgery, the center of the pupil is marked, the corneal thickness at the area of implantation (5.0 or 6.0 mm diameter) is measured with ultrasonic pachymetry, and a disposable suction ring is centred on the pupil. A tunnel is subsequently created at 70% of the corneal thickness, using a 60-kHz to 100-kHz infrared neodymium glass femtosecond laser at a wavelength of 1053 nm. Computer scanners optically focus the 3-mm diameter (spot size) laser beam at a predetermined intrastromal depth ranging from 90 to 400 mm from the anterior corneal surface. The beam forms cavitations and water vapour by photodisruption, with an interconnected series of microbubbles of carbon dioxide forming a dissection plane. The laser software is programmed to an inner diameter of 5.0 or 6.0 mm and an outer diameter of 6.0 to 7.2 mm for a channel width of 1.1 mm and an incision length of 1.7 mm on the steepest topographic axis. The power used to create the channel and the incision is 5 mJ in all eyes. This part of the procedure lasts approximately 15 seconds. The ICRS are implanted immediately after, under the laser microscope, with a dedicated forceps, and under fully aseptic conditions. The segments are placed in their final position with the aid of a Sinskey hook that engages the two positioning holes, one at each end of the segment (figure 26).

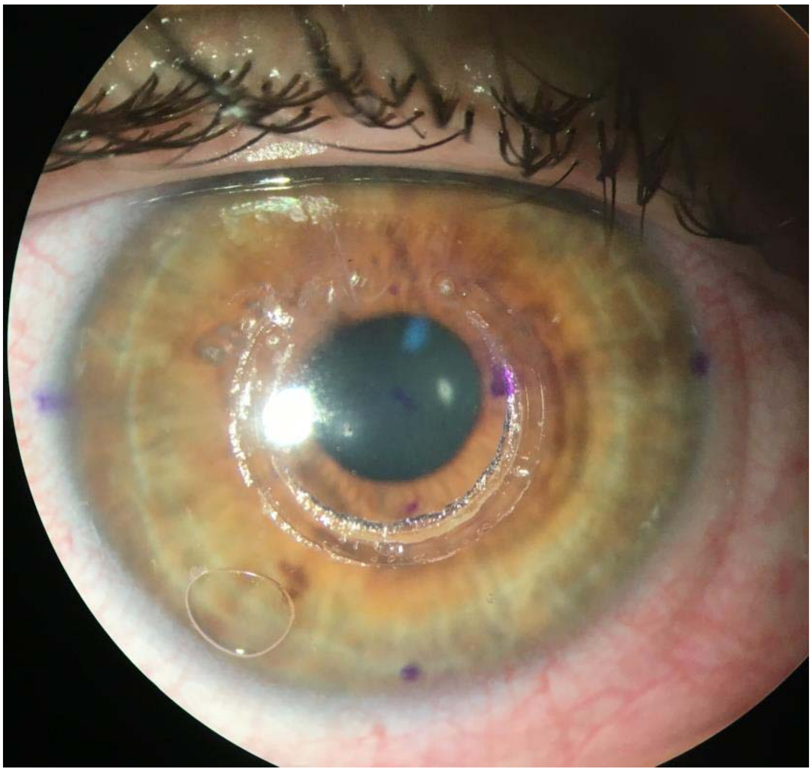

Figure 26. Immediate ICRS postoperative slit-lamp photography (CUFP 602554)

The main theoretical disadvantages of the manual technique are the longer surgical procedure time, the longer learning curve for the surgeon, the lower predictability and consistency of tunnel depth creation, and the higher incidence of complications associated with this technique. The femtosecond-laser surgery is a faster and simpler procedure, performed under topical anaesthesia, has a faster learning curve, a very low incidence of complications[195], promoting quicker healing for the patient.

There is clinical controversy regarding the comparison of both techniques in terms of the efficacy to obtain the precise intended corneal depth planned by the surgeon[184, 196-198]. Previous publications regarding the comparison between both techniques present conflicting results, but most studies report shallower depth than predicted after both surgeries, and no difference between manual or femtosecond laser-assisted surgery [184, 196-199]; all studies but one were performed with Intacs ICRS. The reasons for such reported differences arise mainly because the methods of measurement differ, whether regarding the device being used (Scheimpflug tomography or optical coherence tomography) or the location used for the measurement.

Regarding the visual outcomes and the refractive efficacy of both surgical techniques, earlier studies have addressed this issue; these studies have reported no differences between both techniques; however, all studies available have some limitations. The available publications included patients whose ectasia phenotype or stage was not described; have compared outcomes of patients with different diagnoses (keratoconus and post-Lasik ectasia)[200] and considered very heterogenic populations regarding the Amsler grade (samples with grades 1 to 4)[164, 201]. Some studies have also compared groups of patients with different ICRS designs and surgeon's nomograms of implantation in the same sample[201], used different time points of comparison between samples[202] or used a fixed incision site and implant, regardless of the ectasia grade or phenotypic characteristics[164, 200]. To consistently compare the visual and refractive results of two different surgical techniques, the samples included should be the most homogenous possible (to include only specific phenotypes of keratoconus) and to only include a specific ICRS implant in all patients studied.

Regarding the incidence of surgical complications, there is an empirical sense that the manual mechanical dissection technique is associated with a higher incidence of complications. As previously mentioned, the surgical learning curve is longer in manual surgery, the tunnel depth predictability should be lower, and consequently, a higher incidence of complications should be observed associated with the technique. On the other side, femtosecond-laser assisted surgery has a faster learning curve and a theoretically higher precision in terms of tunnel depth inside the corneal stroma. Taking this assumption into consideration, the incidence of complications should be much lower. No published evidence has compared the incidence and type of complications of both techniques in a similar cohort of patients treated by the same surgeon. There is also limited knowledge about the resolution of complications; most studies available[195, 203] only report about the final visual and topographic results after a complication has occurred, a few studies describe the secondary surgical intervention and the final visual result after its resolution[204, 205].

4.3.4 Clinical application and results

The concept behind ICRS insertion in keratectasia is not to eliminate the ectatic process, but to modify the corneal shape without removing tissue or manipulating the central cornea. The goal of this treatment is to improve spectacle-corrected visual acuity or contact lens tolerance, thus delaying or eliminating the need for a corneal transplant[206]. Intrastromal corneal ring segments as a treatment option offer the added advantage of being removable if not useful or poorly tolerated, with eyes returning to their preoperative refractive status within three months of explantation[207-209]. ICRS can also be a therapeutic, surgical option in cases of post-Lasik ectasia[210], pellucid marginal degeneration[211], or high astigmatism following penetrating keratoplasty[212].

In terms of keratoconus treatment efficacy, a large number of studies have been published regarding their efficacy and safety. A recent "Global Consensus on Keratoconus and Ectatic Diseases", published in 2015[92], includes the use of ICRS as a surgical procedure for keratoconus management, the panellists concluded that the most important surgical techniques to restore the best uncorrected visual acuity possible in keratoconus are DALK, PK and ICRS; this idea reinforces the therapeutic and also refractive efficacy of the ICRS in such situations. Several studies have shown the long-term efficacy and safety of ICRS treatment for keratoconus with variable predictability, maintaining the early satisfactory outcomes regarding visual acuity, keratometry, and corneal thickness[189, 213, 214]. These long-term studies show the continued stabilizing effect of ICRS over time. However, all of the patients included in these studies were adults with stable refraction and no evidence of progressive keratoconus before ICRS implantation. As such, one cannot infer that ICRS implantation stopped the progression of the disease in these patients; however, we can conclude that the refractive procedure itself is stable over a long follow-up time.

When analysing the clinical outcomes of ICRS in keratoconus, two major recent review studies gave an extensive and updated overview[215, 216]. Although most studies are retrospective, they do demonstrate a significant reduction in SE from 0.06 to 5.8 D, with nearly 80% showing a mean reduction of more than 2.0 D. This is accompanied by a reduction in keratometry between 2.0 and 6.0 D in approximately 80% of studies where data are available (range 1.21 to 5.98 D). This improvement in corneal shape is accompanied by an improvement in CDVA in all the studies in which data are available, with 48 to 97% of treated patients experiencing an improvement in visual function.

The planning of the ICRS characteristics to implant is a crucial step in determining the outcome of the surgery. Most of the recent review publications demonstrate the efficacy and safety of the procedure as a whole. However, the main drawback of ICRS implantation as a refractive procedure has been the low refractive predictability associated with it. The most obvious explanation for this fact lies in the keratoconus classifications used to characterize the disease; most of the classifications used are based on a scale of severity of the disease rather than the clinical phenotype of the disease. In the past, a vast majority of patients were treated with the same type of implants even though the topographic morphology of the disease was very heterogeneous. The implant characteristics were chosen according to empirical knowledge. In the past decade, Prof. José Alfonso and his investigation group, at the *Instituto Oftalmológico Fernandez-Vega* have developed a new type of classification of the disease, oriented to the surgical treatment with ICRS. In essence, the classification is based on the disease phenotype rather than its clinical severity; it was specially developed in order to improve the accuracy and efficacy of the refractive treatment associated with ICRS. The objective is to help the surgeon choosing the best ICRS characteristics (arc length, optical zone, thickness, symmetry) regarding the specific morphology of the keratoconus to treat. Several recent publications by this investigation group have confirmed the usefulness and universal applicability of this type of classification dedicated to the surgical correction of the disease[217-219].

4.4 Corneal Keratoplasty

Traditionally, the mainstay of treatment for advanced keratoconus has been either penetrating or deep anterior lamellar keratoplasty (Figure 27). For most of the surgical history of the disease, advanced keratoconus has been treated with PK. Increasingly, however, DALK has been the preferred surgical option, mostly because of an improvement in the operative technique, and now represents 10-20 % of all transplants for keratoconus and 30% when eyes with previous hydrops are excluded[220, 221].

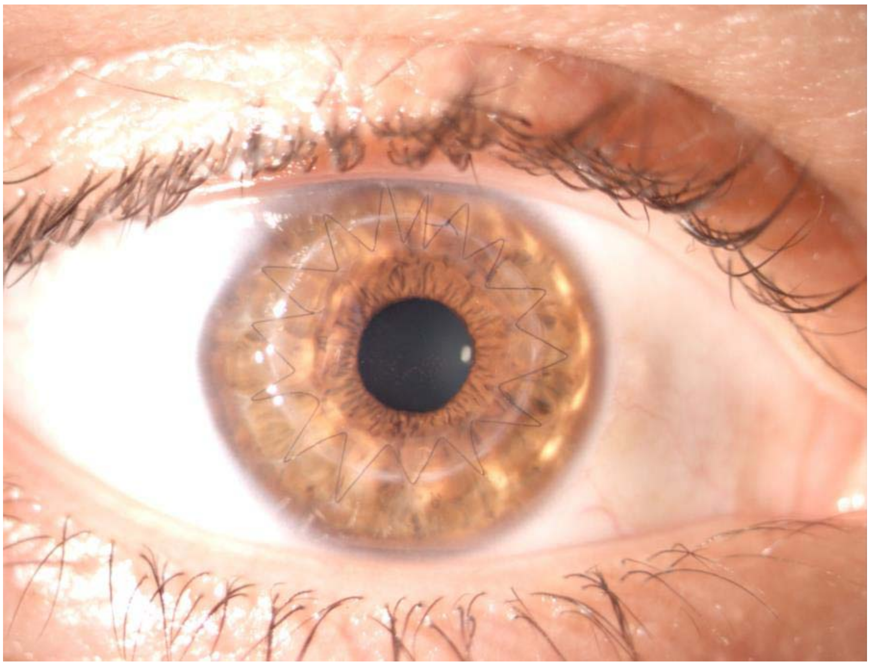

Figure 27. Clinical image of a penetrating keratoplasty (adapted from "Corrección del queratocono com segmentos intracorneales tipo Ferrara: Estrategia personalizada para su implante". Carlos Lisa Fernández, 2017)

Penetrating keratoplasty is the best option in cases with previous corneal hydrops and scarring at the level of the deep stroma, clinical situations that contraindicate DALK because of the higher risk of Descemet's membrane rupture. The main advantage of the lamellar surgery is the preservation of the patient's endothelial layer; this fact imposes a lower rejection rate, a lower endothelial cell loss and subsequently a longer survival time of the graft[(222)]; which is very important, owing to the mean age of patients with keratoconus submitted to keratoplasty. Another significant advantage of DALK over PK is that DALK is considered an extraocular procedure. Being so, DALK has a lower need for topical steroid treatment in the postoperative period, enables an earlier removal of the corneal sutures and allows a better optimization of the donor tissues because the endothelial layer removed from the donor tissue can be used for a posterior lamellar keratoplasty procedure in another patient[(223)]. On the other side, DALK is a more complex surgical technique, demands a prolonged procedure time, and if the corneal dissection does not reach the level of the Descemet's membrane, the visual outcomes will usually be worse than a standard PK procedure[(222)]. Several surgical techniques have been employed to separate the Descemet's membrane from the stroma; the big-bubble technique is the most used because it allows a complete removal of the corneal stroma, improves the quality of the interface, obtaining a similar mean visual acuity to PK[(224, 225)]. Graft survival is generally high, reaching almost 90% after ten years of follow-up[(226-228)].

The success of both surgeries, however, has been somewhat tempered by potential difficulties and complications, both intra and postoperatively. These include suture and wound healing problems, the progression of the disease in the recipient rim, allograft reaction, and persistent irregular astigmatism. Taken together, these have been the inspiration for an ongoing search for less troublesome therapeutic alternatives. More recently (2014), Bowman layer transplantation has been introduced for reversing corneal ectasia in eyes with advanced keratoconus[229], re-enabling comfortable contact lens wear, and allowing PK or DALK to be postponed or avoided entirely. Another new line of investigation is the development of new ICRS designs for implantation in patients with advanced keratoconus and no central corneal scarring.

4.4.1 Penetrating Keratoplasty

The most significant recent advance in PK has been the introduction of the femtosecond laser to trephine the recipient and donor tissues, theoretically providing better apposition and faster healing. After PK for advanced keratoconus, final uncorrected visual acuity ranges from 20/50 to 20/100, with just over 40 % of patients reading 20/40[230-232]. Spectacle correction gives better results with a mean acuity (BSCVA) of 20/30 to 20/40[233-235]. However, these gains may recede over time, owing to the appearance of irregular astigmatism in the graft. On this point, Praminik et al. found that 15 years after PK for advanced keratoconus, although 66% retained a BSCVA > 20/40, 18.9 % had fallen to < 20/200[236]. For some patients (5-60%), contact lenses may be required postoperatively[237-239]. Because visual acuity does not stabilize until at least 12 months after surgery, a primary limitation to PK's visual results is the delay in achieving them[240, 241]. No study has shown that the style or pattern of graft suturing influences the ultimate BCVA. Following PK, substantial degrees of astigmatism are common. The average is 3-5 D but may exceed 10 D, and as a consequence, approximately 20% of patients may require a surgical enhancement postoperatively[242, 243].

4.4.2 Deep Anterior Lamellar Keratoplasty

DALK, adequately performed, probably provides equivalent visual results to PK. The published evidence shows that, provided stromal dissection reaches the level of the Descemet's membrane, all visual outcomes (UCVA, BCVA, and the percent requiring contact lenses) are the same[224, 244, 245]. In studies where the visual results of DALK are inferior to PK, this discrepancy is usually attributed to an incomplete stromal dissection such that the DM is not fully bared. In these “pre-Descemet” DALKs, visual performance tends to be worse overall. The problem seems to be related to the depth of the non-dissected stromal bed, not its regularity or smoothness, since pre-Descemet DALKs performed by laser ablation do not outperform those performed by manual dissection[225, 246]. Compared to PK, visual rehabilitation may be faster, owing to the possibility of earlier suture removal[233].

CHAPTER III

1. Justification

Intrastromal corneal ring segments implantation is a surgical procedure used for the treatment of keratoconus, enabling both a therapeutic and refractive improvement. Both the safety and the refractive efficacy of the implant depend on the correct selection of the implant features and a precise intrastromal surgical implantation. Several studies comparing both the anatomical and functional outcomes of both procedures have reached distinct conclusions. The importance of clarifying the differences between both techniques comes from the fact that both are in current use in different health practice settings; and, there is a large population of patients indicated for surgical treatment of keratoconus. Lastly, to address the demand for future surgical innovations in ICRS surgery and to improve the refractive predictability of the procedure, it is of the utmost importance to establish if both surgical procedures meet the classic refractive surgery requirements to be used for such investigation purposes.

2. Hypothesis

The visual and refractive results obtained after ICRS implantation for keratoconus treatment by manual or laser-assisted surgery are equal as long as a correct morphologic classification of the ectasia was adopted in the preoperative planning; in order to choose the adequate characteristics of the implant.

3. Purposes

3.1 Main Purpose

This Doctoral Thesis proposes to compare the results of the two surgical procedures in terms of anatomical outcomes, visual and refractive results, and also complications incidence and management.

3.2 Specific Purposes

Determine and compare the precision and predictability of intrastromal tunnel creation for ICRS implantation between manual and femtosecond laser-assisted surgery.

Compare the visual, refractive, and aberrometric results of ICRS implantation between both techniques.

Compare the incidence of complications between both surgical techniques for ICRS implantation.

Validate the possibility to adjust the surgical outcomes of both techniques.

CHAPTER IV - Predictability of tunnel depth for Intrastromal corneal ring segments implantation between manual and femtosecond laser techniques

ORIGINAL ARTICLE

Predictability of Tunnel Depth for Intrastromal Corneal Ring Segments Implantation Between Manual and Femtosecond Laser Techniques

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ABSTRACT

PURPOSE: To compare the predictability of intrastromal tunnel depth creation for intrastromal corneal ring segments (ICRS) implantation between manual dissection and femtosecond laser using a high-resolution anterior segment optical coherence tomography (AS-OCT).

METHODS: This multicenter study included patients with keratoconus who had Ferrara-type ICRS implantation at Hospital de Braga using manual dissection and at the Fernandez-Vega Ophthalmological Institute using the femtosecond laser technique. The intended depth of implantation was compared to the achieved postoperative ICRS depth of each case, measured using a swept-source AS-OCT (CASIA SS-1000; Tomey Corporation, Nagoya, Japan) at three points (proximal, central, and distal end of the implant).

RESULTS: The study included 105 eyes in the manual group and 53 eyes in the femtosecond laser group. The differences of the intended versus the achieved depth were statistically higher in the manual group for all positions measured (Wilcoxon ranked-sum, $P < .001$). In the manual group, there were significant differences between the mean values of intended and achieved depth after surgery for the three locations measured (Wilcoxon signed-rank, $P < .05$), whereas there were no significant differences in the femtosecond laser group. In the manual group, the proximal part of the stromal tunnel was significantly shallower (-40.87 ± 69.03 μm) than the central (-25.54 ± 71.00 μm) and distal (-26.52 ± 73.22 μm) parts (Friedman test, $P < .05$).

CONCLUSIONS: ICRS implantation assisted by a femtosecond laser provides a more precise procedure considering dissection depth when compared with the manual dissection technique. Such an advantage may provide more predictable clinical results and safer procedures with the femtosecond laser.

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Intrastromal corneal ring segments (ICRS) implantation is a surgical procedure used for the treatment of keratoconus, enabling both a therapeutic and refractive improvement.[1-3] Both the safety and the refractive efficacy of the implant depend on the correct selection of the implant features and a precise intrastromal surgical implantation. Shallower intrastromal tunnels are associated with complications such as implant exposure due to corneal thinning over the implant, segment migration and extrusion, astigmatism overcorrection, or corneal melting.[4-6] Deeper tunnels can be associated with corneal perforation or endothelial cell damage and a minor refractive and topographic effect on the cornea.[7] Therefore, a precise and predictable tunnel depth creation is crucial for this surgical procedure. The tunnel can be created with manual dissection or assisted by a femtosecond laser device. Previous publications regarding this aspect present conflicting results, but most studies report shallower depth than predicted and no difference between manual or femtosecond laser–assisted surgery[8-12]; all studies but one were performed with Intacs ICRS (Addition Technology Inc., Des Plaines, IL). The reasons for such differences reported arise mainly because the methods of measurement differ, whether regarding the device being used (Scheimpflug tomography or optical coherence tomography) or the location used for the measurement.

The purpose of this study was to compare the precision and predictability of intrastromal tunnel creation for Ferrara-type

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ICRS implantation between the manual mechanical technique and femtosecond laser–assisted surgery using a novel high-resolution swept-source AS-OCT. To our knowledge, this is the first study to compare the intended versus achieved tunnel depth for Ferrara ICRS implantation using OCT and measuring three different locations for each segment with two different surgical techniques.

PATIENTS AND METHODS

The tenets of the Declaration of Helsinki were followed and full ethical approval was obtained from both institutions. After receiving a detailed explanation of the nature and possible consequences of the study and surgery, all patients gave their informed consent. The study included Ferrara-type ICRS implantation in 158 eyes of 158 patients with keratoconus and was conducted at the Ophthalmology Department of Hospital de Braga, Braga, Portugal, and the Fernandez-Vega Ophthalmological Institute, Oviedo, Spain. The criteria required for inclusion in the study were the presence of keratoconus (diagnosis based on the slit-lamp examination and confirmed by Scheimpflug tomography [Pentacam; Oculus Optikgeräte, Wetzlar, Germany]), contact lens intolerance, and a clear cornea, together with a minimum corneal thickness of greater than 400 µm at the optical zone involved in the implantation (a general criterion for surgery). In addition, keratoconus had to be stage I to II according to the Amsler–Krumeich keratoconus classification. The exclusion criteria defined for this study were previous corneal or intraocular surgery, a history of herpetic keratitis, diagnosed autoimmune disease, systemic connective tissue disease, endothelial cell density of less than 2,000 cells/mm^2, cataract, a history of glaucoma or retinal detachment, macular degeneration or retinopathy, neuro-ophthalmic disease, or a history of ocular inflammation.

Data collected were patient gender and age, operated eye, ICRS arc length and thickness, intended depth thickness, and achieved postoperative ICRS depth as measured by a swept-source AS-OCT (CASIA SS-1000; Tomey Corporation, Nagoya, Japan) at three points for each segment (proximal, central, and distal end of the implant). For each point of measurement, we calculated two values: the tunnel depth achieved and the mean difference between intended and achieved depth of implantation, designated as the "delta" value for each location. The delta value was expressed as "relative delta" and "absolute delta." The relative delta is the difference between achieved and intended (a negative value means a superficial implant and a positive value means a deeper implant than intended). The absolute delta is the value of delta without negative or positive signal; it means the overall difference between depths, with no indication regarding superficial or deeper implant.

Ferrara-type ICRS (Mediphacos, Belo Horizonte, Brazil) were implanted in all eyes studied. These polymethylmethacrylate Ferrara-type ICRS have a triangular cross-section that induces a prismatic effect on the cornea. Their apical diameter is 6 mm (flat basis width = 800 mm), with variable thicknesses (150, 200, 250, and 300 mm) and arc lengths (90, 120, 150, and 210 degrees); ICRS implanted was chosen according to the Mediphacos nomogram previously published.[13]

Manual Mechanical Technique

The ICRS implantation surgeries with the manual technique were all performed at the Ophthalmology Department of Hospital de Braga and by the same surgeon (TM). The visual axis was marked by pressing the Sinskey hook on the central corneal epithelium while asking the patient to fixate on the corneal light reflex of the microscope light. Using a marker tinted with gentian violet, a 6-mm optical zone and incision site were aligned to the desired axis in which the incision would be made. The incision site was always performed at the steepest topographic axis of the cornea given by the topographer. A square diamond blade was set at 80% of the thinnest point along the implantation optical zone track and this blade was used to make the incision. Corneal thickness was measured intraoperatively with ultrasonic pachymetry. Using a "stromal spreader," a pocket was formed on each side of the incision. Two (clockwise and counterclockwise) 270 degrees semicircular dissecting spatulas were consecutively inserted through the incision and gently pushed with some quick rotary "back and forth" tunneling movements. Following channel creation, the ring segments were inserted using modified McPherson forceps. The rings were properly positioned with the aid of a Sinskey hook.

Femtosecond Laser–Assisted Surgery

The center of the pupil was marked and four cardinal spots at 4 (for ICRS 5-mm optical zone) or 5 (for ICRS 6-mm optical zone) mm were also placed on the cornea with a caliper to better centrate the laser spot location regarding the visual axis and to avoid pupillary shift after the pressure was applied. The corneal thickness at the area of implantation (5- or 6-mm diameter) was measured with ultrasonic pachymetry and a disposable suction ring was centered on the pupil. A tunnel was subsequently created at 70% of the corneal thickness, using a 60-KHz infrared neodymium glass femtosecond laser (Intralase FS; Abbott Medical Optics, Inc., Abbott Park, IL) at a wavelength of 1,053 nm. The 3-mm diameter (spot size) laser beam was optically focused by computer scanners at a predetermined intrastromal depth ranging from 90 to 400 mm from the anterior corneal surface. The beam formed cavitations and water vapor by photodisruption, with an interconnected series of microbubbles of carbon dioxide forming a dissection plane. The laser software was programmed to an inner diameter of 5 or 6 mm and an outer diameter of 6 to 7.2 mm for a channel width of 1.1 mm and an incision length of 1.7 mm on the steepest topographic axis. The power used to create the channel and the incision was 5 mJ in all eyes. This part of the procedure lasted approximately 15 seconds. The ICRS were implanted 5 minutes later after the gas bubbles had dissolved, with a dedicated forceps and under fully aseptic conditions. The segments were placed in their final position with the aid of a Sinskey hook that engaged the two positioning holes, one at each end of the segment. All femtosecond laser–assisted ICRS surgeries were performed by the same surgeon (JFA).

Postoperative treatment was similar for both surgical procedures and consisted of a combination of antibiotic (tobramycin, 3 mg/mL) and steroid (dexamethasone, 1 mg/mL) eye drops (Tobradex; Alcon Laboratories, Inc., Fort Worth, TX) administered three times daily for 2 weeks, with tapering of the dose over the following 2 weeks.

AS-OCT Examination

AS-OCT was performed using a swept-light source Fourier-domain OCT system (CASIA SS-1000); all examinations were performed and analyzed by the same operator (TM). A high-speed swept-laser source operating at 1,310-nm wavelength can achieve an axial resolution of 10 µm or less and a transverse resolution of 30 µm or less at a rate of 30,000 axial scans (A-scans) per second. Sixteen radial cross-sectional images are therefore obtained for 0.34 second (each cross-sectional image consists of 512 telecentric A-scans). Three scans were analyzed for each segment in relation to the incision site. The first, second, and third measurements were at the proximal, central, and distal portions of the segment, respectively (**Figure A**, available in the online version of this article). The depth was measured as the distance from the corneal epithelial layer to the external border of the segment adjacent to the hyperreflective line depicting the location of the intrastromal tunnel (**Figures B-C**, available in the online version of this article). The meridian of the incision and the scan location differed for each patient because, for each eye, the incision was made in the steepest meridian in reference to the corneal topography. In patients with two segments implanted, only the temporal inferior implant was measured. The ICRS depth measurement was performed 6 months after the ICRS surgery.

Statistical Analysis

The continuous data are presented as the mean ± standard deviation or the median and interquartile range, as appropriate. The normality of quantitative data was checked by the Shapiro–Wilk test. For normally distributed data, the *t* test was used to compare the two treatment groups. The Wilcoxon test was used for comparison of independent samples if normality was not observed. For the delta value of differences between the three points of measurement, a Friedman test analysis of variance was used. When statistically significant differences were found, post hoc tests were performed for multiple comparisons. A *P* value less than .05 was considered statistically significant. All calculations were performed using SPSS software (version 20; SPSS, Inc., Chicago, IL).

RESULTS

We included 105 eyes of 105 patients in the manual group and 53 eyes of 53 patients in the femtosecond laser group. The mean intraoperative corneal thickness was 514.13 ± 35.43 µm in the manual group and 525.38 ± 36.31 µm in the femtosecond laser group (*t* test, $P < .05$).

Comparison Between Manual and Femtosecond Laser–Assisted Surgery

When comparing the delta difference between both groups for each of the three locations measured, the delta difference was significantly higher in the manual group for all locations measured (**Table 1**) in terms of relative and absolute delta (*t* test, $P < .05$ for all values compared).

Manual Group

The difference between intended versus achieved intrastromal depth was significantly shallower in the manual group, for all three locations (Friedman test, $P < .05$, **Table 2** and **Figure DA**, available in the online version of this article). The proximal part of the stromal tunnel was significantly shallower than the central and distal parts (**Table 3** and **Figure DB**). A total of 57.14% of eyes had a superficial implantation shallower than 10 µm from the intended; 27.61% of eyes had a deeper implantation above 10 µm from the intended; and only 15.24% of eyes reached an achieved depth within ±10 µm from the intended (**Figure 1**).

Femtosecond Laser Group

The difference between intended versus achieved intrastromal depth was not significantly different for all three locations (Friedman test, $P > .05$, **Table 2** and **Figure EA**, available in the online version of this article); the dis-

TABLE 1
Values of Relative and Absolute Delta, the Differences Between Achieved and Intended Depth of Implantation[a]

Value	Manual	Femtosecond Laser	*P*
Proximal relative delta	-40.86 ± 69.02 (-263 to 74)	-4.24 ± 11.89 (-27 to 25)	.0004
Proximal absolute delta	56.98 ± 56.32 (0 to 263)	10.01 ± 7.58 (0 to 27)	< .0001
Central relative delta	-25.54 ± 71.00 (-218 to 136)	-3.26 ± 10.58 (-26 to 22)	.01
Central absolute delta	56.70 ± 49.54 (0 to 218)	8.69 ± 6.76 (0 to 26)	< .0001
Distal relative delta	-26.52 ± 73.21 (-211 to 136)	-8.09 ± 11.90 (-56 to 20)	.03
Distal absolute delta	60.02 ± 49.32 (1 to 211)	10.43 ± 9.87 (0 to 56)	< .0001

[a]*Values are presented as mean ± standard deviation (range).*

TABLE 2
Depth of ICRS Implantation Intended and Achieved After Surgery for the Proximal Central and Distal Location of the Implant

	Manual		Femtosecond Laser	
Depth	Mean ± SD (Range) (μm)	*P*[a]	Mean ± SD Range (μm)	*P*[a]
Incision intended	409.14 ± 25.70 (320 to 480)	–	368.28 ± 25.34 (273 to 413)	–
Central	383.60 ± 73.06 (204 to 586)	.001	365.01 ± 28.85 (275 to 417)	.54
Distal	382.61 ± 74.21 (227 to 551)	.0007	360.18 ± 27.70 (280 to 410)	.12
Proximal	368.27 ± 68.23 (181 to 524)	< .0001	364.03 ± 28.53 (277 to 410)	.42

ICRS = intrastromal corneal ring segments; SD = standard deviation
[a]*P value was calculated for the difference between the intended versus achieved depth in each technique for the three different locations measured.*

TABLE 3
Difference Between Achieved Versus Intended for Both Groups in Terms of Relative Delta

	Manual				Femtosecond Laser			
Relative Delta	N	Mean ± SD (Range) (μm)	Comparison	*P*	N	Mean ± SD (Range) (μm)	Comparison	*P*
Central	105	-25.54 ± 71.01 (-218 to 136)	Central vs distal	.38	53	-3.26 ± 10.58 (-26 to 22)	Central vs distal	.003
Distal	105	-26.52 ± 73.21 (-211 to 136)	Central vs proximal	.0002	53	-8.09 ± 11.91 (-56 to 20)	Central vs proximal	.25
Proximal	105	-40.87 ± 69.03 (-263 to 74)	Distal vs proximal	.001	53	-4.24 ± 11.89 (-27 to 25)	Distal vs proximal	.01

SD = standard deviation

tal part of the stromal tunnel was significantly shallower than the central and proximal parts (**Table 3** and **Figure EB**). A total of 22.64% of eyes had a superficial implantation shallower than 10 µm from the intended; 9.44% of eyes had a deeper implantation above 10 µm from the intended; and 67.92% of eyes reached an achieved depth within ±10 µm from the intended (**Figure 1**).

DISCUSSION

Safety and efficacy of ICRS implantation for keratoconus treatment depend on their precise implantation in the corneal stroma. To the best of our knowledge, this is the first study to compare the predictability and accuracy of intrastromal tunnel depth performed by manual dissection technique versus femtosecond laser. Our study found that ICRS implantation assisted by a femtosecond laser is a more accurate and predictable procedure when compared with manual dissection technique, even when the latter is performed by an experienced surgeon.

Most of the previous studies[9,10,12,14] published about this subject report on the use of Intacs ICRS and do not

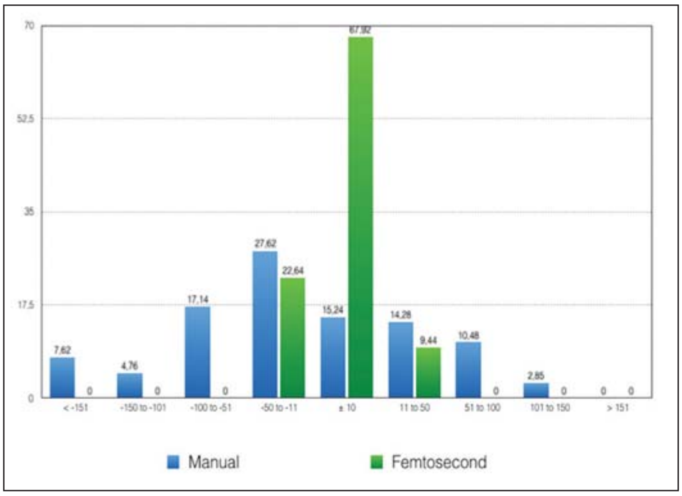

Figure 1. Distribution of patients according to different intervals of the delta between intended and achieved depth at the central location of the stromal tunnel. Values shown in % of total number of eyes.

compare both techniques. Barbara et al.[10] studied with OCT the depth of implantation of Intacs ICRS after manual surgery. Our results, with a larger sample, confirm those reported in this previous study, in which the authors found a shallower than planned intrastromal tunnel performed by mechanical dissection (308 µm instead of the expected 461 µm; $P < .05$). The tunnel depth achieved after surgery was shallower than intended at three different locations (proximal, central, and distal; $P < .05$). At the same line, results in the study by Naftali and Jabaly-Habib.[14] showed a shallower implantation than intended by 120 µm: segment depth was 360 µm, corresponding to 60% of corneal thickness. In a study by Lai et al.,[12] it was suggested that shallow implantation can cause stronger anterior stromal compression and might result in more complications, such as epithelial and stromal breakdown or ring extrusion.

Gorgun et al.[9] also measured with OCT the depth of Ferrara ICRS from the corneal apex in a group of patients who had femtosecond laser–assisted surgery. On average, the segments were implanted 97 µm shallower than intended. However, in a subgroup of eyes with available intraoperative measured tunnel depth data (and before the ICRS implantation), the authors could observe that the tunnel depth achieved was similar to the target depth programmed in the femtosecond laser (336.7 ± 23.5 vs 336.6 ± 25.0 µm, respectively). These subgroup results are equal to and corroborate our results of 53 eyes treated with femtosecond laser–assisted surgery, in which we did not observe any significant difference. Furthermore, it has also been shown that flap thickness is predictable in LASIK with a femtosecond laser.[15] Therefore, we have interpreted this phenomenon as the apex of the ICRS having a pushing and compacting effect on the intrastromal collagen lamellae overlying the implant.

The only published study to date comparing the manual and the femtosecond laser surgery was by Kouassi et al.[8] The authors implanted Intacs ICRS for keratoconus. The results demonstrate a shallower implantation than intended in both groups: 76 µm in the manual and 86 µm in the femtosecond laser–assisted surgery, concluding that there was no difference between the two techniques concerning segment depth. Although their study has some similarities to our study, it is of note that the ICRS rings were of an earlier design with a hexagonal cross-section and the methods of measurement of the tunnel depth were distinct. In our study, the tunnel depth was directly measured by high-resolution OCT after identification of the hyperreflectivity line in the corneal stroma that depicts its presence. This method of evaluation is independent of the corneal stroma compression induced by the ICRS, as mentioned by Gorgun et al.[9]

Another disadvantage observed in previous studies is the method used for intrastromal tunnel depth measurement. The depth is predicted from the distance of the corneal apex to the outer surface of the ICRS or from the distance of the corneal apex to the inner or middle surface of the implant. This method of calculation is indirect and strongly influenced by the corneal stroma compression induced by the ICRS. In our opinion, this is the main reason why all studies demonstrated a statistically and clinically relevant difference between the intended and achieved depth of implantation, which does not correlate with what is observed (for the past decade) in clinical practice and reported in published studies about visual and topographic outcomes of the technique.[16-18] We think that the calculated depth has to derive from a direct measurement of the intrastromal tunnel. To achieve this objective, it is mandatory to use a higher resolution corneal OCT and to identify the line of hyperreflectivity adjacent to the outer border of the implant, which represents the intrastromal tunnel. The AS-OCT used for this study, the CASIA SS-1000, is a new generation Fourier-domain OCT with an axial and transverse resolution of 10 and 30 µm, respectively. The Visante OCT (Carl Zeiss Meditec, Jena, Germany), used in most of the studies published, has a weaker resolution of 18 and 60 µm, respectively, for the axial and transverse cuts. In our study, we observed a mean difference between intended and achieved depth below 10 µm for all three locations measured and in all of the eyes analyzed. In the case of manual mechanical dissection, the achieved depth of implantation was significantly shallower than intended for all measurements: more than half of the eyes (57.14%) had an implantation shallower than 10 µm from intended and almost one-third (29.52%) had a shallower difference of 50 µm or more from intended. As mentioned before, the precision of intrastromal tunnel dissection is critical in achieving a good therapeutic and refractive result. In cases of inadequate ICRS implantation, there is a higher probability of mechanical complications (migration or extrusion), worse visual and refractive outcomes, and weaker topographic and aberrometric improvements.

Another aspect discussed previously is the variability of ICRS tunnel depth along the same path, from the proximal to the distal part of the implant. Our cohort of patients had a statistically significant difference in the manual group: the proximal depth being shallower than the central and distal parts. No difference was found between the central and distal locations of the tunnel. We observed an opposite result in the femtosecond laser group: a significant difference between the distal location when compared to both the central and proximal locations; however, we consider these differences to be clinically irrelevant because they were all less than 10 µm.

A previous study by Lai et al.[12] using AS-OCT to examine the depth of Intacs intracorneal ring segments, which were implanted with the aid of mechanical dissectors, showed that the tunnel depth decreased with increasing distance from the incision site. The authors hypothesized that the weaker and more flexible inferior cornea might bow downward ahead of the mechanical dissector, causing the channel to be progressively shallow during the dissection process. In another study by Kamburoglu et al.[11] intrastromal depth of Intacs ICRS implanted with the aid of a femtosecond laser were measured using Pentacam and the tunnel depth was similar across different points.

Higher precision and predictability of intrastromal tunnel creation are associated with a better safety profile of the procedure. Most mechanical complications of ICRS implantation are associated with shallow implantation in the corneal stroma.[5-7,19] An easier identification of an ICRS implanted more superficially than intended (by a non-invasive, rapid, and reproducible method such as the AS-OCT) will help the surgeon to monitor patients with superficial implants and recognize the need to explant the ICRS to avoid spontaneous extrusion after epithelial breakdown, stromal melting, or even infectious keratitis. A superficial ICRS is the most important risk factor for future implant extrusion or corneal melting.[20]

The implantation of ICRS for keratoconus is a more precise and predictable procedure if performed with the assistance of a femtosecond laser. The importance of a correct implantation regarding the ICRS depth cannot be overemphasized because this fact is crucial for both the achievement of the intended refractive, visual, and topographic results and because it is a guarantee of lower incidence of mechanical complications in the long term, such as ICRS migration or extrusion.

AUTHOR CONTRIBUTIONS

Study concept and design (TM, JFA, NF, FF-C, RA, DM-C); data collection (TM, NF, FF-C, RA, DM-C); writing the manuscript (TM); critical revision of the manuscript (TM, JFA, NF, FF-C, RA, DM-C); supervision (JFA)

REFERENCES

1. Fernández-Vega Cueto L, Lisa C, Poo-López A, Madrid-Costa D, Merayo-Lloves J, Alfonso JF. Intrastromal corneal ring segment implantation in 409 paracentral keratoconic eyes. *Cornea.* 2016;35:1421-1426.
2. Alfonso JF, Fernández-Vega Cueto L, Baamonde B, et al. Inferior intrastromal corneal ring segments in paracentral keratoconus with no coincident topographic and coma axis. *J Refract Surg.* 2013;29:266-272.
3. Lisa C, Fernández-Vega Cueto L, Poo-López A, Madrid-Costa D, Alfonso JF. Long-term follow-up of intrastromal corneal ring segments (210-degree arc length) in central keratoconus with high corneal asphericity. *Cornea.* 2017;36:1325-1330.
4. Ruckhofer J, Stoiber J, Alzner E, Grabner G; Multicenter European Corneal Correction Assessment Study G. One year results of European Multicenter Study of intrastromal corneal ring segments. Part 2: complications, visual symptoms, and patient satisfaction. *J Cataract Refract Surg.* 2001;27:287-296.
5. Zare MA, Hashemi H, Salari MR. Intracorneal ring segment implantation for the management of keratoconus: safety and efficacy. *J Cataract Refract Surg.* 2007;33:1886-1891.
6. 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;25:29-33.
7. 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;89:54-57.
8. Kouassi FX, Buestel C, Raman B, et al. Comparison of the depth predictability of intra corneal ring segment implantation by mechanical versus femtosecond laser-assisted techniques using optical coherence tomography (OCT Visante) [article in French]. *J Fr Ophtalmol.* 2012;35:94-99.
9. Gorgun E, Kucumen RB, Yenerel NM, Ciftci F. Assessment of intrastromal corneal ring segment position with anterior segment optical coherence tomography. *Ophthalmic Surg Lasers Imaging.* 2012;43:214-221.
10. Barbara R, Barbara A, Naftali M. Depth evaluation of intended vs actual Intacs intrastromal ring segments using optical coherence tomography. *Eye (Lond).* 2016;30:102-110.
11. Kamburoglu G, Ertan A, Saraçbasi O. Measurement of depth of Intacs implanted via femtosecond laser using Pentacam. *J Refract Surg.* 2009;25:377-382.
12. Lai MM, Tang M, Andrade EM, et al. Optical coherence tomography to assess intrastromal corneal ring segment depth in keratoconic eyes. *J Cataract Refract Surg.* 2006;32:1860-1865.

13. 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;36:1556-1561.
14. Naftali M, Jabaly-Habib H. Depth of intrastromal corneal ring segments by OCT. *Eur J Ophthalmol.* 2013;23:171-176.
15. Sutton G, Hodge C. Accuracy and precision of LASIK flap thickness using the IntraLase femtosecond laser in 1000 consecutive cases. *J Refract Surg.* 2008;24:802-806.
16. Giacomin NT, Mello GR, Medeiros CS, et al. Intracorneal ring segments implantation for corneal ectasia. *J Refract Surg.* 2016;32:829-839.
17. Poulsen DM, Kang JJ. Recent advances in the treatment of corneal ectasia with intrastromal corneal ring segments. *Curr Opin Ophthalmol.* 2015;26:273-277.
18. Gomes JA, Tan D, Rapuano CJ, et al. Global consensus on keratoconus and ectatic diseases. *Cornea.* 2015;34:359-369.
19. Miranda D, Sartori M, Francesconi C, Allemann N, Ferrara P, Campos M. Ferrara intrastromal corneal ring segments for severe keratoconus. *J Refract Surg.* 2003;19:645-653.
20. Ferrer C, Alió JL, Montañes AU, et al. Causes of intrastromal corneal ring segment explantation: clinicopathologic correlation analysis. *J Cataract Refract Surg.* 2010;36:970-977.

Figure A. Example of an examination performed at three locations in the same eye.

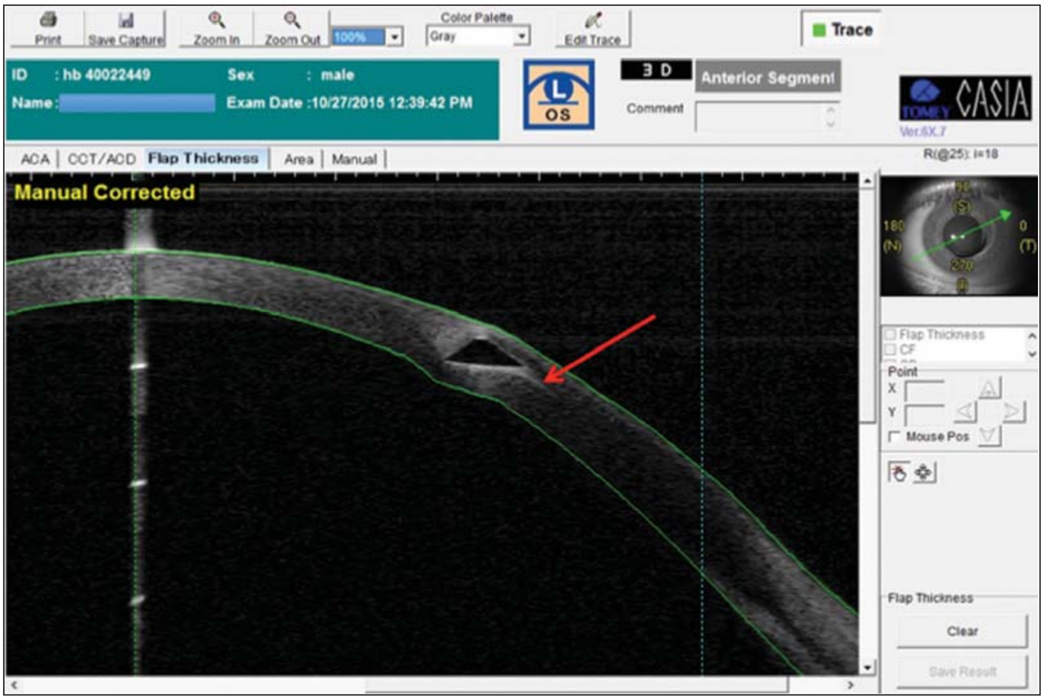

Figure B. Line of hyperreflectivity.

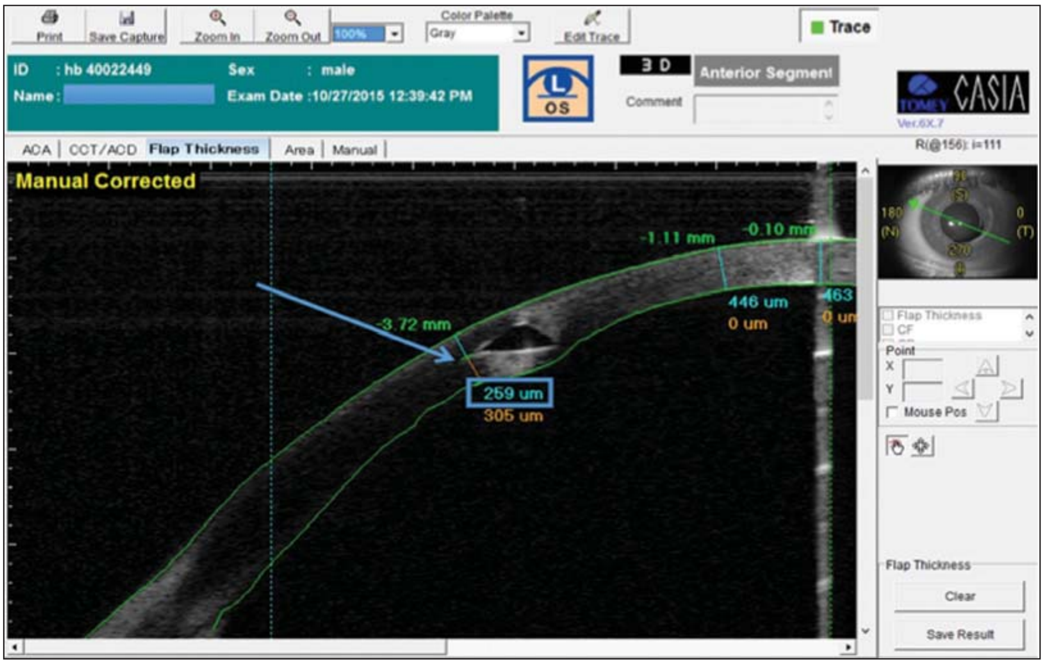

Figure C. Measurements of the tunnel depth with the flap analysis module.

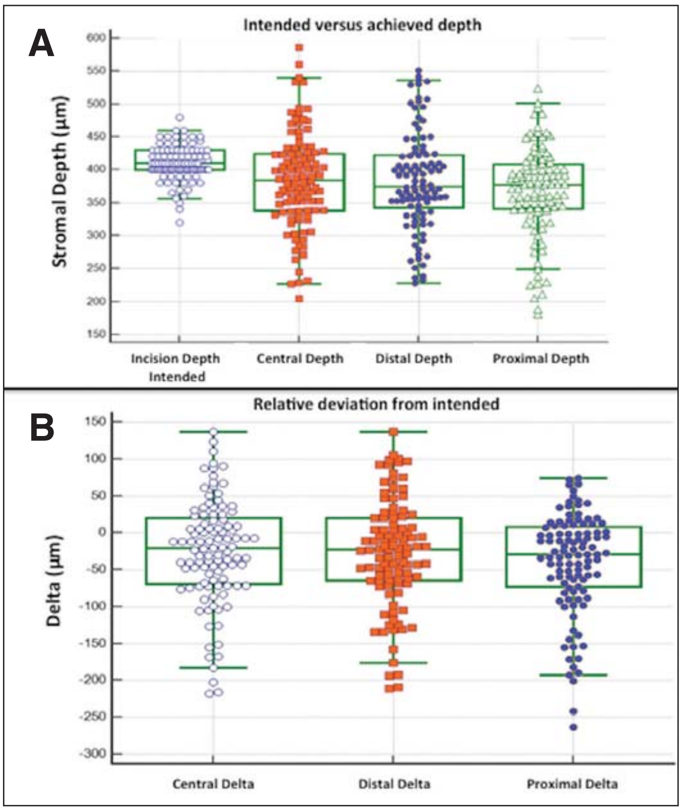

Figure D. Manual technique group. (A) Distribution of intended versus achieved depth of intrastromal corneal tunnel for intrastromal corneal ring segments implantation. All measurements at central, proximal and distal locations were shallower than intended. (B) Distribution of delta values between intended versus achieved for central, distal, and proximal locations.

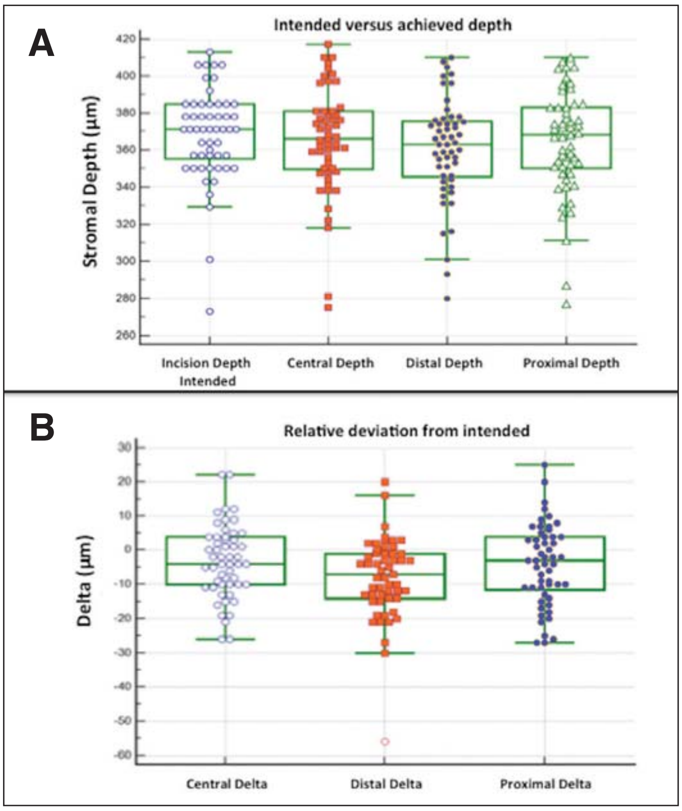

Figure E. Femtosecond laser technique group. (A) Distribution of intended versus achieved depth of intrastromal corneal tunnel for intrastromal corneal ring segments implantation. All measurements at central, proximal, and distal locations were similar to the intended value ($P > .05$). (B) Distribution of delta values between intended versus achieved for central, distal, and proximal locations.

CHAPTER V - Comparison of clinical outcomes between manual and femtosecond laser techniques for intrastromal corneal ring segment implantation

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Comparison of clinical outcomes between manual and femtosecond laser techniques for intrastromal corneal ring segment implantation

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Abstract

Purpose: The purpose was to compare the visual, refractive and aberrometric results of intrastromal corneal ring segments implantation with manual dissection and femtosecond laser–assisted surgery.

Methods: This is a multicentre study, which included consecutive patients with paracentral keratoconus, in which the difference between the axes of the topographic flattest and the coma aberration was $<60°$, who had Ferrara-type intrastromal corneal ring segment implantation using manual dissection or femtosecond laser technique. LogMAR uncorrected (uncorrected distance visual acuity) and corrected (corrected distance visual acuity) distance visual acuity, refractive errors and the root mean square for corneal coma-like aberration were recorded before and at 6 months after surgery.

Results: The study included 84 and 110 eyes in the manual group and in the femtosecond group, respectively. After surgery, there was a statistically significant improvement in uncorrected distance visual acuity and corrected distance visual acuity for both groups ($p < 0.0001$), and there were no statistically significant differences between groups ($p > 0.3$). For both groups, there was a reduction in spherical equivalent after intrastromal corneal ring segment implantation ($p < 0.0001$). There were no statistically significant differences between groups in the magnitude of spherical equivalent reduction ($p = 0.34$) The magnitude of the root mean square coma-like reduction was 0.93 ± 0.76 and $0.83 \pm 0.80\,\mu$m in the manual and femtosecond group, respectively ($p = 0.2$). While in the femtosecond laser group no complications were reported, in the manual group, the intraoperative or postoperative complications rate was 13.09%.

Conclusion: Although both surgical techniques provide comparable visual, refractive and aberrometric outcomes, it should be noted that the femtosecond laser is a safer surgical procedure, with no complications reported.

Keywords

Keratoconus, intracorneal ring segments, manual surgery, femtosecond laser surgery

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Introduction

Intrastromal corneal ring segment (ICRS) implantation is a safe and effective surgical procedure for the treatment of keratoconus, especially in non-progressive ectasias with poor tolerance to rigid contact lenses.[1–3] The possibility to correct both irregular astigmatism and the corneal high-order aberrations makes it a therapeutic and refractive procedure, which has been previously demonstrated to be safe and effective.[2] The evolution of the implantation nomograms has improved the refractive predictability of the procedure in the last 5 years.[4–6] However, the refractive efficacy of this procedure depends not only on the characteristics of the ICRSs (such as the arc length and thickness) but also on an accurate intrastromal tunnel creation for the ICRS implantation. A recent study reported a higher accuracy and predictability of femtosecond laser for the creation of intrastromal tunnel compared to the manual technique.[7] Hence, it seems appropriate to analyse if those results have impact on the visual and refractive outcomes of the ICRS implantation.

Earlier studies have addressed this issue comparing the safety and efficacy of implanting ICRSs with manual or femtosecond laser surgery. These studies reported no differences between both techniques. However, all studies available have some limitations: compare results in a population of patients whose ectasia phenotype or stage is not described, have compared outcomes of patients with different diagnoses (keratoconus and post-LASIK ectasia)[8] and very heterogenic populations with Amsler grade 1–4,[9,10] have compared groups of patients with different ICRS designs and surgeon's nomograms (type of ICRS implanted and corneal incision location) in the same sample,[9] use various time points of comparison between samples[11] or use a fixed incision site and implant, regardless of the ectasia grade or phenotypic characteristics.[8,10] To better compare the efficacy and safety of both surgical procedures, it is essential to compare the results in a group of keratoconus with the same morphologic characteristics, namely the location of the thinnest point and the relationship between the refractive astigmatism, the topographic astigmatism and the coma axis, that is, to compare the surgical technique in keratoconus patients where the same implant characteristics were applied.

The aim of the current study is to compare the visual, refractive and topographic results of ICRS implantation with manual dissection technique and femtosecond laser–assisted surgery in specific phenotypes of keratoconus (paracentral keratoconus), in which the difference between the axes of the topographic flattest and the coma aberration was <60°.

Patients and methods

A multicentre prospective study, which comprised patients with keratoconus who had ICRS implantation with manual dissection and femtosecond laser–assisted surgery, was performed. This study was conducted in accordance with the tenets of the Declaration of Helsinki, and full ethical approval from the institutions involved in the study was obtained. Written informed consent was obtained from patients after explanation of the purpose and possible consequences of the study and surgery

The following inclusion criteria were considered: consecutive patients who had keratoconus stages I and II (according to the Amsler–Krumeich keratoconus classification), contact lens intolerance, a transparent cornea, a corneal thickness of ⩾400 µm at the implantation zone, maximum keratometry (K) reading (simK2) ⩽53 diopters (D) and minimum K reading ⩾40 D. Furthermore, the keratoconus must fulfil the following conditions for phenotype description based on the topography provided by a rotating camera Scheimpflug system (Pentacam®; Oculus GmbH, Germany):

1. The thinnest point on the corneal pachymetric map located in the inferior temporal quadrant and at a distance between 0.7 and 1.7 mm of the pupil centre;
2. The difference between the coma axis and the flattest topographic axis between 30° and 60°('Duck' phenotype,[5] Figure 1) or <30° ('Croissant' phenotype,[4] Figure 2).

Exclusion criteria for this study considered previous ocular surgery, history of herpetic keratitis, diagnosed autoimmune disease, systemic connective tissue disease, endothelial cell density less than 2000 cells/mm² and current or past history of an ocular disease (other than keratoconus).

The ICRSs implanted in all eyes were the Keraring® SI6 ICRS (Mediphacos Inc., Belo Horizonte, Brazil). The ICRS implanted was centred in all patients on the topographic flat axis, the incision was performed at the steepest topographic axis and the ring was implanted at the 6.00-mm optical zone in all patients. The ICRSs were implanted following the nomogram used in previous studies[4,5] and also according to the Mediphacos nomogram:[10] for the 'duck' phenotype (Figure 1), a 150° arc length was used, while for the 'Croissant' phenotype (Figure 2), a 120° arc length was chosen.

Before and after ICRS implantation, patients had a complete ophthalmologic examination including uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), manifest refraction, corneal topography and corneal aberrometry with Pentacam® (Oculus), endothelial cell count, slit-lamp microscopy, Goldmann applanation tonometry and binocular indirect ophthalmoscopy through a dilated pupil. The pachymetry map was performed using the Visante® optical coherence tomography system (Carl Zeiss Meditec, Inc.; Jena, Germany). Contact lens use was discontinued 1 month before corneal topography was performed.

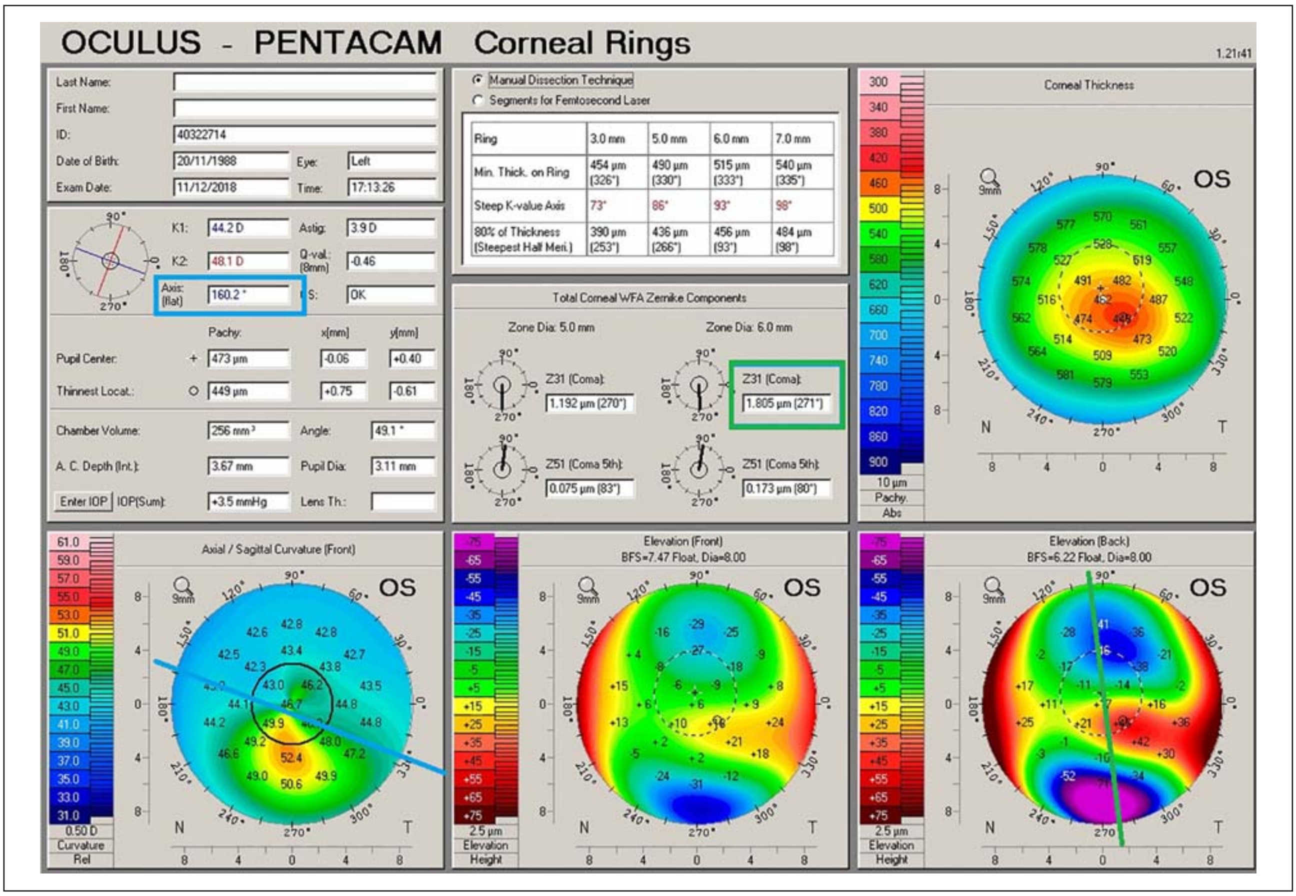

Figure 1. Preoperative corneal topography and coma wavefront map (Pentacam®; Oculus, Germany). Note the topographic (blue arrow) and coma (green arrow) axes.

The implantation axis of the ICRS was coincident with the flattest topographic axis. The same surgeon (T.M.) performed all the manual mechanical surgeries at Hospital de Braga by following the standard procedure previously described.[7] All implantation procedures using femtosecond laser were performed by the same surgeon (J.F.A.) at the Instituto Oftalmológico Fernández-Vega by following the procedure described in previous studies.[4,5,7] Preoperative medications included proparacaine 0.5%, ciprofloxacin 0.3% and oxybuprocaine ClH 0.2%.

Postoperative treatment for both surgical procedures was the same and included a combination of antibiotic (tobramycin, 3 mg/mL) and steroid eye drops (dexamethasone, 1 mg/mL) (Tobradex; Alcon Laboratories, Inc, Fort Worth, TX, USA) three times daily for 2 weeks with tapering of the dose for two more weeks.

Patients had a complete postoperative clinical evaluation at 6 months. The clinical measurements were corneal topography, corneal aberrometry, manifest refraction, UDVA and CDVA. The manifest refraction was analysed using the power vector method of Thibos and Horner.[12]

The Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA) was used for the descriptive statistics, including mean ± standard deviation. Normality of all data samples was first checked using the Kolmogorov–Smirnov test. Student's t test for paired data was used to compare preoperative and postoperative data when normality was present. Where parametric analysis was not possible, the Wilcoxon rank-sum test was used to assess the significance of differences between preoperative data and postoperative data. The unpaired t test and the Mann–Whitney test were used to compare data between non-related samples. In all cases, differences were considered statistically significant when the p value was less than 0.05

Results

The study included 194 eyes (84 and 110 eyes in the manual group and in the femtosecond laser group, respectively); the mean age was 31.80 ± 11.55 and 34.2 ± 12.0 years, respectively. Table 1 shows the patient's demographics.

Visual acuity outcomes

Figure 3 shows the UDVA and CDVA values before and at 6 months after ICRS implantation in both groups. After

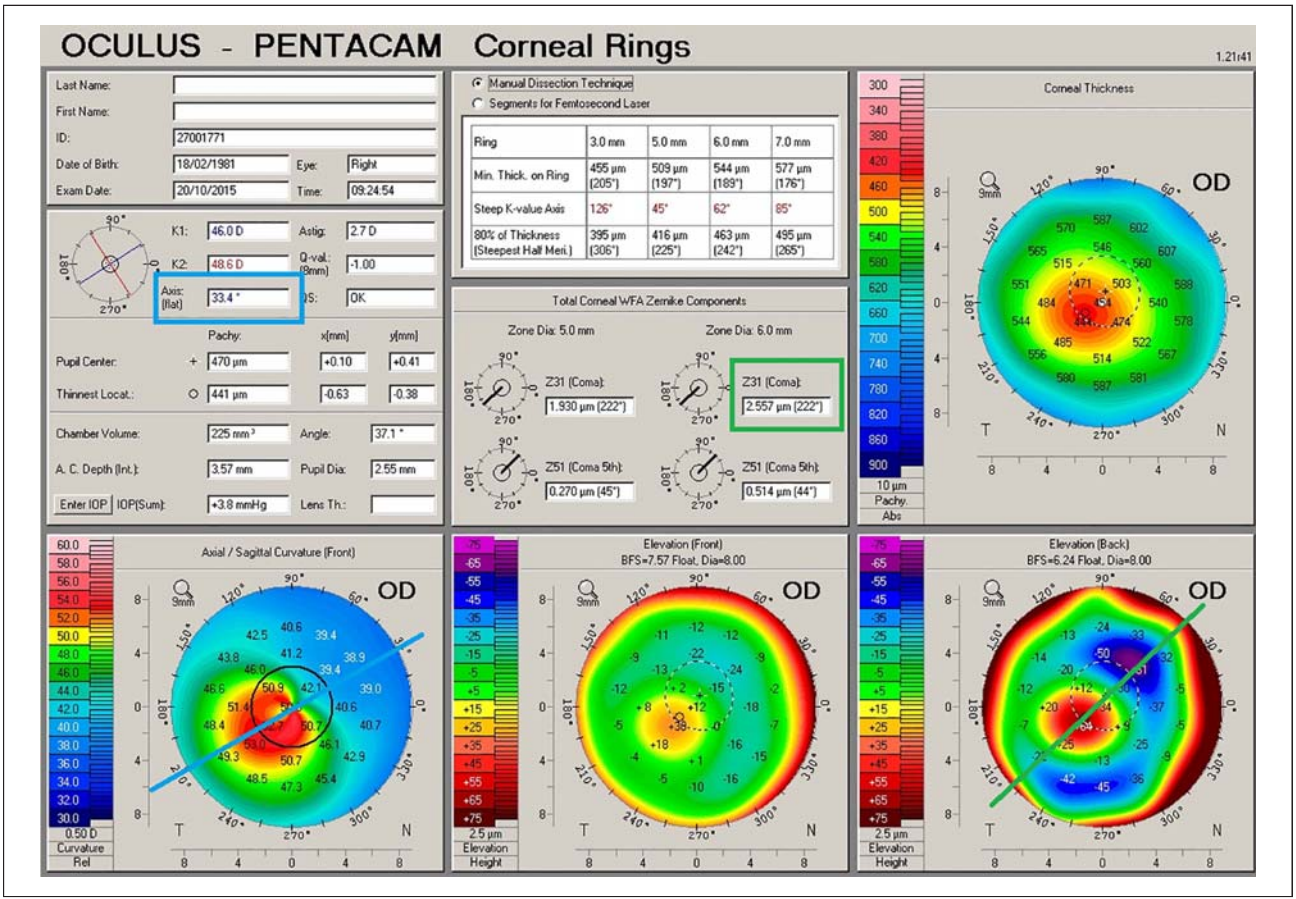

Figure 2. Preoperative corneal topography and coma wavefront map (Pentacam®; Oculus, Germany). Note the topographic (blue arrow) and coma (green arrow) axes.

Table 1. Patients' demographics.

Characteristics	Manual group	Femtosecond laser group	*p* value
Eyes (*n*)	84	110	–
Age (years)	31.80 ± 11.55	34.2 ± 12.0	0.14
Mean SE (D)	−3.17 ± 3.16	−3.51 ± 4.55	0.3
Mean refractive sphere (D)	−1.58 ± 2.88	−1.41 ± 4.48	0.4
Mean refractive cylinder (D)	−3.19 ± 1.70	−4.20 ± 2.32	0.0003
Mean K minimum (D)	44.94 ± 2.62	45.72 ± 2.88	0.02
Range K minimum (D)	38.75–51.75	39.25–54.00	–
Mean K maximum (D)	48.50 ± 2.98	49.42 ± 3.68	0.03
Range K maximum (D)	40.50–56	41.25–58.50	–
UDVA (logMAR)	0.88 ± 0.35	0.86 ± 0.36	0.34
CDVA (logMAR)	0.34 ± 0.21	0.30 ± 0.15	0.10

UDVA: uncorrected distance visual acuity; CDVA: corrected distance visual acuity; ICRS: intrastromal corneal ring segment.
Age, pre-ICRS implantation spherical equivalent (SE), pre-keratometry (K) value,DVA and CDVA shown as mean ± standard deviation (SD) and range.

surgery, we observed a statistically significant improvement in UDVA and CDVA for both groups ($p < 0.0001$), and there were no statistically significant differences between groups ($p > 0.3$). Preoperatively, CDVA was 0.3 logMAR (about 20/40) or better in 61.90% and 66.34% of eyes in the manual and femtosecond laser groups, respectively; after surgery, 89.29% in the manual group and 88.18% in the femtosecond group reached a CDVA value of 0.3 logMAR or better. In the manual group, there was also an increase in the number of eyes reaching a CDVA of 0.1 logMAR (about 20/25) or better: from 13.09% before surgery to 35.7% after ICRS implantation.

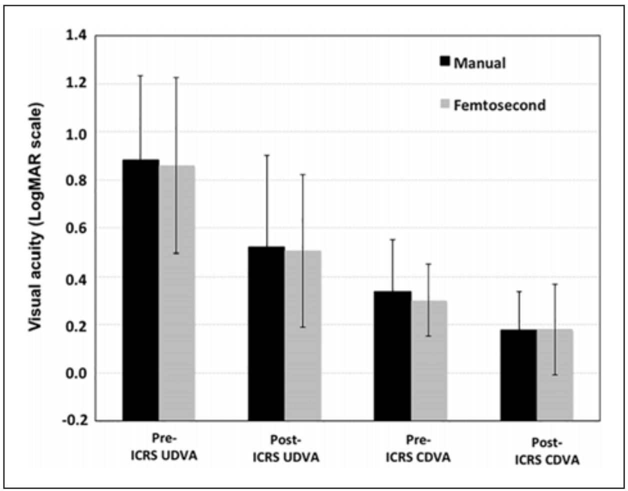

Figure 3. Uncorrected visual acuity (UDVA) and best-corrected visual acuity (CDVA) before and at 6 months after ICRS implantation (efficacy).

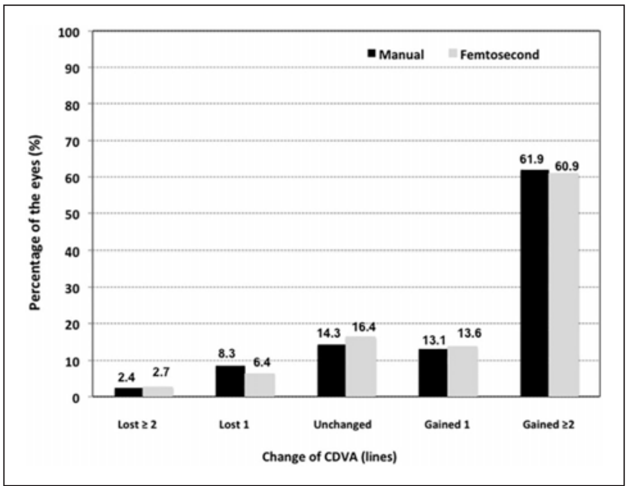

Figure 4. Variation in CDVA 6 months after ICRS implantation (safety).

For the femtosecond laser group, none of the eyes had a CDVA value of 0.1 logMAR or better before surgery; however, after ICRS implantation, 43.64% of the eyes reached a CDVA of 0.1 logMAR or better. Overall, the visual acuity results in terms of safety were similar in both groups, achieving an equivalent proportion of patients with lines of CDVA gained or eyes losing lines of CDVA (Figure 4): in the manual group, 2.4% of eyes ($n=2$) lost two or more lines of CDVA, while 61.9% ($n=52$) gained two or more lines of CDVA; in the femtosecond group, 2.7% of eyes ($n=3$) lost two or more lines of CDVA, while 60.1% ($n=67$) gained two or more lines of CDVA. The 6-month efficacy index (mean postoperative UDVA/mean preoperative CDVA) was 0.79 for the manual group and 0.74 for the femtosecond group. The 6-month safety indexes (postoperative CDVA/preoperative CDVA) were

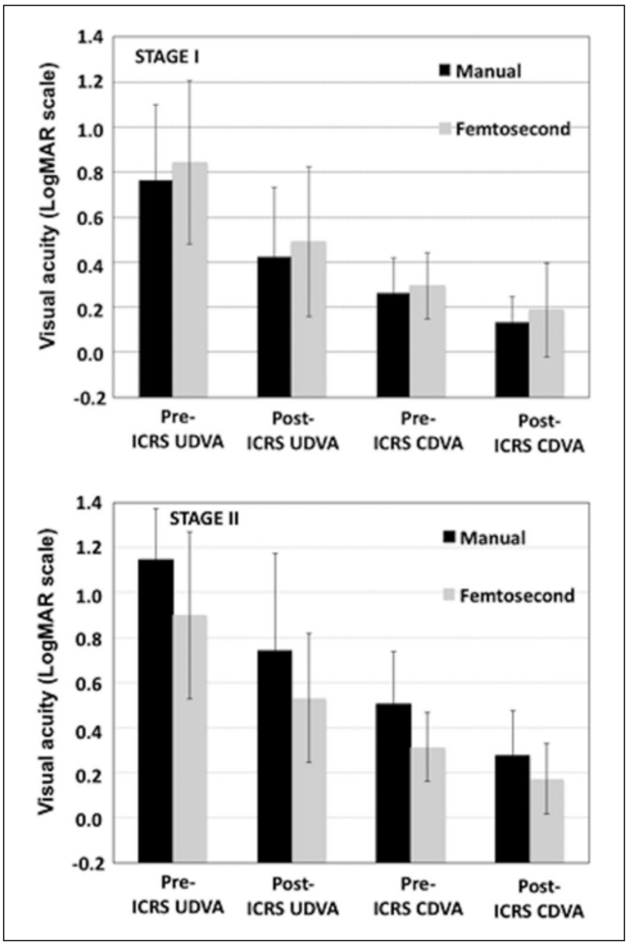

Figure 5. UDVA and CDVA for both groups (efficacy) analysed as a function of the stage of keratoconus.

1.38 and 1.34 for the manual and femtosecond groups, respectively.

Figure 5 shows the UDVA and CDVA for both groups, but in this case, divided as a function of the stage of keratoconus: there were 124 eyes with stage I and 70 with stage II. For stage I, 58 eyes had ICRS implantation with manual technique and 66 eyes with femtosecond laser. There was a statistically significant increase in UDVA and CDVA 6 months after ICRS implantation in both groups ($p < 0.0001$): the mean changes in UDVA values were 0.34 ± 0.29 (logMAR) and 0.31 ± 0.45 for the manual and femtosecond groups, respectively ($p=0.3$). The mean change in the CDVA value, in turn, was 0.13 ± 0.16 (logMAR) for the manual group and 0.11 ± 0.16 for the femtosecond group ($p=0.24$). In the stage II patients, 26 eyes had ICRS implantation with manual technique and 44 eyes with femtosecond laser; we observed a statistically significant increase in UDVA and CDVA 6 months after ICRS implantation in both groups with stage II ($p < 0.0001$). When comparing manual versus femtosecond surgeries, both preoperatively and postoperatively, the UDVA and CDVA were statistically significantly better in the femtosecond group ($p=0.002$ and 0.02 for preoperative and postoperative UDVA and $p<0.001$ and 0.01 for preoperative and postoperative CDVA, respectively). However, there were no statistically significant differences in the magnitude of increase in UDVA and CDVA between groups: the changes in UDVA were 0.41 ± 0.36 (logMAR) and 0.39 ± 0.33 ($p=0.4$) for the manual and femtosecond groups and the changes in CDVA were 0.22 ± 0.21 and 0.14 ± 0.15 ($p=0.06$) for each group, respectively. For both stages, the visual acuity results regarding safety were similar for both techniques, achieving an equivalent proportion of patients with lines of CDVA gained or eyes losing lines of CDVA (Figure 6).

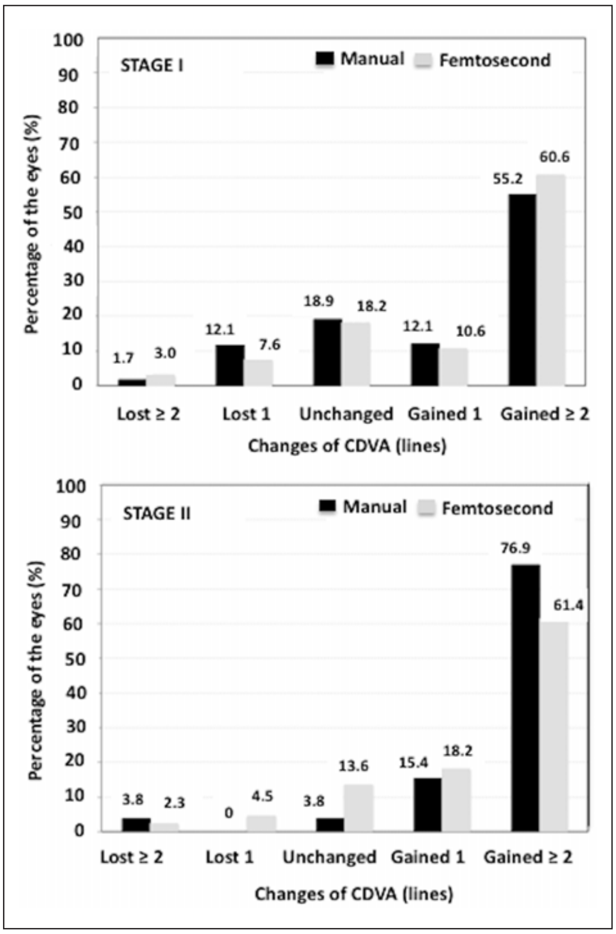

Figure 6. Variation in CDVA 6 months after ICRS implantation (safety) for both groups analysed as a function of the stage of keratoconus.

Refractive and aberrometric outcomes

Table 2 shows a summary of the distribution of manifest refractive error before and after ICRS implantation for each group, following the power vector analysis. For both groups, there was a reduction in the spherical equivalent and in the blur strength (B) value after ICRS implantation ($p<0.0001$). There were no statistically significant differences between groups in the magnitude of spherical equivalent and B value reduction ($p=0.34$ and 0.08 for spherical equivalent and B value, respectively). Figure 7 shows the astigmatism component of the power vector represented by a two-dimensional vector for both groups. The origin of the graph (0, 0) represents an eye free of astigmatism. For both groups, the spread of the post-ICRS implantation data from the origin is more concentrated than the spread of preoperative data. In order to compare the efficacy of the astigmatism correction between groups, an astigmatism index of success (AIS) was defined as the ratio between the induced cylinder and intended cylinder (AIS=(Cyl post−Cyl pre/Cyl pre)). The mean AIS was 0.45 ± 0.51 and 0.50 ± 0.65 for the manual and femtosecond groups, respectively ($p=0.23$); 49 eyes (59.03%) in the manual group, and 67 eyes (61%) in the femtosecond group, had a decrease in cylinder power higher than 50%.

The refractive outcome comparison between both groups, for stage I and II separately, shows no statistically significant differences in any refractive parameters analysed. For stage I, in the manual group, the reduction in spherical equivalent was 0.72 ± 1.27 D, whereas in the femtosecond group, it was 0.54 ± 1.89 D ($p=0.3$). The mean AIS was 0.44 ± and 0.54 ± 0.29, for the manual and femtosecond groups, respectively ($p=0.1$). For stage II, the decrease of spherical equivalent was 1.28 ± 4.51 D for the manual group and 1.82 ± 3.21 D for the femtosecond group ($p=0.3$). The mean AIS was 0.46 ± 0.51 and 0.44 ± 0.37, for the manual and femtosecond groups, respectively ($p=0.4$).

The root mean square (RMS) for corneal coma-like aberrations also decreased significantly at 6 months after ICRS implantation in both groups ($p<0.0001$). The magnitude of the reduction was 0.93 ± 0.76 µm in the manual group and 0.83 ± 0.80 µm in the femtosecond group ($p=0.2$). For stage I, the decrease was 0.83 ± 0.56 µm in the manual group, whereas in the femtosecond group, it was 0.74 ± 0.65 µm ($p=0.07$). For stage II, the magnitude of the reduction was 1.20 ± 1.16 and 1.11 ± 1.04 µm, for the manual and femtosecond groups, respectively ($p=0.4$).

Topographic results

There was a decrease in keratometric values after ICRS implantation for both groups (Table 3). The magnitude of keratometric value reduction was similar in both groups. The mean reduction in the minimum keratometry value was 0.36 ± 1.63 D in the manual group, whereas in the femtosecond group, it was 0.59 ± 1.18 D ($p=0.07$). The mean maximum keratometry value, in turn, decreased to 1.81 ± 1.43 and 2.14 ± 1.55 D, for the manual and femtosecond groups, respectively ($p=0.07$).

Table 2. Summary of distribution of manifest refractive errors before and at 6 months after ICRS implantation, following the power vector method.

	Before	After	*p* value
	Manual group		
M	−3.17 ± 3.16	−2.24 ± 2.86	<0.0001
J_0	−0.37 ± 1.05	−0.08 ± 0.59	0.02
J_{45}	0.19 ± 1.43	0.02 ± 0.71	0.17
B	3.73 ± 3.06	2.63 ± 2.68	<0.0001
	Femtosecond group		
M	−3.51 ± 4.55	−2.46 ± 4.16	<0.0001
J_0	−0.41 ± 1.55	−0.57 ± 0. 71	0.13
J_{45}	−0.12 ± 1.79	0.07 ± 0.72	0.12
B	4.72 ± 4.05	3.16 ± 3.83	<0.0001
	Comparison between groups		
	Manual group	Femtosecond group	
M change	0.89 ± 2.70	1.05 ± 0. 65	0.34
J_0 change	0.27 ± 1.20	−0.17 ± 1.65	0.01
J_{45} change	−0.17 ± 1.74	0.19 ± 2.65	0.08
B change	−1.06 ± 2.65	−1.56 ± 4.65	0.09

ICRS: intrastromal corneal ring segment.
Data are shown as mean ± standard deviation.
Manifest refraction in conventional script notation (S (sphere), C (cylinder) × α (axis)) was converted to power vector coordinates and overall strength blur by the following formulas: $M = S + C/2$, $J_0 = (-C/2)\cos(2\alpha)$, $J_{45} = (-C/2)\sin(2\alpha)$ and $B = (M^2 + J_0^2 + J_{45}^2)^{1/2}$.

Complications

In the manual group, we observed a total of 11 (of 84 eyes) intraoperative or postoperative complications, an overall rate of 13.09%. We report two spontaneous ICRS extrusions (no loss of CDVA because both patients were re-operated), two intraoperative corneal ruptures (with loss of CDVA), one late endothelial perforation due to intense uncontrolled eye rubbing (with loss of CDVA), one decentred intrastromal tunnel (with loss of CDVA) and five eyes with re-interventions due to a shallow intrastromal tunnel, superficial implants and astigmatism overcorrection. In the late cases, the superior nasal ICRS was explanted, and all the eyes gained lines of CDVA.

In the femtosecond laser group, there were no intraoperative or postoperative complications to report.

Discussion

Our study compares the visual, refractive, topographic and aberrometric results between manual and femtosecond laser–assisted surgery for ICRS implantation in a specific and homogeneous population of keratoconus. We have found no difference between both surgical techniques concerning visual, refractive, topographic and aberrometric parameters, achieving a similar proportion of eyes losing or gaining lines of CDVA and the same index of astigmatism correction in both groups. It seems to be more critical for better visual and refractive outcomes to implement a correct classification of the ectasia and a personalized nomogram of implantation, rather than the surgical procedure itself. However, beyond visual and refractive outcomes, it

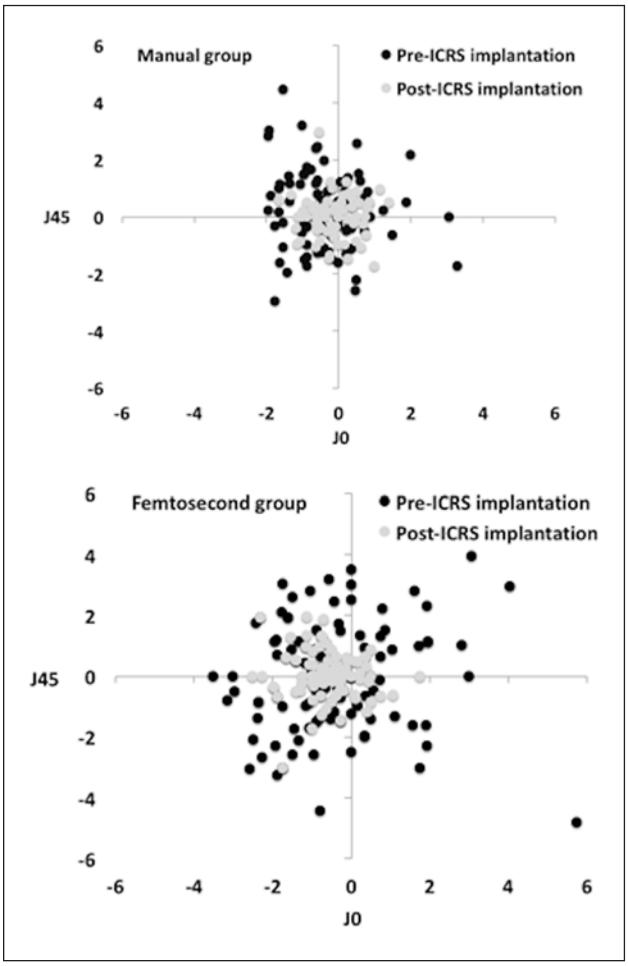

Figure 7. Representation of the astigmatic vector (J_0 and J_{45}) before surgery and at 6 months after ICRS implantation for both groups.

Table 3. Summary of keratometric values before and at 6 months after ICRS implantation for both groups.

	Before	After	*p* value
	Manual group		
K minimum	44.94 ± 2.62	44.67 ± 2.63	0.04
K maximum	48.50 ± 2.98	46.70 ± 0.59	<0.0001
K mean	46.72 ± 2.72	45.72 ± 45.68	<0.0001
	Femtosecond group		
K minimum	45.72 ± 2.88	45.12 ± 2.61	0.02
K maximum	49.42 ± 3.68	47.28 ± 2.93	<0.0001
K mean	47.42 ± 3.04	46.20 ± 2.74	<0.0001

ICRS: intrastromal corneal ring segment.

should be noted the manual mechanical technique had a higher rate of complications than the femtosecond technique, demonstrating, as previously reported,[13] that the femtosecond laser–assisted surgery is a safer procedure.

This is the first published study comparing both techniques of ICRS implantation for the treatment of keratoconus, taking into consideration the morphologic characteristics of the sample: we have included only patients with paracentral keratoconus in which the difference between the coma axis and the flat topographic axis was <60° and all patients were treated with a similar Ferrara-type ICRS arc length at the 6.00-mm optical zone. Previously,[4–6] our investigation group has demonstrated the importance and utility of describing the keratoconus in terms of the morphology of the ectasia; this classification will better enable a more personalized ICRS nomogram development. As mentioned earlier, the previous published studies addressing the comparison of both techniques have demonstrated several limitations, mostly because the populations of study and the nomograms of treatment were different between the groups being compared; this could have weakened the conclusions reached in those studies.

The first study performed comparing manual mechanical dissection and femtosecond laser surgery was published in 2006 by Rabinowitz et al.[11] At that time, the results were similar between both techniques, although the number of patients included was limited, the time points of comparison were different between groups (6 months for the femtosecond group and 12 months for the manual group) and, most of all, the nomogram and the optical zone of implantation varied from patients in the same group. Carrasquillo and Rand[8] also compared both techniques; the authors also found no differences between both techniques for UDVA and CDVA; however, they included in the same sample patients with keratoconus and ectasia post-LASIK, and the type and location of ICRSs were the same for all eyes, regardless of their preoperative characteristics. In 2009, Piñero et al.[9] found no major differences between both procedures, except for a better improvement of CDVA in the femtosecond laser group and also a significant difference for primary spherical aberration, coma and high-order aberrations, favouring the femtosecond group. They concluded that a more limited aberrometric correction is observed for eyes with mechanical implantation. This study comprised a large sample of patients (146 eyes of 103 patients); however, different types of ICRSs were used: 80 eyes were implanted with Intacs (Addition Technology, Inc, Lombard, IL, USA) and 66 eyes were implanted with Keraring (Mediphacos). Intacs were implanted in 87.30% of eyes in the mechanical group and in 31.25% of eyes in the femtosecond group. Hence, these differences could be partly explained by the fact that different ring segment profiles were implanted in each group. On the other hand, more than half of the patients were keratoconus grade 3 or 4.

In 2010, Kubaloglu et al.[10] were the first to publish a randomized clinical trial comparing both surgical procedures in a homogeneous population of keratoconus patients. In their study, the same surgeon, using the same nomogram of implant characteristics, carried out all surgeries: the authors found no difference between both surgical techniques. All ICRSs implanted in that study were at the 5.0-mm optical zone and with a 160° arc length, independently of the keratoconus morphologic characteristics, which the authors do not describe. Also in Kubaloglu's sample, half of the eyes treated were Amsler–Krumeich grade 3 or 4.

From these previous studies, it seems that both techniques provide comparable visual and refractive outcomes. However, the variability in the characteristics of the eyes analysed, the nomograms and ICRSs used make it difficult to assess whether both procedures are really comparable. One important aspect to emphasize from our sample is that we compared only patients with the same morphologic characteristics of the ectasia: the thinnest point located between 0.7 and 1.6 mm from the pupil centre (paracentral type) and having a difference between the topographic flattest axis and the coma aberration axis lower than 60°. Furthermore, as ICRS implantation has shown to be more effective for moderate keratoconus,[14] we included only keratoconus with grade 1 or 2 of the Amsler–Krumeich classification. Both groups (manual and femtosecond laser) were treated with the same ICRS type and according to the same nomogram, which was shown to be effective and safe for these types of keratoconus.[4,5] Our results show a significant improvement in UDVA, CDVA, refractive error and RMS for corneal coma-like aberrations after ICRS implantation in both groups, and differences were not found between both surgical techniques at any of the parameters analysed. However, as mentioned earlier, the number of complications with the manual technique is higher than that with the femtosecond technique.

The vectorial analysis performed in our sample corroborates the efficacy of both surgical techniques in terms of astigmatism correction. There was a significant improvement in the magnitude of the astigmatic vector. This result confirms that both methods offer a safe reduction of astigmatism without inducing a significant change in the direction of the vector, which could produce an overcorrection and a considerable change in the axis of astigmatism. No previous studies comparing both techniques have used a vectorial analysis calculation to perform the comparison. Our results show a similar efficacy in terms of astigmatism correction for both techniques: the mean AIS was 0.45 ± 0.51 and 0.50 ± 0.65, for the manual and femtosecond groups, respectively ($p = 0.23$); 49 eyes (59.03%) in the manual group, and 67 eyes (61%) in the femtosecond group, had a decrease in cylinder power higher than 50%. Once again, these results suggest that both the surgical technique and the correct ICRS nomogram (based on a morphological classification of the ectasia) are the mainstays of success in ICRS surgery for keratoconus correction.

Before the advent of femtosecond laser technology, channel creation required for ICRS implantation was only achievable manually using mechanical devices. Studies have shown that manual channel creation for ICRS implantation has been associated with various potential complications, including infectious keratitis, epithelial defects, anterior or posterior corneal perforations, corneal stromal oedema around the incision, extension of the incision towards the central visual axis or the limbus and asymmetric segment placement.[13–17] We have previously reported that ICRS implantation with femtosecond laser–assisted surgery is a more precise technique, achieving a more accurate implantation depth, with no difference between the intended and the achieved depth of implantation, when compared to a manual mechanical procedure.[7] Safety parameters are the main difference observed between techniques in our study. Although the proportion of eyes losing two or more lines of CDVA was similar in both groups (2.4% in the manual group vs 2.7% in the femtosecond laser group), in the manual group, there was a higher rate of mechanical complications, both intraoperative or postoperative, and some of them inducing loss of lines of CDVA. In some cases, however, the patients were re-operated 3 months afterward, regaining lines of UDVA and CDVA at the last follow-up visit evaluation. In the femtosecond laser group, the loss of lines of CDVA can be attributed to a loss of efficacy of the implant or the nomogram, while in the manual group, the occurrence of intraoperative or postoperative complications can be directly related to a loss of visual acuity. However, many complications can be overcome by a new surgical procedure or ICRS adjustment surgery. This can be explained by the fact that ICRS implantation is a reversible and adjustable procedure, and in cases of complications or refractive surprises, the procedure can be adjusted, whether by changing the type of implant or just by repeating the procedure, once the cornea has regained its original status.[18]

In order to adequately address the surgical treatment of keratoconus by the implantation of ICRSs and to obtain a good visual and refractive result, it is more critical to apply an accurate classification of the disease based on the phenotype characteristics of the ectasia and to choose the most specific implant type and combination correctly. The surgical procedure used for the implantation seems to be less critical for the visual and refractive outcomes. Nonetheless, it should be noted that the femtosecond laser is a safer surgical procedure, with no complications reported. Furthermore, it should be considered that in the current study, the postoperative follow-up was 6 months; perhaps the rate of extrusions could increase over a longer follow-up time, mainly with the manual technique due to the lower predictability for the tunnel creation.[7]

In conclusion, our study demonstrates that there are no significant differences between the two surgical techniques available for ICRS implantation regarding visual, refractive, topographic and aberrometric outcomes. However, the femtosecond laser–assisted procedure showed a safer profile, with no intraoperative or postoperative complications reported in a large sample of patients included.

Declaration of conflicting interests

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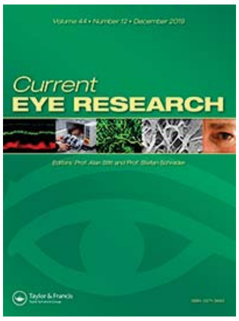
References

1. Gomes JA, Tan D, Rapuano CJ, et al. Global consensus on keratoconus and ectatic diseases. *Cornea* 2015; 34(4): 359–369.
2. Giacomin NT, Mello GR, Medeiros CS, et al. Intracorneal ring segments implantation for corneal ectasia. *J Refract Surg* 2016; 32: 829–839.
3. Poulsen DM and Kang JJ. Recent advances in the treatment of corneal ectasia with intrastromal corneal ring segments. *Curr Opin Ophthalmol* 2015; 26(4): 273–277.
4. Fernandez-VegaCueto L, Lisa C, Poo-Lopez A, et al. Intrastromal corneal ring segment implantation in 409 paracentral keratoconic eyes. *Cornea* 2016; 35(11): 1421–1426.
5. Alfonso JF, Fernandez-VegaCueto L, Baamonde B, et al. Inferior intrastromal corneal ring segments in paracentral keratoconus with no coincident topographic and coma axis. *J Refract Surg* 2013; 29(4): 266–272.
6. Lisa C, Fernandez-VegaCueto L, Poo-Lopez A, et al. Long-term follow-up of intrastromal corneal ring segments (210-degree arc length) in central keratoconus with high corneal asphericity. *Cornea* 2017; 36(11): 1325–1330.
7. Monteiro T, Alfonso JF, Franqueira N, et al. Predictability of tunnel depth for intrastromal corneal ring segment (ICRS) implantation between manual or femtosecond laser: comparative study. *J Refract Surg* 2018; 34: 188–119.
8. Carrasquillo KG and Rand J. Intacs for keratoconus and post–lasik ectasia – mechanical versus femtoscond laser assisted channel creation. *Cornea* 2007; 26: 956–962.
9. Piñero DP, Alio JL, ElKady B, et al. Refractive and aberrometric outcomes of intracorneal ring segments for keratoconus: mechanical versus femtosecond-assisted procedures. *Ophthalmology* 2009; 116(9): 1675–1687.
10. 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): 1556–1561.
11. Rabinowitz YS, Li X, Ignacio TS, et al. INTACS inserts using the femtosecond laser compared to the mechanical spreader in the treatment of keratoconus. *J Refract Surg* 2006; 22(8): 764–771.

12. Thibos LN and Horner D. Power vector analysis of the optical outcome of refractive surgery. *J Cataract Refract Surg* 2001; 27(1): 80–85.
13. Monteiro T, Alfonso JF, Freitas R, et al. Comparison of complication rates between manual and femtosecond laser-assisted techniques for intrastromal corneal ring segments implantation in keratoconus. *Curr Eye Res*. Epub ahead of print 1 July 2019. DOI: 10.1080/02713683.2019.1635165.
14. Alfonso JF, Lisa C, Fernandez-Vega L, et al. Intrastromal corneal ring segment implantation in 219 keratoconic eyes at different stages. *Graefes Arch Clin Exp Ophthalmol* 2011; 249(11): 1705–1712.
15. Zare MA, Hashemi H and Salari MR. Intracorneal ring segment implantation for the management of keratoconus: safety and efficacy. *J Cataract Refract Surg* 2007; 33(11): 1886–1891.
16. Kanellopoulos AJ, Pe LH, Perry HD, et al. Modified intracorneal ring segment implantations (INTACS) for the management of moderate to advanced keratoconus: efficacy and complications. *Cornea* 2006; 25(1): 29–33.
17. Ruckhofer J, Stoiber J, Alzner E, et al. One year results of European Multicenter Study of intrastromal corneal ring segments. Part 2: complications, visual symptoms, and patient satisfaction. *J Catar Refract Surg* 2001; 27: 287–296.
18. Monteiro T, Mendes JF, Faria-Correia F, et al. Adjustment of intrastromal corneal ring segments after unsuccessful implantation in keratoconic eyes. *Cornea* 2018; 37(2): 182–188.

CHAPTER VI - Comparison of complication rates between manual and femtosecond laser-assisted techniques for intrastromal corneal ring segments implantation in keratoconus



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Comparison of Complication Rates between Manual and Femtosecond Laser-Assisted Techniques for Intrastromal Corneal Ring Segments Implantation in Keratoconus

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Comparison of Complication Rates between Manual and Femtosecond Laser-Assisted Techniques for Intrastromal Corneal Ring Segments Implantation in Keratoconus

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ABSTRACT

Purpose: To compare the incidence of complications between manual and femtosecond-laser assisted surgery for intrastromal corneal ring segments (ICRS) implantation.

Material and methods: This study included keratoconus patients who had ICRS implantation using manual dissection and using the femtosecond laser with a minimum follow-up of 12 months. Uncorrected (UDVA) corrected (CDVA) distance visual acuity (CDVA), refraction, corneal topography and aberrometry, pachymetry map and slit-lamp microscopy were assessed before and after surgery.

Results: The study included 265 eyes in the manual group and 111 in the femtosecond laser group. In the manual group, there were complications in 48 eyes (18.11%); while in the femtosecond laser 4 eyes had a complication (3.6%). In the manual group, the most frequent complications were ICRS exchange/adjustment for visual and refractive enhancement (25 eyes; 9.43%) and late ICRS spontaneous extrusion (15 eyes; 5.66%). In the manual group, 81.25% of complications were observed during the first 3 years of surgeon's experience. Eyes who suffered a complication had preoperatively higher mean refractive (p = .002) and topographic cylinder (p = .003) and lower UDVA (p = .005) and CDVA (p = .002). After a second surgical procedure for complication management visual, refractive and topographic outcomes significantly improved.

Conclusion: Manual mechanical ICRS surgery shows a higher rate of intra- and postoperative mechanical and refractive complications when compared to femtosecond laser assisted technique. The incidence is specially higher during the surgeon's first years of implementation of the technique.

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Introduction

The success of intrastromal corneal ring segments (ICRS) implantation for the treatment of keratoconus, as with any refractive procedure, depends on two main factors: efficacy and safety. Efficacy is determined by a correct indication for surgery and the appropriate characteristics of the implant according to the preoperative morphological characteristics of the ectasia (location; relationship between the flattest topographic axis and the coma axis, amount of astigmatism, among others.)[1–5] Safety is determined by the surgeon's experience (specially in manual procedure) and by a correct and precise implantation inside the corneal stroma, avoiding complications such as corneal perforation, shallow implantation and late spontaneous extrusion.

Earlier studies have shown that manual channel creation for ICRS implantation has been associated with various potential complications, including epithelial defects, anterior or posterior corneal perforations, extension of the incision towards the central visual axis or the limbus and asymmetric or superficial segment placement.[6–8] The rate of extrusion and implant explantation varies from 1.0% to 13.3% with Intacs-ICRS[8–11] and 1.0% to 19.6% with Ferrara-ICRS;[12–14] refractive adjustment from 10.3% to 14.0%,[15,16] decentration from 3.9% to 4.4%,[14,17] superficial implants from 3.6% to 7.6%[13,18] and asymmetric implants from 3.0% to 3.8%.[18,19] In turn, it has been recently reported that femtosecond laser assisted surgery is more precise regarding depth predictability of the tunnel;[20] the incidence of complications reported is much lower.[9,21–23] However, none of the studies published reporting complications with ICRS surgery was able to establish a relationship between complications and preoperative patient demographics, visual, refractive or topographic characteristics. Other important aspects which were not addressed in previous studies were the frequency of complications during the surgeon's learning curve or the visual and topographic final outcomes after its surgical resolution.

The objective of the current study was to investigate and compare the incidence of complications between manual

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and femtosecond laser assisted surgery by the same surgeon and its relationship with the preoperative patient and ectasia characteristics as well as the final result after its resolution.

Material and methods

Study design

This retrospective multicentre study included patients with keratoconus that had ICRS implantation at the Ophthalmology Department of Hospital de Braga, Portugal (manual surgery) and the Ophthalmology Department of Hospital CUF, Porto, Portugal (femtosecond laser surgery) between 2011 and 2017 and a minimum follow-up of 12 months. The tenets of the Declaration of Helsinki were followed, and full ethical approval from the institute was obtained. After receiving a full explanation of the nature and possible consequences of the study and surgery, all patients provided informed consent.

Inclusion criteria were keratoconus, contact lens intolerance, a clear cornea, maximum keratometry (K) reading (simK2) up to 58 diopters (D), minimum K reading of 40 D or more, and minimum corneal thickness of 400 µm. Also, inclusion criteria considered stages I to IV according to the Amsler-Krumeich keratoconus classification. All eyes included must have fulfilled the classic clinical, slit-lamp and topography findings to confirm the diagnosis of keratoconus. Topography was provided by a rotating camera Scheimpflug system (Pentacam, Oculus Optikgeräte GmbH, Wetzlar, Germany).

Exclusion criteria included previous corneal or intraocular surgery, history of herpetic keratitis, diagnosed autoimmune disease, systemic connective tissue disease, endothelial cell density less than 2,000 cells/mm^2, cataract, history of glaucoma or retinal detachment, macular degeneration or retinopathy, neuro-ophthalmic disease, and history of ocular inflammation.

Ferrara-type ICRS

All eyes in the study received the Keraring® SI 5 and SI6 ICRS (Mediphacos® Inc., Belo Horizonte, Brazil). These Ferrara-type ICRS are made of polymethylmethacrylate with a triangular cross-section that induces a prismatic effect on the cornea. The apical diameter of the ICRS is 5.0 or 6.0 mm, and the flat basis width is 600 to 800 µm with variable thickness (150, 200, 250, and 300 µm) and arc lengths (90°, 120°, 150° and 210º). The ICRS were implanted following the nomogram used in previous studies[1–4] and also according to the Mediphacos nomogram.[9]

Preoperative examination

Before and after ICRS implantation, patients had a complete ophthalmologic examination including uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), manifest refraction, corneal topography and corneal aberrometry with Pentacam® (Oculus®, Germany), endothelial cell count (Tomey EM-3000 Specular Microscope; Tomey Corp, Japan), slit-lamp microscopy, Goldmann applanation tonometry and binocular indirect ophthalmoscopy through a dilated pupil. The pachymetry map was performed using the Visante® (optical coherence tomography system (Carl Zeiss® Meditec, Inc., Germany). Contact lens use was discontinued one month before corneal topography was performed.

Surgical technique

The same surgeon (Tiago Monteiro) performed all the manual mechanical surgeries at Hospital de Braga and all implantation procedures using femtosecond laser at the Hospital CUF Porto. Preoperative medications included proparacaine 0.5%, ciprofloxacin 0.3%, and oxybuprocaine ClH 0.2%.

Manual mechanical surgery

Using a marker tinted with gentian violet, a 5.00 or 6.00 mm optical zone and incision site were aligned to the desired axis in which the incision would be made. The incision site was always performed 90 degrees away from the flattest topographic axis of the cornea given by the topographer. A square diamond blade was set at 80% of the thinnest point along the implantation optical zone track; this blade was used to make the incision. Corneal thickness was measured intraoperatively with ultrasonic pachymetry. Using a "stromal spreader", a pocket was formed on each side of the incision. Two (clockwise and counterclockwise) 270º semicircular dissecting spatulas were consecutively inserted through the incision and gently pushed with some quick, rotary "back and forth" tunneling movements. Following channel creation, the ring segment was inserted using modified McPherson forceps and properly positioned with the aid of a Sinskey hook, centered on the flattest topographic corneal axis.

Femtosecond laser surgery

After the center of the pupil was marked and corneal thickness at the area of implantation (5.0 or 6.0-mm diameter) was measured by ultrasonic pachymetry, a disposable suction ring was placed and centered with respect to the pupil center. A tunnel was created at 70% corneal thickness using a 200-KHz femtosecond laser (FS 200®; Alcon WaveLight®, USA). This infrared neodymium glass femtosecond laser has a wavelength of 1,053 nm. The laser beam, which has a 3-µm diameter (spot size), is optically focused at a predetermined intrastromal depth by computer scanners, which gives a focus (dissection) range between 90 and 400 µm from the corneal anterior surface. The beam forms cavitations, microbubbles of carbon dioxide, and water vapor by photodisruption, and the interconnecting series of these bubbles form a dissection plane. An inner diameter of 4.9 or 5.9 mm and an outer diameter of 6.1 or 7.1 mm was programmed with the laser software, giving a tunnel width of 1.2 mm and an incision length of 1.7 mm on the steepest topographic axis. In all eyes, the power used to create the tunnel and the incision was 5 mJ. The procedure lasted approximately 15 seconds. Five minutes later, and after clearance of the gas bubbles, the ICRS were implanted under full aseptic conditions with dedicated forceps. The implant was placed in the final position with a Sinskey hook through a dialing hole at both ends of the segment.

Postoperative treatment for both surgical procedures was the same and included a combination of antibiotic (tobramycin, 3 mg/ml) and steroid eye drops (dexamethasone, 1 mg/ml) (Tobradex; Alcon Laboratories, Inc., Forth Worth, TX) three times daily for 2 weeks with tapering of the dose for 2 more weeks.

Postoperative examination

Patients were scheduled for postoperative clinical evaluation at 1 day, 1 week, 1, 6 and 12 months. A standard ophthalmologic examination, including manifest refraction, slit-lamp biomicroscopy, Goldmann applanation tonometry, binocular indirect ophthalmoscopy, corneal topography, corneal aberrometry, UDVA, and CDVA, was performed at all follow-up visits. All examinations were performed by the same ophthalmic technician who was unaware of the objective of the study.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA) was used for the descriptive statistics, including means ± standard deviations. Normality of all data samples was first checked using the Kolgomorov-Smirnov test. The Student's t-test for paired data was used to compare preoperative and postoperative data when normality was present. Where parametric analysis was not possible, the Wilcoxon rank sum test was used to assess the significance of differences between preoperative data and postoperative data and the Mann-Whitney test to compare data between non-related samples. To analyze multiple outcome measures a repeated-measures analysis of variance (ANOVA) or Friedman test and Bonferroni test was performed to compare outcomes. In all cases, differences were considered statistically significant when the p value was less than 0.05.

Results

Sample

The study included 376 eyes of 376 patients; 265 in the manual group and 111 in the femtosecond laser group. Table 1 shows the patients demographics before surgery. A similar distribution of age, Amsler grade and mean keratometry between both groups was observed; however, the manual group presented a significantly higher mean value of Kmax (p = .001). The pachymetry map revealed no significant difference between the thinnest value measured along the optical zone of ICRS implantation. The overall thinnest pachymetry value was significantly lower in the manual group) than in the femtosecond group.

Visual acuity and refractive outcomes

Preoperatively, no significant differences were observed between groups for UDVA, CDVA and sphere (Table 2). The mean refractive cylinder was higher in the manual group preoperatively (−3.39 ± 2.04 D versus −2.78 ± 1.47 D, p = .03) and also postoperatively at 12 months follow up (−1.57 ± 1.50 D versus −1.20 ± 0.94 D, p = .006); however, the magnitude of astigmatism correction was similar between both groups (46.3% in the manual group and 43.2% in the femtosecond group). After 12 months, UDVA was similar for both groups; however, the mean CDVA was significantly higher in the femtosecond laser group when compared to the manual (0.73 ± 0.19 and 0.65 ± 0.25, respectively; p = .001).

Topography and aberrometric outcomes

At 12 month's follow-up, no difference was observed between groups for K1, K2, Coma and asphericity (Q) (Table 2). There was a significantly higher mean topographic cylinder value in the manual group, both pre (p = .004) and postoperatively (p = .01). The magnitude of topographic cylinder reduction was 31.8% in the manual group and 36.6% in the femtosecond group.

Complications – whole sample

Table 3 describes the complications observed in each group. In the manual group, we observed a total of 48 complications in 265 eyes (18.11%) and in the femtosecond laser 4 complications in 111 eyes (3.6%). In the manual group, the most frequent complications described were ICRS exchange/adjustment for visual and refractive enhancement (25 eyes; 9.43%) and late ICRS spontaneous extrusion (15 eyes; 5.66%). In the manual group, the majority of complications (81.25%) were observed during the first 3 years of experience (2011–2014), while 12.75% appeared during the last 3 years of experience (2015–2017).

Complications in manual group

In the manual group, when comparing all eyes with or without complications (Table 4), we observed that eyes who suffered a complication had preoperatively higher mean

Table 1. Patients demographics: preoperative parameters for each group. ICRS: intrastromal corneal ring segments; K: keratometry; OZ: optical zone.

	Manual Surgery	Femtosecond Surgery	p value
Age	32.42 ± 11.49	33.54 ± 10.05	0.4
Amsler Grade	1 = 141 (53.2%)	1 = 64 (57.6%)	
	2 = 101 (38.1%)	2 = 40 (36.0%)	
	3 = 15 (5.6%)	3 = 5 (4.5%)	
	4 = 8 (3.1%)	4 = 2 (1.8%)	
Kmean (D)	47.82 ± 3.58	47.02 ± 2.96	0.07
Overall Thinnest Pachimetry (µm)	451.49 ± 37.77	460.83 ± 37.04	0.04
ICRS OZ Thinnest Pachimetry (µm)	527.58 ± 36.14	527.88 ± 37.69	0.9
Kmax (D)	55.88 ± 5.62	53.23 ± 6.86	0.001

Table 2. Visual. refractive and topographic outcomes of both samples: manual and femtosecond laser. Results shown as mean ± standard deviation (SD) for pre and postoperative evaluations inside each group and as a comparison between both groups.

Parameters	Manual	Femto	p value (For comparison between groups)
Sphere (D)			
Pre	−2.31 ± 3.82	−1.86 ± 2.97	0.8
Post	−1.39 ± 2.84	−1.59 ± 2.81	0.3
p-value (for pre and post surgery comparison)	<0.0001	0.049	
Refractive Cylinder (D)			
Pre	−3.39 ± 2.04	−2.78 ± 1.47	0.03
Post	−1.57 ± 1.50	−1.20 ± 0.94	0.006
p-value (for pre and post surgery comparison)	<0.0001	<0.0001	
UDVA			
Pre	0.18 ± 0.16	0.15 ± 0.11	0.4
Post	0.40 ± 0.26	0.40 ± 0.25	0.9
p-value (for pre and post surgery comparison)	<0.0001	<0.0001	
CDVA			
Pre	0.46 ± 0.20	0.49 ± 0.21	0.1
Post	0.65 ± 0.25	0.73 ± 0.19	0.001
p-value (for pre and post surgery comparison)	<0.0001	<0.0001	
K1 (D)			
Pre	45.92 ± 3.68	45.40 ± 3.04	0.2
Post	45.13 ± 3.72	44.95 ± 2.92	0.7
p-value (for pre and post surgery comparison)	<0.0001	0.06	
K2 (D)			
Pre	49.74 ± 3.69	48.64 ± 3.07	0.009
Post	47.73 ± 3.63	47.06 ± 3.09	0.1
p-value (for pre and post surgery comparison)	<0.0001	<0.0001	
Topographic Cylinder (D)			
Pre	3.81 ± 1.83	3.23 ± 1.44	0.004
Post	2.60 ± 1.82	2.05 ± 1.39	0.01
p-value (for pre and post surgery comparison)	<0.0001	<0.0001	
Comatic aberration (μm)			
Pre	2.56 ± 1.29	2.37 ± 1.24	0.2
Post	1.67 ± 0.99	1.70 ± 1.12	0.9
p-value (for pre and post surgery comparison)	<0.0001	<0.0001	
Asphericity (Q)			
Pre	−0.83 ± 0.47	−0.76 ± 0.43	0.3
Post	−0.54 ± 0.47	−0.62 ± 0.68	0.05
p-value (for pre and post surgery comparison)	<0.0001	0.007	

Table 3. Complication type and rate for each group, results shown as number of eyes and percentage. Complications divided in sub-groups: Corneal perforation, ICRS extrusion, ICRS exchange surgery or others. In addition, it is shown if the complication occurred during the first 3 years of surgeon's experience or when the surgeon had more than 3 years of surgical experience.

	Manual Surgery (n = 265)	Femtosecond Laser Surgery (n = 111)
Corneal Perforation	4 (1.51%)	1 (0.9%)
-First 3 Years	3	
-Last 3 Years	1	
ICRS extrusion	15 (5.66%)	0
-First 3 Years	12 (4.52%)	
-Last 3 Years	3 (1.14%)	
ICRS surgery exchange	25 (9.43%)	2 (1.8%)
-First 3 years	21 (7.92%)	
-Last 3 years	4 (1.51%)	
Others		
Corneal infection	3 (1.13%)	1 (0.9%)
Decentration	0	0
Late endothelial rupture	1 (0.38%)	0
Corneal Neovascularization	0	0
Total	48 (18.11%)	4 (3.6%)

refractive cylinder ($p = .002$) and topographic cylinder ($p = .003$) and lower UDVA ($p = .005$) and CDVA ($p = .002$) values. No differences were observed between groups for age, refractive sphere, K1, K2, Kmean, Kmax, Coma, Q and corneal pachymetry (overall thinnest point or ICRS OZ thinnest point).

ICRS extrusion

A total of 15 of 265 eyes (5.66%) suffered from postoperative later ICRS spontaneous extrusion. Sub-group analysis of this complication demonstrates worst preoperative UDVA and CDVA; higher levels of refractive and topographic cylinder as well as higher levels of K2 and coma than the no-complications group. No significant differences were observed for Kmean, Kmax, overall thinnest point and ICRS optical zone (OZ) thinnest point. After the initial complication, all refractive and topographic parameters remained stable, except for a worsening of CDVA ($p < .05$) and a decrease of topographic cylinder ($p < .05$). After a secondary procedure was performed (at least 6 months later), we observed a significant improvement ($p < .05$) of all parameters evaluated: UDVA, CDVA, refractive and topographic cylinder, K2, coma and Q (Table 5).

Corneal perforation

A total of 4 of 265 eyes (1.51%) suffered from intraoperative corneal tunnel perforation. Similarly to the ICRS extrusion, the sub-group analysis of this complication demonstrated worse preoperative UDVA; higher levels of refractive and topographic cylinder as well as higher levels of K2 than the no-complications group (Table 4). After a secondary procedure was performed (at least 6 months later), we observed a significant improvement ($p < .05$) in the following parameters: UDVA, CDVA, refractive cylinder, K1, K2 and Q (Table 6).

Table 4. Manual Group: Preoperative parameters for each sub-group regarding visual, refractive and topographic results. Sub-groups: no complications, all complications, perforation, extrusion and ICRS exchange surgery. Results are shown as mean ± standard deviation. Ref. Cyl: Refractive cylinder; SE: Spherical equivalente; UDVA: Uncorrected distance visual acuity; CDVA: Corrected distance visual acuity; K: keratometry; OZ: optical zone; ICRS: intrastromal corneal ring segments; OZ: optical zone.

Preoperative values	No Complication	All Complications	Extrusion	Perforation	Exchange
Eyes (n)	217	48	15	4	25
Age (years)	32.55 ± 11.35	31.81 ± 11.39	28.84 ± 12.78	32.25 ± 12.45	32.96 ± 9.80
Sphere (D)	−2.32 ± 3.82	−2.39 ± 3.72	−2.28 ± 3.82	−1.94 ± 1.42	−2.23 ± 3.16
Ref. Cyl (D)	−3.34 ± 2.02	−4.09 ± 1.95*	−4.27 ± 2.16**	−5.62 ± 3.04***	−3.96 ± 1.88$^{\Phi}$
SE (D)	−3.92 ± 4.06	−4.44 ± 3.79	−4.41 ± 3.83	−3.75 ± 2.33	−4.21 ± 3.27
UDVA	0.18 ± 0.17	0.12 ± 0.11*	0.10 ± 0.05**	0.11 ± 0.06***	0.14 ± 0.14
CDVA	0.48 ± 0.19	0.38 ± 0.22*	0.32 ± 0.17**	0.43 ± 0.17	0.41 ± 0.22
K1 (D)	45.94 ± 3.71	45.78 ± 3.58	46.27 ± 4.11	45.65 ± 2.49	45.62 ± 2.83
K2 (D)	49.61 ± 3.68	50.32 ± 3.73	51.69 ± 4.35**	51.00 ± 4.32***	49.66 ± 2.48
Kmean (D)	47.78 ± 3.59	48.05 ± 3.55	48.98 ± 4.16	48.33 ± 3.31	47.64 ± 2.53
Topographic Cylinder (D)	3.66 ± 1.81	4.53 ± 1.73*	5.43 ± 1.58**	5.35 ± 2.41***	3.98 ± 1.63
Overall Thinnest Pachimetry (μm)	461.69 ± 39.07	451.69 ± 39.07	447.53 ± 27.89	454.50 ± 20.53	454.40 ± 36.02
ICRS OZ Thinnest Pachimetry (μm)	526.91 ± 36.87	528.50 ± 32.87	532.16 ± 24.98	528.50 ± 23.62	530.40 ± 38.80
Kmax (D)	55.88 ± 5.81	55.85 ± 4.70	58.36 ± 4.67	55.58 ± 4.97	54.30 ± 3.73
Comatic aberration (μm)	2.51 ± 1.28	2.75 ± 1.29	3.34 ± 1.27**	2.29 ± 0.58	2.32 ± 1.21
Asphericity (Q)	−0.81 ± 0.45	−0.93 ± 0.58	−0.99 ± 0.44	−0.73 ± 0.39	−0.92 ± 0.65

*Statistically significant differences between no complication group and all complications. **Statistically significant differences between no complication group and extrusion group.
***Statistically significant differences between no complication group and perforation group. $^{\Phi}$Statistically significant differences between no complication group and exchange group.

Table 5. Complications with manual surgery – subgroup analysis Extrusion. UDVA: Uncorrected distance visual acuity; CDVA: Corrected distance visual acuity; K: keratometry.

Parameter	Preoperative	After Complication (extrusion)	After Reoperation
UDVA	0.10 ± 0.05	0.08 ± 0.04	0.22 ± 0.23**, $^{\Phi}$
CDVA	0.31 ± 0.17	0.23 ± 0.16*	0.45 ± 0.30**, $^{\Phi}$
Sphere (D)	−2.47 ± 3.79	−1.94 ± 3.65	−1.37 ± 3.23**, $^{\Phi}$
Refractive Cylinder (D)	−4.25 ± 2.14	−3.59 ± 3.51	−2.48 ± 1.74$^{\Phi}$
Topographic Cylinder (D)	5.46 ± 1.58	4.28 ± 2.17*	3.49 ± 2.44$^{\Phi}$
K1 (D)	46.11 ± 4.02	46.15 ± 4.49	46.36 ± 4.39
K2 (D)	51.56 ± 4.28	50.44 ± 4.35	49.84 ± 4.03$^{\Phi}$
Comatic aberration (μm)	3.39 ± 1.24	3.16 ± 1.21	2.42 ± 1.22**, $^{\Phi}$
Asphericity (Q)	−1.02 ± 0.45	−0.82 ± 0.48	−0.77 ± 0.45$^{\Phi}$

*Statistically significant differences between preoperative and after complication. **Statistically significant differences between after complication and after reoperation. $^{\Phi}$Statistically significant differences between preoperative and after reoperation.

Table 6. Complications with manual surgery – subgroup analysis Perforation. UDVA: Uncorrected distance visual acuity; CDVA: Corrected distance visual acuity; K: keratometry.

Parameter	Preoperative	After Complication (Perforation)	After reoperation
UDVA	0.11 ± 0.06	0.11 ± 0.07	0.42 ± 0.39 **, $^{\Phi}$
CDVA	0.43 ± 0.17	0.32 ± 0.22	0.60 ± 0.42 **, $^{\Phi}$
Sphere (D)	−0.38 ± 1.42	0.00 ± 0.58	0.00 ± 3.01
Refractive Cylinder (D)	−5.62 ± 3.04	−4.17 ± 4.19*	−1.42 ± 2.74 **, $^{\Phi}$
Topographic Cylinder (D)	5.35 ± 2.41	4.60 ± 2.90	4.25 ± 3.44 $^{\Phi}$
K1 (D)	45.65 ± 2.49	45.90 ± 2.11	44.25 ± 2.42**, $^{\Phi}$
K2 (D)	51.00 ± 4.32	50.50 ± 4.98	47.70 ± 4.22**, $^{\Phi}$
Comatic aberration (μm)	2.29 ± 0.58	2.31 ± 0.73	1.92 ± 0.80**, $^{\Phi}$
Asphericity (Q)	−0.73 ± 0.39	−0.54 ± 0.39	−0.33 ± 0.50$^{\Phi}$

*Statistically significant differences between preoperative and after complication. **Statistically significant differences between after complication and after reoperation. $^{\Phi}$Statistically significant differences between preoperative and after reoperation.

ICRS exchange surgery

A total of 25 of 265 eyes (9.43%) were submitted to ICRS adjustment surgery: exchange for a different ICRS type or explantation of 1 ICRS in case of 2 ICRS implanted originally. No significant preoperative differences were observed between non-complicated group and exchange group, except for the mean refractive cylinder, which was higher in the group submitted to ICRS exchange (p = .03) (Table 4). Table 7 shows the results of this sub-group after the first surgery and after the adjustment procedure, performed at least 6 months after the first surgery. When comparing the data after the first and secondary procedures, we observe that after the adjustment surgery, there is a significant improvement ($p < .05$) in UDVA, CDVA, refractive cylinder, topographic cylinder and coma.

Complications – femtosecond laser group

With femtosecond laser surgery we had one case of corneal intraoperative perforation; two cases of ICRS exchange, and one case of corneal infection (which was the same eye of one of the ICRS exchange). In the case of intraoperative corneal perforation, no ICRS was implanted; surgery was repeated 3 months later:

Table 7. Complications with manual surgery – subgroup analysis ICRS Exchange. UDVA: Uncorrected distance visual acuity; CDVA: Corrected distance visual acuity; K: keratometry.

Parameter	Preoperative	After First Surgery	After Exchange Surgery
UDVA	0.14 ± 0.14	0.13 ± 0.09	0.31 ± 0.23**, Φ
CDVA	0.41 ± 0.22	0.36 ± 0.20	0.61 ± 0.21**, Φ
Sphere (D)	−2.23 ± 3.16	−0.79 ± 2.99*	−1.24 ± 2.32 Φ
Refractive Cylinder (D)	−4.08 ± 1.91	−3.17 ± 2.27	−1.84 ± 1.02**, Φ
Topographic Cylinder (D)	4.02 ± 1.61	3.48 ± 1.43	2.13 ± 1.36**, Φ
K1 (D)	45.78 ± 2.90	43.80 ± 3.70*	45.43 ± 2.81**
K2 (D)	49.86 ± 2.64	47.30 ± 3.62*	47.55 ± 2.79Φ
Comatic aberration (μm)	2.31 ± 1.19	2.22 ± 0.97	1.59 ± 0.99**, Φ
Asphericity (Q)	−0.91 ± 0.63	−0.40 ± 0.63*	−0.67 ± 0.37**, Φ

*Statistically significant differences between preoperative and after first surgery. **Statistically significant differences between after first surgery and after exchange surgery. ΦStatistically significant differences between preoperative and after exchange surgery.

CDVA (snellen decimal) improved from 0.2 to 0.6; refractive astigmatism decreased from −2.50 D to −1.25 D. This complication occurred in the first surgeries performed with the femtosecond laser. In the case of ICRS exchange surgeries, both eyes improved visual acuity and refraction after exchange; in the eye with corneal infection, medical treatment was applied and no visual acuity loss was reported.

Discussion

Our study compares the results and the incidence of complications of ICRS implantation after manual or femtosecond laser surgery; visual, refractive and topographic results are similar between techniques; however, the incidence of complications was significantly higher in the manual group (18.11% vs. 3.98%) and four times higher during the first years of the surgeon's learning curve. Even though the incidence of complications was higher in manual group, a secondary surgical procedure was able to improve the visual, refractive and topographic results in cases of intraoperative corneal perforation, late ICRS extrusion or ICRS adjustment surgery.

A higher precision and predictability of intrastromal tunnel creation is associated with a better safety profile of the procedure. We previously found that ICRS implantation assisted by a femtosecond laser device is a more accurate and predictable procedure when compared with manual dissection technique.[20] In the current study we have confirmed that the manual mechanical technique for ICRS is associated with a higher incidence of corneal and refractive complications; however, the visual and refractive results are comparable to a femtosecond laser assisted technique. All the major complications observed; namely corneal perforation, ICRS extrusion or improper ICRS implantation can be overcome with a subsequent procedure, allowing a significant improvement in visual acuity, refraction and topographic indices.

When we compare the risk factors associated with intraoperative corneal perforation or late spontaneous ICRS extrusion, we have surprisingly not found in our sample an association with lower pachymetric values, younger age or higher maximum or mean corneal curvatures. We would assume that the risk of superficial implant inside the corneal stroma would be associated with thinner corneas or younger patients; both associated with higher probability of disease progression, atopy and frequent eye rubbing.

We have found this complication to be associated with worse preoperative visual acuity, higher levels of astigmatism and coma. Khan et al,[24] have shown a higher extrusion rate of 19.3% in their study with the manual technique; they only included patients with moderate to severe keratoconus (mean keratometry of 54.83 ± 4.16 D and mean corneal astigmatism of 5.85 ± 1.91D); they had no intraoperative complications. The authors justified the rate based on thinner corneas, history of atopy and eye rubbing, although they have not described the mean corneal thickness or age for each group. In our study we have not found a direct relationship between younger age and thinner corneas with spontaneous ICRS extrusion and neither with mean keratometry values. Kubaloglu et al.[9] reported a 5.8% rate of mechanical complications: 2 eyes with intraoperative perforations (both cases had a stage III ectasia, and in both cases a reoperation was carried out, however no final results were shown) and 1 segment extrusion, also a stage III keratoconus in a frequent eye rubbing patient. Kwitko et al.[14] reported a 9.8% spontaneous extrusion rate for Ferrara-type ICRS (5 eyes of 51 eyes); according to the investigators this was due to tunnel depth related to the surgeon's learning curve. In their sample, the mean keratometry was 48.76 ± 3.97D, a similar value we have obtained from our sample. In our sample, most of the spontaneous extrusions occurred in the first 3 years of the surgeon's surgical experience, while in the last 3 years we have reported a lower rate of 1.14% of spontaneous extrusion. Piñero et al.[25] reported a spontaneous extrusion rate of 9.46% for mechanical ICRS and 4.82% for femtosecond laser ICRS; the higher extrusion rate in the manual group was associated with a more significant corneal irregularity and higher levels of corneal aberrometry. Similarly, in our sample, we have found the extrusion eyes to have also higher levels of corneal astigmatism and coma. Differently from all other studies described, our study is the first to describe the results after the complication occurred and later after its resolution with a new surgical procedure. Our findings suggest that it is possible that even after a corneal perforation or a spontaneous ICRS extrusion occur, a new surgical procedure with ICRS re-implantation can improve all visual, refractive and topographic parameters studied.

When we analysed the incidence rate of corneal perforation or implant extrusion with femtosecond laser surgery, we had only one eye with a corneal endothelial perforation (0.9%) and no eye with late spontaneous extrusion, corneal melting or ICRS migration. The complication case occurred during the surgeon's learning curve and was later resolved with a second procedure. Our complication rate with femtosecond laser is very low and similar to other studies. Coskunseven et al.[21] have published the largest series of patients describing the incidence of complications during ICRS implantation with femtosecond laser; they have described a 0.6% rate (5 eyes) of endothelial perforations: in 2 cases the ICRS was displaced to the anterior chamber and the other 3 had the surgery repeated later. In the case of segment extrusion or migration, Coskunseven et al.[21] described a 1.3% rate; a total of 11 eyes, 4 of which were explanted to avoid corneal melting; 2 eyes (0.2%) had corneal melting and implant extrusion due to superficial implant inside the corneal stroma. Other studies have described similar rates of ICRS complications with femtosecond laser assisted-surgery: Kubaloglu et al.[9] 1.0% of extrusions and 1.0% perforation; Ertan et. al.[22] 0.9% extrusion rate. In the past five years, the recent largest series published regarding ICRS implantation with femtosecond laser surgery do not describe any mechanical intra- or postoperative complications.[1–4,22,26,27]

Regarding ICRS exchange surgery due to poor visual results, we found a higher rate of this complication in the manual group than in the femtosecond group (9.43% vs. 1.8%). Apart from the nomogram improvement in the last few years, the fact that with manual surgery the implant depth predictability is lower than with femtosecond, can induce shallow or asymmetric tunnels and astigmatism overcorrection[20], and could justify the higher rates of ICRS exchange surgery with manual surgery. Furthermore, our study demonstrated the reversibility of the procedure. These findings are in accordance with those previously published.[11,28–31] Colin et al.[10] first described a rate of 12.2% ICRS explantation due to poor visual results or other optical complaints, none of the eyes was submitted to a secondary procedure; the same author published one year later a paper[11] reporting a 10.3% of refractive adjustment after Intacs ICRS implantation. Alió et al.[29,30] and Pokroy et al.[31] were the first to publish on the possibility of adjustment with ICRS surgery, proving the reversibility of the procedure. More recently, our research group published the largest series[28] of ICRS exchange for a different ICRS implant or combination of implants, in cases of eyes with no visual acuity improvement after the first surgery. The findings of this previous study showed ICRS implantation is a reversible and adjustable surgical procedure. At the same time, the finding of the current study highlights the fact that this type of complication is more frequent during the surgeon's learning curve: 21 eyes (7.92%) in the first 3 years and 4 eyes (1.51%) in the last 3 years of experience. This is probably related not the surgical learning curve but to the nomogram's learning curve and personal adjustments. When comparing the preoperative characteristics of the eyes with no ICRS exchange with those eyes which had a surgical adjustment surgery during the follow-up, we have found only a statistically significant difference in the value of preoperative mean refractive cylinder; while the UDVA and CDVA values and all topographic parameters were not different between both groups.

As a study limitation, we have to point out that some of the preoperative characteristics were not similar between the manual and femtosecond laser groups. Consequently, some of the cases which suffered a complication in the manual group could be related either to the technique or perhaps to the preoperative characteristics. On the other hand, beyond the potential complications, an interesting finding in this study is that these complications mainly occur during the first years of the surgeon's learning curve. This fact should be considered by surgeons. The results obtained in this study could help the less experienced surgeons to select the cases that have preoperative characteristics with a low risk of potential complications. Either way, the other important aspect to note is that these complications can be easily solved with a secondary procedure.

In conclusion, manual mechanical ICRS surgery shows a higher rate of intra- and postoperative mechanical and refractive complications when compared to femtosecond laser assisted technique. The incidence is specially higher during the surgeon's first years of implementation of the technique. However, the refractive, visual and topographic results are comparable between both techniques, mainly due to the reversibility and the possibility to adjust the first surgery or even to perform a second surgical procedure to overcome a primary complication or insufficient visual outcome after the first surgery.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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References

1. Lisa C, Fernández-Vega Cueto L, Poo-López A, Madrid-Costa D, Alfonso JF. Long-term follow-up of intrastromal corneal ring segments (210-degree arc length) in central keratoconus with high corneal asphericity. Cornea. 2017;36(11):1325–30. doi:10.1097/ICO.0000000000001339.
2. Fernández-Vega Cueto L, Lisa C, Madrid-Costa D, Merayo-Lloves J, Alfonso JF. Long-term follow-up of intrastromal corneal ring segments in paracentral keratoconus with coincident corneal keratometric, comatic, and refractive axes: stability of the procedure. J Ophthalmol. 2017;2017:4058026. doi:10.1155/2017/4058026.
3. Fernández-Vega Cueto L, Lisa C, Poo-López A, Madrid-Costa D, Merayo-Lloves J, Alfonso JF. Intrastromal corneal ring segment implantation in 409 paracentral keratoconic Eyes. Cornea. 2016;35(11):1421–26. doi:10.1097/ICO.0000000000000978.
4. Alfonso JF, Fernández-Vega Cueto L, Baamonde B, Merayo-Lloves J, Madrid-Costa D, Montés-Micó R. Inferior intrastromal corneal ring segments in paracentral keratoconus with no coincident topographic and coma axis. J Refract Surg. 2013;29(4):266–72. doi:10.3928/1081597X-20130318-06.
5. Ferrara G, Torquetti L, Ferrara P, Merayo-Lloves J. Intrastromal corneal ring segments: visual outcomes from a large case series. Clin Exp Ophthalmol. 2012;40(5):433–39. doi:10.1111/j.1442-9071.2011.02698.x.

6. Coskunseven E, Kymionis GD, Tsiklis NS, Atun S, Arslan E, Jankov MR, Pallikaris IG. One-year results of intrastromal corneal ring segment implantation (KeraRing) using femtosecond laser in patients with keratoconus. Am J Ophthalmol. 2008;145(5):775–79. doi:10.1016/j.ajo.2007.12.022.
7. Ruckhofer J, Stoiber J, Alzner E, Grabner G. Multicenter European corneal correction assessment study group. One year results of European multicenter study of intrastromal corneal ring segments. Part 2: complications, visual symptoms, and patient satisfaction. J Cataract Refract Surg. 2001;27(2):287–96. doi:10.1016/S0886-3350(00)00740-9.
8. Zare MA, Hashemi H, Salari MR. Intracorneal ring segment implantation for the management of keratoconus: safety and efficacy. J Cataract Refract Surg. 2007;33(11):1886–91. doi:10.1016/j.jcrs.2007.06.055.
9. Kubaloglu A, Sari ES, Cinar Y, Cingu K, Koytak A, Coşkun E, Ozertürk Y. 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. doi:10.1016/j.jcrs.2010.04.028.
10. Colin J. European clinical evaluation: use of Intacs for the treatment of keratoconus. J Cataract Refract Surg. 2006;32(5):747–55. doi:10.1016/j.jcrs.2006.01.064.
11. Colin J, Cochener B, Savary G, Malet F. Correcting keratoconus with intracorneal rings. J Cataract Refract Surg. 2000;26(8):1117–22. doi:10.1016/S0886-3350(00)00451-X.
12. Kubaloglu A, Sari ES, Cinar Y, Koytak A, Kurnaz E, Ozertürk Y. Intrastromal corneal ring segment implantation for the treatment of keratoconus. Cornea. 2011;30(1):11–17. doi:10.1097/ICO.0b013e3181e2cf57.
13. Gharaibeh AM, Muhsen SM, AbuKhader IB, Ababneh OH, Abu-Ameerh MA, Albdour MD. KeraRing intrastromal corneal ring segments for correction of keratoconus. Cornea. 2012;31(2):115–20. doi:10.1097/ICO.0b013e3182215a15.
14. Kwitko S, Severo NS. Ferrara intracorneal ring segments for keratoconus. J Cataract Refract Surg. 2004;30(4):812–20. doi:10.1016/j.jcrs.2003.12.005.
15. Colin J, Malet FJ. Intacs for the correction of keratoconus: two-year follow-up. J Cataract Refract Surg. 2007;33(1):69–74. doi:10.1016/j.jcrs.2006.08.057.
16. Hellstedt T, Makela J, Uusitalo R, Emre S, Uusitalo R. Treating keratoconus with intacs corneal ring segments. J Refract Surg. 2005;21(3):236–46. doi:10.3928/1081-597X-20050501-06.
17. Sansanayudh W, Bahar I, Kumar NL, Shehadeh-Mashour R, Ritenour R, Singal N, Rootman DS. Intrastromal corneal ring segment SK implantation for moderate to severe keratoconus. J Cataract Refract Surg. 2010;36(1):110–13. doi:10.1016/j.jcrs.2009.07.040.
18. Siganos D, Ferrara P, Chatzinikolas K, Bessis N, Papastergiou G. Ferrara intrastromal corneal rings for the correction of keratoconus. J Cataract Refract Surg. 2002;28(11):1947–51. doi:10.1016/S0886-3350(02)01495-5.
19. Pesando PM, Ghiringhello MP, Di Meglio G, Romeo S. Treatment of keratoconus with ferrara ICRS and consideration of the efficacy of the ferrara nomogram in a 5-year follow-up. Eur J Ophthalmol. 2010;20(5):865–73. doi:10.1177/112067211002000509.
20. Monteiro T, Alfonso JF, Franqueira N, Faria-Correira F, Ambrósio R Jr, Madrid-Costa D. Predictability of tunnel depth for intrastromal corneal ring segment (ICRS) implantation between manual or femtosecond laser: comparative Study. J Refract Surg. 2018;34(3):188–94. doi:10.3928/1081597X-20180108-01.
21. Coskunseven E, Kymionis GD, Tsiklis NS, Atun S, Arslan E, Siganos CS, Jankov M, Pallikaris IG. 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):54–57. doi:10.1111/j.1755-3768.2009.01605.x.
22. Ertan A, Kamburoglu G, Bahadir M. Intacs insertion with the femtosecond laser for the management of keratoconus: one-year results. J Cataract Refract Surg. 2006;32(12):2039–42. doi:10.1016/j.jcrs.2006.08.032.
23. Kotb AM, Hantera M. Efficacy and safety of Intacs SK in moderate to severe keratoconus. Middle East Afr J Ophthalmol. 2013;20(1):46–50. doi:10.4103/0974-9233.106386.
24. Khan MI, Injarie A, Muhtaseb M. Intrastromal corneal ring segments for advanced keratoconus and cases with high keratometric asymmetry. J Cataract Refract Surg. 2012;38(1):129–36. doi:10.1016/j.jcrs.2011.07.031.
25. Pinero DP, Alio JL, El Kady B, Coskunseven E, Morbelli H, Uceda-Montanes A, Maldonado MJ, Cuevas D, Pascual I. Refractive and aberrometric outcomes of intracorneal ring segments for keratoconus: mechanical versus femtosecond-assisted procedures. Ophthalmology. 2009;116(9):1675–87. doi:10.1016/j.ophtha.2009.05.016.
26. Haddad W, Fadlallah A, Dirani A, El Rami H, Fahd D, Khanafer D, Fahed S. Comparison of 2 types of intrastromal corneal ring segments for keratoconus. J Cataract Refract Surg. 2012;38(7):1214–21. doi:10.1016/j.jcrs.2012.02.039.
27. Alfonso JF, Lisa C, Fernandez-Vega L, Madrid-Costa D, Montes-Mico R. Intrastromal corneal ring segment implantation in 219 keratoconic eyes at different stages. Graefes Arch Clin Exp Ophthalmol. 2011;249(11):1705–12. doi:10.1007/s00417-011-1759-9.
28. Monteiro T, Mendes JF, Faria-Correia F, Franqueira N, Madrid-Costa D, Alfonso JF. Adjustment of intrastromal corneal ring segments after unsuccessful implantation in keratoconic eyes. Cornea. 2018;37(2):182–88. doi:10.1097/ICO.0000000000001449.
29. Alio JL, Artola A, Ruiz-Moreno JM, Hassanein A, Galal A, Awadalla MA. Changes in keratoconic corneas after intracorneal ring segment explantation and reimplantation. Ophthalmology. 2004;111(4):747–51. doi:10.1016/j.ophtha.2003.08.024.
30. Alio JL, Pinero DP, Esin S, Anin K. Implantation of new intracorneal ring segments after segment explantation for unsuccesful outcomes in eyes with keratoconus. J Cataract Refract Surg. 2010;36(8):1303–10. doi:10.1016/j.jcrs.2010.02.017.
31. Pokroy R, Levinger S. Intacs adjustment surgery for keratoconus. J Cataract Refract Surg. 2006;32(6):986–92. doi:10.1016/j.jcrs.2006.02.032.

CHAPTER VII - Adjustment of intrastromal corneal ring segments after unsuccessful implantation in keratoconic eyes

Adjustment of Intrastromal Corneal Ring Segments After Unsuccessful Implantation in Keratoconic Eyes

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Purpose: To evaluate visual, refractive, and corneal topography outcomes in eyes with keratoconus that have undergone exchange/adjustment surgery with a new intrastromal corneal ring segment (ICRS) combination after unsuccessful visual and/or refractive outcomes after primary ICRS surgery.

Methods: A retrospective nonrandomized case series was conducted including consecutive eyes of patients with keratoconus that underwent ICRS adjustment after an unsuccessful visual outcome. Patients were divided into 2 groups: group 1 was made up of patients with Intacs ICRSs that were exchanged for the Ferrara ICRS type, and group 2 consisted of patients who maintained the same ICRS type after undergoing ICRS adjustment surgery (change of the arc length or thickness). Uncorrected distance visual acuity, best-corrected distance visual acuity (CDVA), keratometry, asphericity, higher-order aberrations, and corneal regularity indexes (ISV and IHD) (Pentacam HR; OCULUS) were assessed preoperatively and 12 months after each procedure.

Results: Twenty-six eyes from 26 patients were included, 8 eyes in group 1 and 18 eyes in group 2. The eyes in both groups improved their CDVA values after ICRS exchange, in group 1 from 0.27 ± 0.11 preoperatively to 0.54 ± 0.17 postoperatively (P = 0.001), and in group 2 from 0.34 ± 0.22 to 0.61 ± 0.15 ($P < 0.0001$). In both groups, there was also a significant improvement in the refractive cylinder, topographic cylinder, and coma after ICRS adjustment ($P < 0.05$).

Conclusions: ICRS implantation has been shown to be a reversible and adjustable surgical procedure for keratoconus treatment. Good outcomes can be obtained after ICRSs are exchanged.

Key words: keratoconus, intrastromal corneal ring segments, adjustment

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In patients with stable keratoconus who develop contact lens intolerance and insufficient distance corrected visual acuity with spectacles (CDVA), implantation of intrastromal corneal ring segments (ICRS) is a safe and effective procedure for correcting irregular astigmatism and higher-order aberrations (HOAs) and improving uncorrected distance visual acuity (UDVA) and CDVA.[1–3] ICRS surgery is an additive non-ablative surgical procedure that in theory is reversible in cases of unfavorable results. Clinical, refractive, and histological reversibility after ICRS explantation has recently been described in an animal model[4] and in clinical studies.[5–9]

There are several reasons for performing ICRS explantation, the most frequent being spontaneous extrusion due to a superficial corneal tunnel or loss of CDVA.[10] Although ICRS implantation is a safe procedure in patients with keratoconus, with most patients maintaining or improving CDVA lines after surgery, some studies have reported a small percentage of eyes losing CDVA lines after surgery.[1,11–14] Apart from surgical problems, a possible explanation for the loss of CDVA after ICRS implantation may be an incorrect choice of the ICRS to be implanted, which could induce astigmatism overcorrection and/or an increase in irregular astigmatism or HOAs. Bearing in mind that ICRS implantation is a reversible procedure, and that the ICRS can safely be explanted,[4] it seems interesting to explore the idea that adjusting ICRS implantation in patients who have lost CDVA lines because of an incorrect choice of the ICRS is a safe and effective option. The purpose of this study was to evaluate the refractive, visual, topographic, and aberrometric results after the exchange or adjustment of the Intacs (Addition Technology, Inc) or Ferrara ICRS (Mediphacos, Inc) for a new ICRS type or combination after unsuccessful primary surgery. All of the patients included had no gain of CDVA with spectacles after the first ICRS surgery.

PATIENTS AND METHODS

This retrospective study analysis reviewed the outcomes of all consecutive eyes that underwent ICRS adjustment after unsuccessful implantation (that is, the exchange of the Intacs for the Ferrara ICRS, or the exchange of the Ferrara ICRS for different arc lengths, thicknesses, and/or numbers of the ICRS implanted). Surgery was performed between January 2010 and January 2015. The study was approved by the local ethics committee and followed the tenets of the Declaration of Helsinki. All cases included were unilateral. The keratoconus diagnosis was based on clinical history, slit-lamp examination, and corneal tomography (Pentacam HR; OCULUS, Germany). In all patients, primary ICRS implantation for clear corneal keratoconus was uneventful; reoperation was necessary during the follow-up period. The main indications for primary surgery were contact lens intolerance and CDVA with spectacles of ≤20/40. Exclusion criteria for primary surgery were any of the following, discovered during the preoperative examination: advanced keratoconus with maximum curvature over 58.00 diopters (D), significant apical opacity and scarring, hydrops, minimum corneal thickness below 400 μm at the implantation optic zone as evaluated by the pachymetry map (Pentacam HR; OCULUS), and active allergic/atopic conjunctivitis, with no response to medical therapy. The indication for reoperation was loss of UDVA or CDVA or no significant improvement after primary ICRS surgery. Eyes with explantation secondary to extrusion, corneal neovascularization, or other complications were not included in this study.

Intacs ICRS

The Intacs ICRS (Addition Technology, Inc) consists of crescent-shaped 150-degree polymethylmethacrylate segments with a hexagonal transverse shape, an external diameter of 8.10 mm, and an internal diameter of 6.77 mm, of different thicknesses (0.25–0.45 mm) in 0.05 mm increments. There is an additional Intacs design (keratoconus) with an inner diameter of 6.00 mm, an oval cross-section and 2 different thicknesses (0.40, 0.45 mm). The ICRS to be implanted was chosen according to the manufacturer's nomogram, based on mean keratometry, spherical equivalent, and the type of keratoconus: asymmetrical cone, global cone, or central cone.[15]

Ferrara ICRS

Ferrara ICRSs (Mediphacos, Inc) are made of polymethylmethacrylate with a triangular cross-section that induces a prismatic effect on the cornea. The apical diameter of the ICRS is 5.0 or 6.0 mm, and the flat basis width is 600/800 μm with variable thicknesses (150, 200, 250, and 300 μm) and arc lengths (90, 120, 150, 160, and 210 degrees). The nomogram for the application of the Ferrara ICRS was based on the Mediphacos nomogram, published previously.[16]

Preoperative and Postoperative Examination

A complete ophthalmic examination was performed on all eyes before initial ICRS surgery, 12 months after initial ICRS surgery and 12 months after ICRS explantation/exchange surgery. The examinations included UDVA, CDVA, manifest refraction, biomicroscopy, indirect ophthalmoscopy through a dilated pupil, Goldmann applanation tonometry, corneal tomography, a pachymetry map, corneal aberrometry, and corneal regularity indexes, that is, the index of surface variance (ISV) and the index of height descentration (IHD) using the Pentacam HR (Oculus, Inc). In addition, the following topographic data were recorded in all cases: flattest corneal dioptric power in the 3.0-mm central zone (K1), steepest corneal dioptric power in the 3.0-mm central zone (K2), mean corneal power in the 3.0-mm zone (simK), and corneal asphericity (Q) in the 6.0-mm central zone. Corneal aberrometry was recorded, and the corneal aberration coefficients and root mean square (RMS) values were calculated for a 6.00-mm pupil, mainly primary coma RMS, computed from Zernike terms Z (3, 1) and Z (3, −1). Refractive and topographic astigmatism was also evaluated by vector analysis. The refraction obtained before and 12 months after ICRS implantation was assessed using the power vector method of Thibos and Horner.[17] All clinical examinations were performed in a standardized manner by an experienced examiner.

Surgical Technique

Corneal tunnels for implantation of the initial ICRS and the new ICRS were created by manual mechanical dissection. No suction devices were applied to assist surgery. All primary surgeries and reoperations were performed by the same surgeon (T.M.).

Tunnel Creation

For Intacs ICRS

An ICRS incision and placement marker was pressed lightly onto the cornea, leaving inked margins to indicate the proper position of the radial incision and ICRS. The projection on the corneal plane of the center of the pupil was used to center the ICRS. A 1.2-mm incision was made to a depth of 80% of the corneal thickness at a 6.00-mm circular zone around the pupil center, and intraoperative ultrasound pachymetry was used to measure corneal thickness under the incision site. The incision was performed on the steepest axis of the topography map. A lamellar stromal spreader was inserted at the base of the incision, and tissue was spread laterally to prepare an entry pocket on each side. An ICRS vacuum-centering guide was used to maintain proper positioning of the lamellar dissectors during creation of the intrastromal tunnels. The leading end of each segment was inserted through the incision into the intrastromal tunnel. The segments were positioned symmetrically around the incision, after which the incision was closed with a single interrupted 10-0 nylon suture.

For Ferrara ICRS

All surgeries were performed using the manual mechanical dissection technique. The visual axis was marked by pressing a Sinskey hook onto the central corneal epithelium while asking the patient to fixate on the corneal light reflex of the microscope light. Using a marker tinted with gentian violet, a 6.00-mm optical zone and incision site were aligned to the desired axis on which the incision would be made. The incision was always performed at the steepest topographic axis of the cornea given by the topographer. A square diamond blade was set at 80% of corneal thickness at the incision site and used to make the incision. Using a "stromal spreader," a pocket was formed at each side of the incision. Two (clockwise and counterclockwise) 270-degree semicircular dissecting spatulas were consecutively inserted through the incision and gently pushed with quick, rotary "back and forth" tunneling movements. After channel creation, the ring segments were inserted using modified McPherson forceps. The rings were properly positioned with the aid of a Sinskey hook.

ICRS Explantation Technique

For ICRS removal, after the primary corneal incision was made, an inverted Sinskey hook was used to engage the segment hole from beneath, and it was pulled out of the tunnel. A 10-0 nylon corneal suture was put in place at the end of the procedure.

The postoperative treatment regimen for all surgeries consisted of moxifloxacin 0.5% (Vigamox; Alcon, Ft. Worth, TX) and tobramycin 0.3%-dexamethasone 0.1% (Tobradex; Alcon) eye drops 4 times a day for 2 weeks. The patient was instructed to avoid rubbing the eyes and to frequently use preservative-free artificial tears. Patients were examined at 1 day and 1, 3, 6, and 12 months after the primary procedure and after the secondary exchange procedure.

Secondary Implantation Technique

In cases in which the explanted ICRS was positioned at the correct depth in the corneal stroma, the new ICRS implant was positioned using the same corneal incision and the same intrastromal depth. The ICRS position inside the corneal stroma was measured by an anterior segment high-resolution swept-source OCT (CASIA SS-1000, Tomey Corp, Japan). If the previous explanted ICRS was found to be in a shallower position than what was required, the depth of implantation for secondary implantation surgery was deeper (20–40 μm) than the initial depth.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS, Chicago, IL) was used for descriptive statistics, including mean ± SD. Normality of all data samples was first checked using the Kolmogorov–Smirnov test. The Student *t*-test for paired data was used to compare preoperative and postoperative data when normality was present. Where parametric analysis was not possible, the Wilcoxon rank-sum test was used to assess the significance of differences between preoperative data and postoperative data. In all cases, differences were considered statistically significant when the *P* value was less than 0.05.

RESULTS

This study was performed on 26 eyes from 26 patients (14 males and 12 females) with a mean age of 35.0 ± 10.8 (range 17–57 years). Patients were divided into 2 groups: group 1 consisted of patients with the Intacs ICRS exchanged for the Ferrara ICRS type and group 2 of patients who maintained the same ICRS type but underwent ICRS adjustment surgery (change of the arc length or thickness). Group 1 comprised 8 eyes, all of which had undergone primary surgery for implantation of 2 symmetrical Intacs ICRSs. All of them had the initial implants substituted for only one Ferrara ICRS (asymmetric implantation) with a different arc length (Table 1, OV, online version). Group 2 comprised 18 eyes from 18 patients. Fifteen eyes underwent explantation of 1 segment (all eyes had 2 ICRS implanted), and 3 patients had an ICRS exchange for a different arc length. Before the initial ICRS surgery, and in accordance with the Amsler–Krumeich grading system, 10 eyes (38.5%) had ectasia grade 1, 14 eyes (53.9%) had grade 2, and 2 eyes (7.7%) had grade 3. None of the cases included showed any progressive corneal

TABLE 1. Topographic and Corneal Aberrometric Parameters Shown as Mean ± SD and Range for Group 1

Parameter	Preoperatively	After Intacs ICRS (Before ICRS Exchange)	*P*	After Ferrara ICRS (After ICRS Exchange)	*P*
K1, D	46.10 ± 2.63	41.30 ± 3.21	0.003	44.44 ± 1.88	0.001
Range	42.20 to 49.70	37.30 ± 47.40		41.30 to 48.10	
K2, D	51.06 ± 3.19	46.54 ± 2.77	0.004	48.23 ± 2.53	0.056
Range	47.20 to 55.70	43.00 to 50.90		44.50 to 51.30	
Cylinder, D	4.95 ± 2.54	5.24 ± 1.95	0.84	3.59 ± 1.58	0.042
Range	1.80 to 8.08	2.80 to 9.30		0.60 to 6.30	
Kmean, D	48.57 ± 2.64	43.86 ± 2.83	0.002	46.16 ± 2.02	0.003
Range	44.95 to 51.50	40.60 to 49.15		43.00 to 49.50	
Kmax, D	56.43 ± 4.76	53.41 ± 5.51	0.002	53.68 ± 5.28	0.56
Range	50.30 to 63.70	47.30 to 63.20		47.70 to 64.70	
Q	−1.66 ± 0.68	−0.52 ± 0.77	0.02	−0.85 ± 0.42	0.03
Range	−2.56 to −0.67	−1.55 to 0.73		−1.63 to 0.27	
Coma, μm	3.37 ± 1.46	3.18 ± 1.27	0.23	1.62 ± 1.49	0.041
Range	1.80 to 6.48	1.54 to 5.85		0.34 to 4.46	
ISV	112.57 ± 34.58	105.0 ± 37.57	0.17	97.75 ± 47.78	0.63
	77.0 to 183.0	67.0 to 183.0		38.0 to 170.0	
IHD	0.09 ± 0.06	0.12 ± 0.06	0.46	0.12 ± 0.08	0.81
	0.05 to 0.22	0.05 to 0.22		0.02 to 0.27	

ICRS, intrastromal corneal ring segment; IHD, index of height descentration; ISV, index of surface variance.

steepening, aberrometric increase, or corneal thinning after the first ICRS implantation.

Visual and Refractive Outcomes

Supplemental Digital Content 1 (see Tables 1 and 2, http://links.lww.com/ICO/A597, http://links.lww.com/ICO/A598) shows the individual result for each case. For group 1, there were no statistically significant changes in UDVA and CDVA after Intacs implantation: preoperative decimal (Snellen scale) UDVA of 0.08 ± 0.05 to postoperative 0.11 ± 0.03 ($P = 0.17$) and preoperative decimal CDVA of 0.33 ± 0.23 to postoperative 0.27 ± 0.11 ($P = 0.2$). After ICRS exchange, all eyes improved their UDVA and CDVA values, and the mean CDVA increased from the preoperative 0.27 ± 0.11 to a postoperative of 0.54 ± 0.17 ($P = 0.001$). In terms of refractive outcomes, a significant reduction in refractive astigmatism was observed after the ICRS adjustment surgery: from −3.21 ± 1.42 D to −1.82 ± 1.15 D ($P = 0.011$). Figure 1 shows the astigmatism component of the power vector represented by a 2-dimensional vector (J0 and J45) for each case analyzed. The origin of the graph (0, 0) represents an eye free of astigmatism. It can be seen that in all cases, the data move toward the origin of the graph (0, 0) after ICRS exchange.

In group 2, we observed that most of the eyes maintained or lost lines of CDVA after the first surgery. However, after ICRS adjustment, all eyes improved their CDVA values, and 94.4% of the eyes (17 eyes) improved their CDVA compared with what it was before the first surgery. After the adjustment procedure, the mean UDVA improved from 0.16 ± 0.13 to 0.27 ± 0.15 ($P = 0.001$) and the mean CDVA from 0.34 ± 0.22 to 0.61 ± 0.15 ($P < 0.0001$). In terms of refractive parameters, Figure 2 also shows that after ICRS adjustment, the spread of data from the origin was more concentrated than the spread of preoperative and post-first surgery data; mean refractive astigmatism was reduced from −4.18 ± 1.45 D to −2.05 ± 1.03 D ($P < 0.0001$) after exchange surgery.

Corneal Topography Outcomes

Tables 1 and 2 describe the keratometric and aberrometric outcomes during follow-up in groups 1 and 2, respectively. After the first ICRS implantation surgery (Intacs), there was a statistically significant reduction in group 1 (Table 1) in the anterior keratometric parameters (K1, K2, Kmean, and Kmax) and in corneal asphericity. There was no change in topographic astigmatism, coma, ISV and IHD parameters. After the Intacs ICRS were explanted and a Ferrara ICRS combination was implanted, a significant reduction was observed in the values of topographic astigmatism ($P = 0.041$) and coma ($P = 0.042$). In parallel with this reduction, we observed an increase in the anterior topographic parameters K1 ($P = 0.001$), K2 ($P = 0.056$), and Kmean ($P = 0.003$). The values of Kmax, ISV, and IHD remained unchanged ($P = 0.56$, 0.63, and 0.81, respectively). In group 2 (Table 2), we observed a significant change ($P < 0.05$) in K1, K2, topographic cylinder, and Kmean after the first ICRS implantation and after ICRS adjustment surgery. Coma was reduced ($P > 0.05$) in both procedures; in the IHD and ISV parameters, we observed a statistically significant change in the ISV parameter only after ICRS adjustment surgery.

Complications

During the 12-month follow-up period after each procedure, there were no cases of segment extrusion or migration after the first implantation or after ICRS exchange surgery. No intraoperative complications were observed.

DISCUSSION

The main objective of our study was to evaluate the results of ICRS explantation and exchange due to unsatisfactory visual and refractive results. In summary, we found that ICRS exchange/adjustment surgery appears safe and effective; UDVA, CDVA, refractive and topographic astigmatism, and corneal HOA were improved, and no complications were reported. This improvement may be explained by the fact that the ICRS implanted was adjusted according to an analysis of the phenotype of the keratoconus being treated, rather than just the grade of ectasia (mean keratometry and spherical equivalent of the patient). To describe the phenotype of the keratoconus, the authors considered the location of the ectasia (distance between the center of the cornea and the point of thinnest pachymetry) and the relationship between the flattest topographic axis and the coma axis, as described previously.[18–20] To our knowledge, this is the largest published cohort of patients who underwent ICRS exchange surgery to improve visual and refractive results.

The classic nomograms that supported the Intacs ICRS were based on mean keratometry and spherical equivalent values, that is, on the grade of severity of the ectasia: the steeper the cornea, the thicker the ICRS to be implanted. The normal recommendation was to perform implantation that was symmetric and thick (350–450 μm) (2 segments). The use of Ferrara ICRS, with more arc lengths and thicknesses available, enables the surgeon to address the morphology of the keratoconus (the phenotype) in more detail, instead of the severity of the disease. Previous studies[18–20] published the results of Ferrara ICRS implantation in different subtypes of ectasia, proving that classifying ectasia in terms of the morphology can improve both visual and refractive results after ICRS implantation.

The possibility of ICRS explantation and exchange due to unsatisfactory visual and refractive results, and/or complications, such as segment migration and segment extrusion, has already been described and published. The first publications regarding this aspect examined case series of patients with myopia treated with Intacs ICRS implantation. Asbell et al[21] were the first to report the results of performing an ICRS exchange. In their series of 4 eyes with the Intacs ICRS, UDVA improved in all the patients and no eye lost lines of CDVA. Chan et al[22] also reported on the results of Intacs ICRS exchange surgery. UDVA improved by at least 1 line and median UDVA improved from 20/40 to 20/20. With

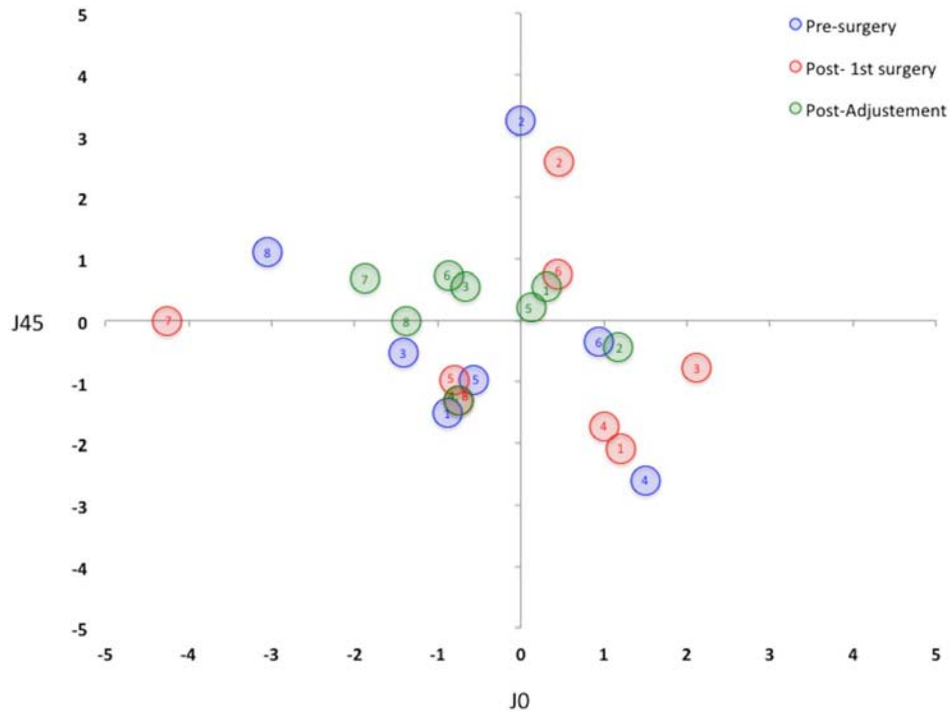

FIGURE 1. Astigmatic power vector (J_0 and J_{45}) before surgery, 12 months after Intacs implantation, and 12 months after ICRS adjustment (group 1) for each case analyzed.

regard to keratoconus, Alió[6] published the first report on ICRS exchange surgery, performed on a cohort of 5 eyes, which had all undergone surgery because of corneal complications after ICRS implantation, namely corneal melting or implant migration. In 4 of the 5 eyes, the ICRS was explanted without any ICRS reimplantation, and all the eyes recovered their preoperative UDVA and CDVA. Pokroy et al[7] were the first to describe the results of ICRS exchange surgery for eyes with poor visual results: in their cohort of patients, 7 eyes underwent an exchange mainly because of an increase in irregular astigmatism and overcorrection (secondary hyperopia). Five eyes had improved UDVA and CDVA after surgery. Alió et al[8] showed significant visual and refractive improvement after implanting a new ICRS combination in 21

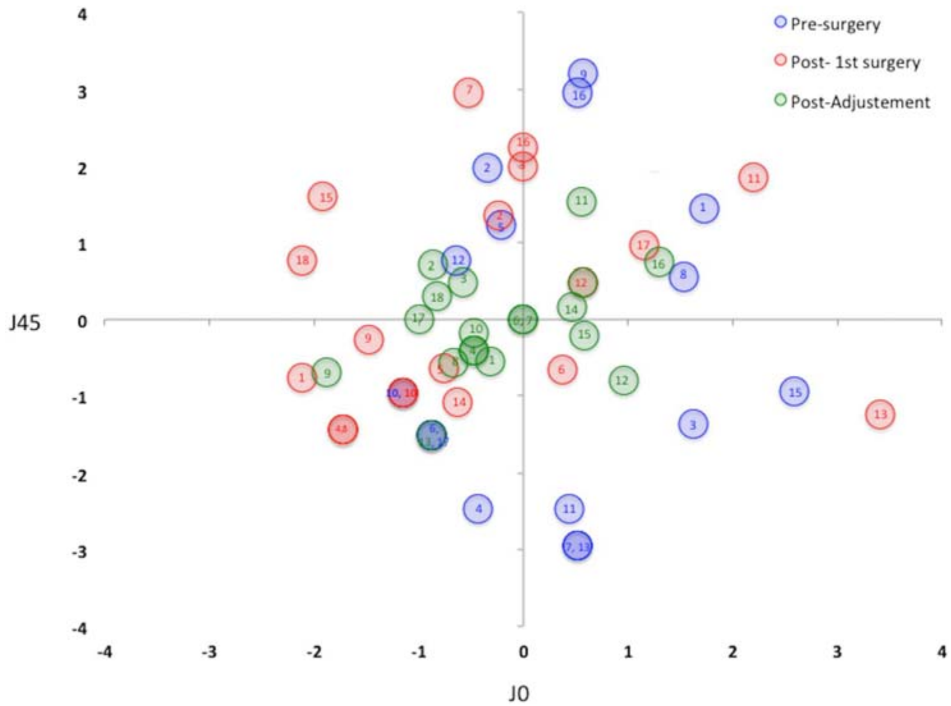

FIGURE 2. Astigmatic power vector (J_0 and J_{45}) before surgery, 12 months after Ferrara ICRS implantation, and 12 months after ICRS adjustment (group 2) for each case analyzed.

TABLE 2. Topographic and Corneal Aberrometric Parameters Shown as Mean ± SD and Range for Group 1

Parameter	Preoperatively	After First ICRS (Before ICRS Exchange)	P	After Ferrara Exchange	P
K1, D	46.78 ± 3.29	44.08 ± 4.16	<0.0001	46.17 ± 2.83	<0.0001
Range	42.10 to 52.00	37.10 ± 51.40		42.10 to 52.10	
K2, D	50.98 ± 3.25	47.42 ± 4.13	<0.0001	48.20 ± 3.45	0.04
Range	44.20 to 56.10	41.10 to 55.30		42.70 to 54.10	
Cylinder, D	4.33 ± 1.39	3.34 ± 1.31	0.03	2.11 ± 1.41	0.003
Range	1.60 to 6.60	1.20 to 5.20		0.10 to 5.20	
Kmean, D	48.88 ± 3.18	45.74 ± 4.09	<0.0001	46.83 ± 2.84	0.002
Range	43.15 to 53.90	39.10 to 53.70		42.40 to 52.20	
Kmax, D	55.76 ± 4.41	54.09 ± 5.15	0.36	53.32 ± 4.56	0.16
Range	46.90 to 63.40	47.10 to 65.40		45.90 to 61.10	
Q	−1.08 ± 0.51	−0.49 ± 0.81	0.013	−0.79 ± 0.45	0.022
Range	−1.89 to −0.31	−1.70 to 1.39		−1.57 to 0.06	
Coma, μm	2.12 ± 1.37	1.79 ± 1.23	0.42	1.70 ± 0.94	0.83
Range	0.23 to 4.46	0.04 to 3.99		0.05 to 3.48	
ISV	87.82 ± 35.30	85.55 ± 23.77	0.88	75.42 ± 25.25	0.004
	37.0 to 151.0	59.0 to 142.0		35.0 to 133.0	
IHD	0.11 ± 0.06	0.11 ± 0.05	0.87	0.10 ± 0.04	0.45
	0.009 to 0.23	0.03 to 0.20		0.02 to 0.18	

ICRS, intrastromal corneal ring segment; IHD, index of height descentration; ISV, index of surface variance.

eyes after a previous ICRS combination that was unsuccessful. However, the results cannot be compared with our sample because the author's sample that underwent explantation contains 2 different types of ICRSs (Intacs and Ferrara), and the postoperative results were not analyzed separately according to the type of the ICRS being exchanged. With regard to Ferrara ICRS exchange surgery, Torquetti et al[9] described a population of 37 eyes that underwent ICRS removal (n = 6), exchange (n = 11), reposition (n = 4), or addition (n = 16), demonstrating a significant improvement in UDVA, CDVA, mean keratometry, and corneal asphericity. In our case, in which patients in group 1 had previous Intacs exchanged for a new Ferrara ICRS combination, we observed an improvement in UDVA, CDVA, and the refractive cylinder. This can be explained because after ICRS exchange surgery, we were able to better address the irregular astigmatism, corneal HOAs, decrease in the topographic cylinder, and coma. All 8 eyes in group 1 were primary implanted with 2 symmetric Intacs ICRSs. After adjustment, all eyes were implanted with only one ICRS (asymmetric implant). All of these had a different arc length from the primary implant, mostly a shorter arc, which is more effective for correcting astigmatism. In our sample of patients with the Ferrara ICRS (see Table 2, Supplemental Digital Content 2, http://links.lww.com/ICO/A598), the majority of the eyes had an initial overcorrection of refractive and topographic astigmatism; in these cases, the procedure of choice was to explant the superior-nasal ICRS. Using this principle, we were able to significantly improve both UDVA and CDVA and the refractive cylinder. In terms of topographic results, after the first ICRS implantation in group 2, we observed a significant decrease in keratometry readings and the topographic cylinder. However, this decrease was due to an overcorrection and axis change of the astigmatism, as we can confirm from the changes induced in the J0 and J45 vectorial analysis (Fig. 2). After ICRS adjustment surgery, we improved the astigmatism value, the coma, the ISV, and the IHD. The improvement in astigmatism overcorrection was observed in the vectorial analysis of group 2 because in all cases, the data moved toward the origin of the graph (0, 0) after ICRS adjustment, as shown in Figure 2.

Another possible treatment option for patients with unsuccessful ICRS implantation is to perform penetrating keratoplasty after explantation of the ICRS. Chhadva et al[23] describe a cohort of patients, previously treated with the Intacs ICRS, without visual acuity improvement, who all underwent ICRS explantation with no reimplantation procedure. None of them showed improved UDVA or CDVA after ICRS explantation. Four eyes subsequently underwent a keratoplasty procedure. The authors took into consideration neither the possibility of performing an exchange procedure nor the possibility of directly performing the deep anterior lamellar keratoplasty procedure without explanting the ICRS. Having the ICRS in place would have facilitated the deep stromal dissection. Our study proves that visual refractive parameters and topographic indexes can be improved if a different combination of the Ferrara ICRS is implanted in accordance with a more accurate analysis of the ectasia morphology before initial ICRS surgery. Fontana et al[24] performed a deep anterior lamellar keratoplasty procedure in a cohort of 5 patients previously treated with the Intacs ICRS for keratoconus with no visual improvement. Both UDVA and CDVA significantly improved after the keratoplasty procedure.

The findings of this study demonstrate that ICRS implantation remains a good option for improving visual acuity in patients with keratoconus who cannot tolerate contact lenses whose disease is not at an advanced stage. The results demonstrate that ICRS surgery is reversible and adjustable in cases of patients with no improvement of visual or refractive parameters and has no intraoperative or postoperative complications. Significant improvement was obtained in UDVA, CDVA, refractive astigmatism, topographic astigmatism, and corneal high-order aberration in all patients who underwent ICRS adjustment.

REFERENCES

1. Ziaei M, Barsam A, Shamie N, et al. Reshaping procedures for the surgical management of corneal ectasia. *J Cataract Refract Surg.* 2015; 41:842–872.
2. Poulsen DM, Kang JJ. Recent advances in the treatment of corneal ectasia with intrastromal corneal ring segments. *Curr Opin Ophthalmol.* 2015;26:273–277.
3. Gomes JA, Tan D, Rapuano CJ, et al. Global consensus on keratoconus and ectatic diseases. *Cornea*. 2015;34:359–369.
4. Ibares-Frias L, Gallego P, Cantalapiedra-Rodriguez R, et al. Clinical, refractive and histological reversibility of corneal additive surgery in deep stroma in an animal model. *Curr Eye Res.* 2016;41:1192–1201.
5. Asbell PA, Ucakhan OO, Abbott RL, et al. Intrastomal corneal ring segments: reversibility of refractive effect. *J Refract Surg.* 2001;17:25–31.
6. Alio JL, Artola A, Ruiz-Moreno JM, et al. Changes in keratoconic corneas after intracorneal ring segment explantation and reimplantation. *Ophthalmology*. 2004;111:747–751.
7. Pokroy R, Levinger S. Intacs adjustment surgery for keratoconus. *J Cataract Refract Surg.* 2006;32:986–992.
8. Alio JL, Pinero DP, Esin S, et al. Implantation of new intracorneal ring segments after segment explantation for unsuccesful outcomes in eyes with keratoconus. *J Cataract Refract Surg.* 2010;36:1303–1310.
9. Torquetti L, Ferrara G, Almeida F, et al. Clinical outcomes after intrastromal corneal ring segments reoperation in keratoconus patients. *Int J Ophthalmol.* 2013;6:796–800.
10. Ferrer C, Alio JL, Montanes AU, et al. Causes of intrastromal corneal ring segment explantation: clinicopathologic correlation analysis. *J Cataract Refract Surg.* 2010;36:970–977.
11. Colin J, Malet J. Intacs for the correction of keratoconus: two-year follow-up. *J Cataract Refract Surg.* 2007;33:69–74.
12. Alio JL, Shabayek MH, Belda JI, et al. Analysis of results related to good and bad outcomes of Intacs implantation for keratoconus correction. *J Cataract Refract Surg.* 2006;32:756–761.
13. Ertan A, Kamburoglu G, Bahadir M. Intacs insertion with the femtosecond laser for the management of keratoconus: one-year results. *J Cataract Refract Surg.* 2006;32:2039–2042.
14. Kymionis GD, Siganos CS, Tsiklis NS, et al. Long-term follow-up of intacs in keratoconus. *Am J Ophthalmol.* 2007;143:236–244.
15. Colin J. European clinical evaluation: use of intacs for the treatment of keratoconus. *J Cataract Refract Surg.* 2006;32:747–755.
16. 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;36:1556–1561.
17. Thibos LN, Horner D. Power vector analysis of the optical outcome of refractive surgery. *J Cataract Refract Surg.* 2001;27:80–85.
18. Lisa C, Fernández-Vega Cueto L, Poo-López A, et al. Long-Term follow-up of intrastromal corneal ring segments (210-degree arc length) in central. Keratoconus with high corneal asphericity. *Cornea*. 2017;36: 1325–1330.
19. Alfonso JF, Fernandez-Vega Cueto L, Baamonde B, et al. Inferior intrastromal corneal ring segments in paracentral keratoconus with no coincident topographic and coma axis. *J Refract Surg.* 2013;29:266–272.
20. Fernandez-Vega Cueto L, Lisa C, Poo-Lopez A, et al. Intrastromal corneal ring segment implantation in 409 paracentral keratoconic eyes. *Cornea*. 2016;35:1421–1426.
21. Asbell PA, Ucakhan OO, Durrie DS, et al. Adjustability of refractive effect for corneal ring segments. *J Refract Surg.* 1999;15:627–631.
22. Chan SM, Khan HN. Reversibility and exchangeability of intrastromal corneal ring segments. *J Cataract Refract Surg.* 2002;28:676–681.
23. Chhadva P, Yesilirmak N, Cabot F, et al. Intrastromal corneal ring segment explantation in patients with keratoconus: causes, technique, and outcomes. *J Refract Surg.* 2015;31:392–397.
24. Fontana L, Parente G, Sincich A, et al. Deep anterior lamellar keratoplasty after intacs implantation in patients with keratoconus. *Cornea*. 2009;28:32–35.

CHAPTER VIII - DISCUSSION

1. Tunnel depth predictability

The depth achieved inside the corneal stroma to perform the ICRS implantation is crucial in terms of both the short-term incidence of mechanical complications and the long-term stability of the procedure. It has been previously demonstrated that femtosecond laser-assisted surgery allows the creation of a corneal flap with a precise thickness, similar to the preoperatively planned thickness[247, 248]. Taking this statement into consideration, one could assume the same predictability in cases of creation of intrastromal tunnels for ICRS implantation in keratoconus corneas. However, several previous publications have reported on the tendency to create shallower tunnels than predicted for ICRS insertion in cohorts of patients treated both with manual and femtosecond-laser assisted surgery[184, 196, 197, 249, 250], surprisingly demonstrating no anatomical benefit of the femtosecond-laser assisted surgery. However, one study in a small sub-group of patients was able to measure the tunnel depth immediately after its surgical creation and before the insertion of the ICRS[199]; in this study, six eyes had an achieved tunnel depth precisely the same to the depth programmed in the femtosecond laser platform (336.7 ± 23.5 vs. 336.6 ± 25.0 μm, respectively). These preliminary results confirmed that the femtosecond laser-assisted surgery is highly predictable in terms of accuracy to create a tunnel inside the cornea at a predetermined depth and encouraged our investigation group to proceed in the direction of demonstrating the superior accuracy of the femtosecond laser to create precise intrastromal tunnels. The main differences of our work (**Chapter IV**) relative to the previous publications mentioned lie on the methodology used to perform the measurements:

- First, we used a higher resolution swept-source AS-OCT (CASIA SS-1000, Tomey Corporation®, Japan), with a depth resolution of 10 μm and transverse resolution of 15 μm, in opposition to the spectral-domain OCT (VISANTE OCT, Carl Zeiss®, Germany), which has a depth resolution of 30 μm and a transverse resolution of 60 μm).
- Second, we took a different reference point inside the corneal stroma to mark the depth of the intrastromal tunnel: a hyperreflective line on the base of the outer corner of the implant (figure 28). This line, which can only be appreciated with a higher resolution OCT, marks the position of the tunnel and is not influenced by the stromal compression that occurs above the implant. In all the studies mentioned before, the method used to measure the tunnel depth is

imprecise, since the authors use the ICRS apex as the reference point, making the manual measurement from that point towards the anterior corneal surface. Probably, the apex depth is shallower than intended because the stromal lamellae above the implant are highly compressed, and no compensation of the implant thickness was considered. Compression of the anterior lamellae derives from the pushing effect of the apex and from the high rigidity of the most anterior part of the stroma that tends to maintain the anterior curvature and shape.

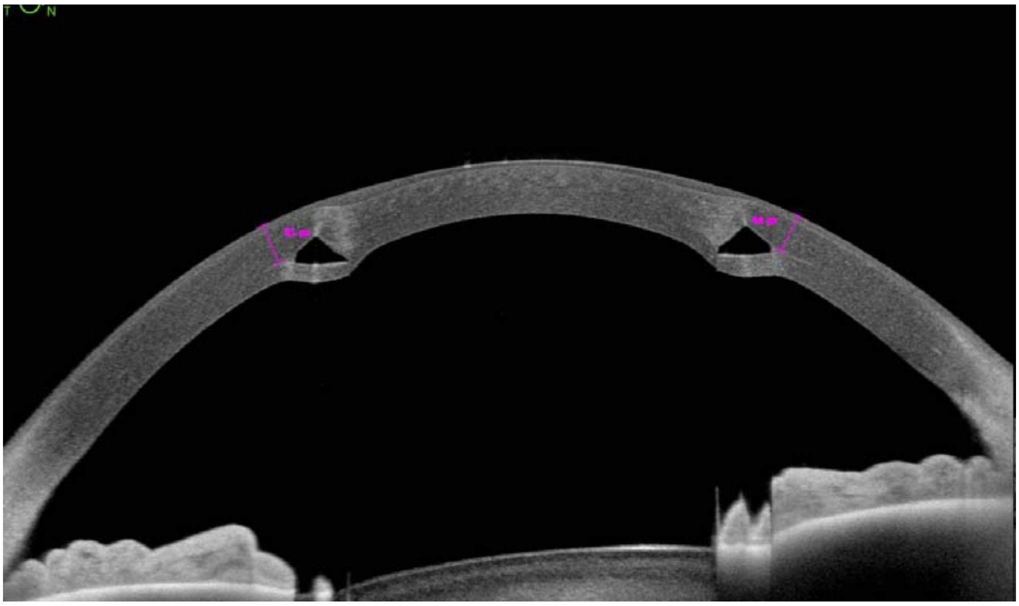

Figure 28. OCT image with ICRS tunnel depth measurement, clinical example (HB 40369658)

Considering the methodology changes that we have introduced regarding the intrastromal tunnel depth measurement, our published results (**Chapter IV**) regarding the predictability of intrastromal depth are similar to the ones reported by Gorgun et al. in their sub-group of 6 patients[199], and very similar to several results published regarding the LASIK flap thickness predictability when performed with a femtosecond laser. In our study, the mean deviation from intended to achieved depth was 4.24 ± 11.89 μm at the proximal end; 3.26 ± 10.58 μm at the central portion; and 8.09 ± 11.91 μm at the distal end. In the case of a LASIK flap, the most recent publications indicate that the mean difference between the intended and the achieved flap thickness is around or below 10 μm. Eldaly et al. reported a difference of 12.93 ± 8.89 μm[247]; Torky et al. calculated a postoperative mean flap thickness of 100.12 ± 16.1 μm (81 to 122 um) for an intended flap thickness of 100 μm[251]; Liu et al. have presented a mean deviation between achieved and attempted flap thickness of 5.18 ± 3.71 μm using the Wavelight FS200 laser and 8.68 ± 7.42 μm using the Intralase FS60[248].

In the short-term follow-up, the importance of a precise depth of implantation inside the corneal stroma is mainly related to the incidence of mechanical complications like implant migration, spontaneous extrusion, corneal melting, and corneal neovascularization. All of these complications have been related to a shallower location of the implant, together with local inflammatory and allergic status, both of which promote constant eye rubbing, mechanical trauma to the cornea, epithelial thinning over the implant, and subsequent corneal erosions, stromal thinning and implant exposure. We have described (**Chapter IV**) that in manual surgery, 7.62% of patients had the implant shallower than 151 μm; 4.76% between 150 and 101 μm and 17.14% between 100 and 51 μm; in total, 12,38% of patients had the implant shallower than 100 μm above the intended depth, which is a high-risk factor for spontaneous segment extrusion. This rate is coincident with the rate of implant extrusion and explantation, which varies from 1.0% to 13.3% with Intacs-ICRS and 1.0% to 19.6% with Ferrara-ICR(215). In **Chapter VI**, we describe a large sample of patients submitted to ICRS with manual and femtosecond-laser assisted surgery, the overall rate of ICRS extrusion was 5.66% in the manual surgery group (n=265 eyes), and 0.0% in the femtosecond-laser group (n= 111 eyes). Coskunseven et al.(195), in a review paper describing the incidence of complications associated with femtosecond-laser surgery, report a very similar rate of ICRS extrusions (0.8%; n=850 eyes).

In a long-term clinical perspective, the ability to achieve a precise intrastromal tunnel depth in the posterior third of the cornea is essential to ensure the highest biocompatibility of the implant and extended longevity inside the corneal stroma. The several decades of experience with a variety of intracorneal inlays for refractive correction of hyperopia and aphakia have demonstrated that even a water impermeable material (like the PPMA used for ICRS), if small enough and implanted deep enough, could remain within the corneal stroma without producing complications(252). This finding supported the theoretical work of Maurice(253) that suggested that if a 4.0 mm diameter water-impermeable material was implanted deep within the cornea, the nutrient flow could circumvent the material and maintain the health of the overlying cornea. More recent studies support his assertions(254): Larrea et al., through a corneal model that simulates the nutrient transport in the cornea, have concluded that the minimum oxygen tension in the cornea was found to be higher when the implant lens was placed at ¾ of the corneal thickness. Moreover, in this position, the influence of the inlay in the transport of nutrients through the cornea was smaller than at a more anterior or posterior location. Recently, several corneal inlays designated to be implanted in the superficial cornea for presbyopia correction were withdrawn from the clinical application because of biocompatibility issues, mainly because their anterior location in the cornea negatively influenced the corneal nutrition and hydration physiological processes[252]. The importance of precise implantation of the ICRS in the posterior corneal stroma cannot be overemphasized, especially if we consider that the population of candidates to this type of surgery is very young; it is, therefore, desirable that the implant remains stable inside the stromal collagen fibers, without altering the fundamental metabolic and nutritional functions of the cornea.

In summary, one can definitely state that femtosecond laser-assisted ICRS implantation surgery is a more precise and predictable procedure when compared to manual mechanical surgery. In essence, the predictability and precision of intrastromal tunnel creation are significantly higher with the femtosecond laser. Once the implant is placed in the correct depth inside the corneal stroma, the short and long-term biocompatibility of the implant is highest, as it does not impact the corneal physiological nutrition and metabolism, the corneal epithelial thickness and the stromal collagen fibers spatial orientation. This fact is fundamental to assume ICRS implantation as a safe procedure in the mid and long-term follow-up, with a very residual rate of mechanical complications, making it a safe procedure to indicate in cases of very young patients (pediatric population) with a diagnosis of keratoconus and surgical indication based on disease progression or low visual acuity.

2. Visual and Refractive results

Some recent review publications have confirmed the overall performance of Ferrara-type ICRS in keratoconus treatment: a significant reduction in SE of between 0.06 D to 5.8 D, (with nearly 80% showing a mean reduction of more than 2.0 D); a reduction in keratometry between 2.0 D and 6.0 D; an improvement in CDVA, with 48% to 97% of treated patients experiencing an improvement in visual function[215], a safety index above 1.0 and an efficacy index between 0.6 and 0.9[255]. A recent meta-analysis[216], published in 2019, confirmed the previous observations: in a total of 1325 eyes analysed, UCVA improved 0.23 ± 0.28 logMAR, and CDVA improved 0.06 ± 0.21 logMAR; sphere improved 2.81 ± 1.54 D, cylinder improved 1.49± 0.83 D, and mean keratometry improved 3.41 ± 2.13 D within 12 months of follow-up. The studies analysed demonstrate refractive and visual improvement of patients with keratoconus treated with ICRS implantation technique. In this last meta-analysis; with manual technique, the mean UDVA, CDVA, and keratometry improved 0.03 logMAR, 0.05 logMAR, and 3.55 D, respectively; with femtosecond laser mean UDVA, CDVA, and keratometry improved 0.36 logMAR, 0.07 logMAR, and 3.32 D. These results indicated better improvement in UDVA with the femtosecond laser technique, but this was not statistically significant. If we specifically compare the results of both techniques regarding visual, refractive, and topographic results, there are limited reported comparison outcomes between both techniques, only four published publications address this comparison. Generally, as long as the ICRS is safely implanted inside the corneal stroma at the intended depth, there should be no difference between both procedures in terms of visual acuity. In 2006, Rabinowitz published the first comparative study between both procedures using Intacs ICRS: visual and refractive results were better in the femtosecond laser group; however, the differences were not statistically significant, the sample was small and different nomograms were applied to the same sample. In a similar study using Intacs ICRS[(202)], a small sample of 33 eyes was included, a similar combination of implants and a temporal corneal incision was used for all cases, no differences were reported for both groups. Piñero et al. published in 2009 a multicentre retrospective study (146 eyes included) comparing both techniques[(201)], they concluded that ICRS implantation using both mechanical and femtosecond laser-assisted procedures provide similar visual and refractive outcomes; the only difference noted was a better aberrometric correction in eyes treated with a femtosecond laser procedure. However, this study included surgeries performed by six different surgeons, three different corneal topographic systems were used to analyse the topographic results across the sample, and most of all, both comparison groups include a mixture of patients implanted with Intacs and Ferrara-type ICRS. The heterogeneous characteristics of the samples, the different measurement techniques, and the variability in the implants used are major weak points of the study to consider when concluding that femtosecond laser could induce a more efficient aberrometric improvement. The most recent paper, published in 2010 by Kubaloglu et al.[(164)], includes 100 eyes, all treated exclusively with Ferrara ICRS; however, all patients were treated indifferently with a 5,00 mm diameter 160-degree arc length. The authors have confirmed that both samples had a similar distribution regarding the Amsler grade of the disease, they have found no statistically significant difference between both groups for visual, refractive and topographic results; they also found a similar rate of patients with a decreased CDVA after surgery in both groups (6% in the manual group and 4% in the femtosecond laser group). Since then, in the last decade, a new classification of the disease was established, a classification based on the phenotype characteristics of the disease rather than just a grading classification; this new classification was developed towards a better ICRS nomogram development, in order to improve the refractive predictability of the surgical procedure. As previously mentioned, the phenotype classification was developed by Jose Alfonso and took into consideration the location of the ectasia (location of the thinnest point), the corneal asphericity, and the relationship between the topographic flattest axis and the

HOA coma axis. In summary, three similar grade 2 keratoconus patients can have different phenotype characteristics and be indicated for ICRS implantation with different implants: a 5.00 mm 300-degree ICRS in the case of central high asphericity ectasia or a 6.00 mm 150-degree implant in the case of paracentral non-coincident axis ectasia. To better compare the efficacy and safety of both surgical procedures, it is essential to compare the results in a group of homogeneous keratoconus with the same morphologic characteristics, namely the location of the thinnest point and the relationship between refractive astigmatism, topographic astigmatism and the coma axis, that is, to compare the surgical technique in keratoconus patients where the same implant characteristics were applied. In **Chapter V**, we present the first published results of a comparison study, which included just two specific keratoconus phenotypes, in which a certain type of ICRS implant is recommended for all patients. All the previously published studies in the last two decades have included very diverse patients, treated with the same implant specifications even though the ectasia morphology was not the same. In the study by Pinero[201], two completely different implants (Intacs with a hexagonal shape and Ferrara with a triangular shape) were included in the same sample groups for comparison. In their study, they have found a significant difference in terms of HOA correction, favouring femtosecond-laser surgery. In our study, presented in **Chapter V**, we have demonstrated no significant difference in terms of visual acuity, refraction, and topographic parameters between both techniques, including $Z3^{-1}$ Coma, which is the main corneal HOA present in keratoconus patients. We have also compared the results dividing the sample in terms of ectasia grading: in a sub-group of grade 1 and another of grade 2 (Amsler-Krumeich), similar results were obtained with both surgical techniques. At six month follow-up, the overall efficacy index was 0.79 for the manual group and 0.74 for the femtosecond group, a similar improvement was observed in both groups overall in terms of UCVA and CDVA. The results remained equal when stage 1 and 2 Amsler sub-groups were analysed separately. In the paper by Kubaloglu et al[164], half of the patients included were grades 3 and 4, which could have an impact on the comparison results, since ICRS are not recommended in patients with grade 4 and are normally less efficient in cases of grade 3.

The vectorial analysis performed in our sample (**Chapter V**) corroborates the efficacy of both surgical techniques in terms of astigmatism correction. There was a significant improvement in the magnitude of the astigmatic vector. Even though the result of the vectorial analysis confirms that both methods offer a safe reduction of astigmatism without inducing a significant change in the direction of the vector, there is a higher tendency for the manual mechanical surgery to produce overcorrection and a considerable change in the axis of astigmatism, this difference was not statistically significant but is clinically relevant. A higher sample of patients could statistically confirm this observation in the future; no previous studies comparing both techniques have used a vectorial analysis calculation to perform the comparison. Our results show similar efficacy in terms of astigmatism correction for both techniques: the mean AIS was 0.45 ± 0.51 and 0.50 ± 0.65, for the manual and femtosecond groups, respectively (p = 0.23); 49 eyes (59.03%) in the manual group, and 67 eyes (61%) in the femtosecond group, had a decrease in cylinder power higher than 50%. In summary, if both surgical procedures would demonstrate similar complications rate, one could assume both to be similar and comparable. However, manual surgery is associated with a higher rate of complications, and thus, cannot be fully considered equal to femtosecond laser surgery, at least during each surgeon´s learning curve.

3. Complications

As generally accepted, the efficacy and safety of any type of surgical procedure involving the placement of an implant inside the human body depend on high implant biocompatibility and proper implant positioning. Thus, the safety of ICRS and the complication rate associated with the procedure depend on the biocompatibility of the material inside the corneal stroma after a precise implantation in the deep corneal layers.

The implantation of ICRS inside the corneal stroma is considered as an extremely high biocompatible procedure; previous studies have demonstrated no inflammatory material on the surface of ICRS explanted because of a refractive failure, showing the biocompatibility of the PMMA in the area of ICRS implantation[(191)]. Histological reaction after ICRS insertion in the corneal stroma is difficult to study; a few histopathological studies available in corneas with ICRS and no postoperative mechanical complications have demonstrated no evidence of inflammatory cells, foreign-body granulomas, or neovascularization. All the corneas studied appeared to have a structurally healthy stroma with parallel collagen lamellar fibers[(256)]. However, in cases where a mechanical complication occurred (like an extrusion), scanning electron microscopy analysis of ICRS has shown the presence of an inflammatory cellular reaction at the extrusion site and surrounding the implant; indicating that epithelial breakdown and close contact between the corneal stroma and the tear film play a role in triggering this reaction. Migration of macrophages to the wound site, localized edema[(257)], and activation of keratocytes to fibroblast and myofibroblasts phenotypes would be consistent with the normal tissue response to surgical trauma[(258)], a large number of cells and cell debris was documented on the surfaces of extruded ICRS[(191)].

Such an inflammatory reaction does not occur when the segment is placed in the stroma without complications but rather triggered when the epithelial barrier is broken. This reaction is amplified when a foreign body prevents wound closure, as it is the case when the ICRS migrates towards the corneal incision or in cases where the implant itself is left near the corneal wound at the end of the procedure. Histopathological studies have also demonstrated the appearance of epithelial hypoplasia overlying the area of the ICRS[(256, 259)]. Together with the findings suggesting a relationship between the epithelial barrier damage and the presence of inflammatory cells, it can be inferred that in cases where the implant is placed superficially in the anterior stroma of the cornea, these histologic and biochemical findings are the precursors of epithelial and stromal layers thinning, melting and subsequently lead to implant extrusion. In summary, the presence of an ICRS inside the deep corneal stroma is a fully biocompatible procedure; whenever the implant is superficially placed, a cascade of reactions led by the initial changes in the epithelial layer and secondarily perpetuated by the presence of inflammatory cells can lead to a latter implant extrusion.

Regarding intra and postoperative complications, they can be divided into two groups: mechanical complications or refractive/topographic complications. In general, a proper implant positioning in the deep corneal stroma is the most important factor to ensure a low probability of a serious mechanical complication; it depends on the type of surgical technique applied and the surgeon's learning curve. In the case of manual procedure, the ability to reach a deep incision and a well-constructed intrastromal tunnel is the main surgical steps to achieve a proper result. As shown in **Chapter IV**, the precision of the manual mechanical procedure is lower than the femtosecond-laser procedure, so it would be expected to have a higher rate of mechanical complications in the manual procedure. Also related to mechanical complications like ICRS extrusion is the so-called *"Pachymetry Rule"*. The rule states that the thickness of the ring inside the stromal bed cannot exceed half the thickness of the cornea along the correspondent optical zone of implantation; if the desired ICRS thickness exceeds half the thickness of the cornea a thinner implant must be selected even if the correction is likely to be smaller than desired[(170)]. Since this rule began to be followed, the incidence of extrusion has decreased significantly[(260)]; and the nomograms have evolved on the knowledge that thinner segments achieve the same or better results than thicker segments used in the past[(261)]. One of the most feared complications of ICRS, ring extrusion, has decreased because the 350 or 400 μm thick rings are seldom implanted.

In **Chapter VI**, we have demonstrated that manual mechanical ICRS surgery shows a higher rate of intra and postoperative mechanical complications when compared to femtosecond laser-assisted technique. The incidence of all complications is higher during the surgeon's first years of implementation of the technique, clearly demonstrating the existence of a learning curve of the procedure: in the manual group, the majority of complications (81.25%) were observed during the first three years of experience (2011-2014), while 12.75% appeared during the last three years of experience (2015-2017). As Ferrara previously published[170]: "Once the surgical procedure is mastered, the complication rate related to the surgery itself is very low". The mechanical complications can be divided into two groups: intra or postoperative. Intraoperative complications include decentred tunnel creation, superficial or asymmetric tunnel creation, corneal surface perforation, or anterior chamber perforation. Among postoperative complications, the most important to analyse are segment migration, implant extrusion, infectious keratitis, neovascularization, and white deposits in the stromal tunnel. In previous publications regarding manual surgery[215, 262], the rate of extrusion and segment explantation varies from 1.0% to 13.3% with Intacs-ICRS and 1.0% to 19.6% with Ferrara-ICRS, decentration from 3.9% to 4.4%, superficial implants from 3.6% to 3.8%; if we analyse those articles with a high number of implantations, the explantation rate varies between 0% and 1.4%. In our series (**Chapter VI**) with manual surgery, the incidence of ICRS extrusion was 5.66%, corneal intraoperative perforation 1.51%, and corneal infection 1.13%. Femtosecond laser treatment is associated with a reduced incidence of complications; however, it has introduced new complications to ICRS implantation like incomplete channel creations or vacuum loss. The majority of complications associated with FS-laser have no serious impact on the final visual outcome[195]. In our series (**Chapter VI**) with femtosecond-assisted surgery, we reported one case of corneal perforation (0.9%), no cases of ICRS extrusion, and one case of corneal infection (0.9%). When analysing the overall complication rates reported in the literature, it is frequently stated that the higher rates of complications are solely associated with the type of surgery performed. Interestingly, no relationship has been studied between the complication's rate and the patient's preoperative characteristics; no specific risk factors associated with the corneal morphology or disease grade have been studied that could alert the surgeon to a higher risk procedure in a specific patient. In **Chapter VI**, we have analysed the patients and the topographic characteristics of the whole sample with or without complications. Contrary to what could be empirically considered, younger patients, thinner corneas, higher Kmean, higher Kmax, and higher HOA (coma) were not associated with a higher incidence of mechanical complications. In the case of intraoperative corneal perforation or late ICRS extrusion, a higher incidence of such complications was significantly associated with patients with higher levels of refractive and topographic astigmatism and lower preoperative visual acuity. Hypothetically, younger patients have a higher risk of continuous progressive disease, atopy, and frequent eye rubbing; these factors could lead to corneal thinning, and subsequently to ICRS migration and extrusion, our study has not found a direct relationship between these clinical factors. The ICRS extrusion was solely associated with highly aberrated corneas, with higher corneal astigmatism, higher coma and higher K2. This fact could explain that in corneas with very asymmetric morphology, the ability to perform manual surgery and to deliver a constant parallel intrastromal tunnel depth along the corneal stromal dissection is more difficult to achieve, especially when compared with a similar grade keratoconus (with equal Kmean) with a more symmetric anterior surface, with lower astigmatism and coma. Piñero et al.[201] reported a spontaneous extrusion rate of 9.46% for manual surgery and 4.82% for femtosecond laser ICRS, the higher extrusion rate in the manual group was associated with a more significant corneal irregularity and higher levels of corneal HOA, similarly to what we have found in our sample. In **Chapter VI**, we have also been able to study and confirm the reversibility of the procedure and the ability to perform a secondary intervention after a previous complication. In both the sub-groups of ICRS extrusion and corneal perforation, a secondary surgical procedure was done 6 to 12 months later, with a new ICRS implanted; visual, refractive, and topographic parameters significantly improved in all patients. With femtosecond laser surgery, we had only one eye with a corneal endothelial perforation (0.9%) and no eyes with late spontaneous extrusion, corneal melting or ICRS migration; our complication rate after femtosecond laser-assisted surgery is very low and similar to recent publications, which report an incidence of complications below 1.5% to 2.0%[164, 195]. The most recent publications by the Fernandez-Vega investigation group about the results of ICRS in several different phenotypes of the disease, all performed with laser-assisted surgery, have reported no intra or postoperative complications[217-219].

Regarding the incidence of refractive and topographic complications, which could be defined as a perfect anatomic outcome (proper ICRS position in the corneal stroma) with an undesired visual or topographic outcome, the ICRS nomogram evolution and refinement together with the surgeon's personal experience are normally associated with a progressive decrease in the incidence of such visual or refractive complications (visual acuity loss and astigmatism overcorrection are the most frequent). In **Chapter VI,** we have demonstrated that there is also a surgeon's learning curve for the ICRS personal nomogram refinement; the incidence of ICRS exchange surgery significantly decreased from 7.92% in the first three years of experience to 1.51% in the last three years of analysis. We have also found a higher incidence of ICRS exchange surgery due to improper visual outcomes in the manual group (9.43%) versus the femtosecond-laser group (1.8%). The only preoperative characteristic associated with a higher risk of

ICRS exchange after surgery was the preoperative level of subjective refractive astigmatism, all of the other parameters of both samples were equal between the group with no complications and the ICRS exchange group. This difference between the incidences observed on both techniques could be explained by the fact that in higher levels of corneal astigmatism, normally, two short-arc length implants are used. In these situations, the fact that manual surgery is more prone to tunnel decentrations and the different tunnel's achieved depth could explain the higher incidence of the unexpected topographic outcome, most of which correspond to astigmatism overcorrection.

In **Chapter VII**, we have made a more specific analysis about the reversibility of the procedure, demonstrating the efficacy of exchanging a certain type of ICRS (Intacs-ICRS) for a different implant type (Ferrara-ICRS) or the adjustment surgery maintaining the same type of ICRS, just changing the implant characteristic (number of implants, thickness or arc length). In both groups (all performed with manual surgery), there was a significant improvement in CDVA, refractive cylinder, topographic cylinder, and HOA (coma). Although ICRS is a safe procedure in patients with keratoconus, some studies have reported a small percentage of eyes losing CDVA lines after surgery[215, 263]. Apart from surgical problems, a possible explanation for the loss of CDVA after ICRS implantation could be an incorrect parameter choice of the ICRS to be implanted, which could induce astigmatism overcorrection or an increase in irregular astigmatism or HOAs.

It would be expected that the femtosecond-laser group would have a lower incidence of ICRS exchange in the follow-up period; this could be explained by the fact that a higher precision of ICRS implantation leads to higher predictability of the visual and topographic result. On the contrary, if the ICRS is improperly placed in a shallower or deeper position than intended, the visual outcome that was predicted for a given ICRS arc length and thickness can no longer be achieved, and the result is usually more unpredictable. During several decades (mainly before 2010), when the femtosecond-laser technology was not available for ophthalmic surgery, a main drawback attributed to ICRS surgery was the higher level of uncertainty and unpredictable results. Surely, the main factor to this observation is demonstrated in our work: manual surgery is less precise in terms of the ICRS depth of implantation, and this leads to a higher necessity to perform ICRS exchange surgery to overcome poor visual acuity results. Since the advent of FS-laser surgery in corneal surgery, the precision of ICRS implantation raised, the complication rate decreased, the surgeon's experience and nomogram refinement improved, and ICRS has become a more predictable surgery, offering, in general, a very satisfactory visual and refractive result. All the clinical and anatomical advantages demonstrated in **Chapters IV, V** and **VI** about the FS-laser assisted ICRS implantation surgery compared to the original manual surgery have paved the way to the recent creation of new clinical indications for the procedure and a "solid ground" for future perspectives and research developments to enhance further the predictability and the final result of the surgery. Recently**,** it has been demonstrated the clinical results of a long-term clinical study of ICRS in a paediatric population[264]. Paediatric keratoconus is usually associated with higher risk features for ICRS late extrusion: uncontrolled allergy and ocular surface inflammation, severe eye rubbing, and frequent progressive disease. As previously mentioned before, the combination of shallow ICRS implantation and epithelial layer hypoplasia and disruption is the principal trigger for stromal inflammatory reactions, progressive epithelial and stromal thinning overlying the implant, ICRS migration, corneal melting, and implant spontaneous extrusion. The paediatric population is a specific keratoconus population where the safety and predictability of the procedure are of the utmost importance. Taking this into consideration, and the results obtained and explained in Chapters II, III and IV, we think that the ICRS implantation with a femtosecond-laser assisted surgery fulfils the safety requirements to be applied in such a high-risk population; opposite to manual surgery, which should not be recommended in this specific type of keratoconus population. The results obtained have confirmed our research group expectations, having achieved a safe, effective, and stable procedure over a 5-year follow-up period[264]. All the visual acuity (UDVA and CDVA) parameters, refractive parameters (mean spherical equivalent, mean refractive cylinder), and topographic parameters (minimum K, maximum K, and coma aberration) have improved after surgery and remained stable over time. In the same sample, no intra or postoperative complications (like ICRS migration or extrusion) were reported. It is also essential to mention that apart from the surgical procedure being performed with a femtosecond-laser technique, a significant contribution to the overall success of the procedure was the medical treatment of the ocular surface allergy and inflammation and the recommendations to the patients that eye rubbing should be completely avoided.

4. Future Perspectives

Taking into consideration the results produced by the current research doctoral thesis, some aspects can be inferred in terms of short and long-term application of the ICRS implantation surgical technique for keratoconus:

- Manual mechanical surgery has a higher incidence of mechanical and visual complications when compared to femtosecond-laser assisted surgery, has lower vectorial astigmatism correction predictability, and hence, should have a lower refractive efficacy if analysed from a refractive point of view. However, these negative aspects associated with the procedure should not diminish its importance in the general clinical practice of ophthalmology, and in particular, in the clinical context of public health institutions where there is no access to high technology devices like a femtosecond-laser device. All the major mechanical and refractive complications can be overcome with a second surgical procedure, with full recovery and improvement of visual, refractive and topographic parameters. Manual surgery can be considered a suitable surgical treatment to perform in public institutions, offering adult patients who do not have access to private practice institutions the opportunity to have their disease treated and their quality of life improved. Even though the complication's rate after the surgeon's learning curve is around 3.02%, it continues to be one of the first-line treatments for keratoconus, with specific and distinct indications complementary to corneal collagen cross-linking.

- The higher predictability and safety of intrastromal tunnel creation with the FS-laser assisted surgery, the demonstration of the high biocompatibility of the implant inside the deep corneal stroma and the current evolution of the ICRS nomogram driven by a specific new classification of the disease by phenotypic morphology created by José Alfonso at the "*Instituto Oftalmológico Fernandez-Vega*" has increased the refractive predictability of the procedure, expanded the classic indications of ICRS for keratoconus and enabled the research and development of new ICRS designs to apply in specific cases of ectasia. Nevertheless, the increase of the refractive predictability of the procedure associated with the clinical developments previously mentioned will provide further improvement; however, the final result of the surgery is also limited and influenced by each patients' corneal biomechanical unique response. This individual aspect of the surgery still cannot be predicted or neither controlled preoperatively.
- About the new indications, the paediatric group is a clear example of how the development of a specific surgical technique, the achievement of safety standards, and a very low complication rate, such as the one obtained with contemporary ICRS surgery with FS-laser device has led to the clinical indication and application of a surgical procedure that was, in the beginning, mostly reserved for adult patients. It becomes evident that having a surgical procedure with such a high safety profile and stable results over time, could allow corneal surgeons to apply it to paediatric patients, offering this specific population excellent visual

acuity results and stable topographic outcomes over time. If other research groups acquire this evidence in the near future, there could be a paradigm shift in the treatment of paediatric progressive keratoconus.

- Another recent advance in the field of keratoconus treatment with ICRS is the development of new ICRS designs. In manual mechanical surgery, where only 15.24% of eyes reached an achieved depth of implantation within ± 10 um from the intended, it is challenging to develop and analyse new ICRS designs, since the predictability of its implantation in the corneal stroma is low, and this aspect impacts negatively on the analysis made regarding the new ICRS design in terms of its beneficial result when compared to the standard ICRS designs. Just recently, two specific ICRS designs where developed to address specific morphologies of keratoconus, and their primary indications are to be implanted through a femtosecond-laser assisted procedure in order to achieve their maximum estimated benefit: the progressive asymmetric thickness ICRS and the 300-degree arc length ICRS.
- The asymmetric progressive thickness implant becomes interesting because a large proportion of patients, between 25 to 30% of the patients submitted to ICRS implantation have a specific type of ectasia where the axis of the flattest topographic axis differs more than 30 degrees from the axis of the coma HOA. Classically, the current nomogram indicated the implantation of a 150 or 160-degree arc length segment, centered between the two axes mentioned above. Alternatively, it could be beneficial to place an implant centered on the middle of both axes but with asymmetric thickness in order to balance the therapeutic effect depending on the specific clinical case. The higher efficacy of this type of implant is one of the clinical research trials being conducted by our investigation group, applying the same nomogram and a specific depth of implantation using the femtosecond-laser device exclusively to assist the surgery.
- The new 5.0 mm optical zone implant, of 300 to 320-degree arc length, has been developed in order to address a specific type of ectasia with grade 3 of Amsler-Krumeich classification, high central corneal asphericity and no corneal striae at the apex of the cornea. Before the introduction of this type of implant, the only design available was a similar implant with just 210-degrees arc length, but the visual and refractive results for such type of patients was somewhat disappointing. The first clinical studies published about the application of the 320-degree arc implant have shown promising clinical outcomes[183]. They should be analysed

taking into consideration that most of these patients would have been otherwise proposed to surgical treatment with penetrating keratoplasty or deep anterior lamellar keratoplasty. This type of implant procedure is mandatory to be accomplished with a femtosecond-laser assisted technique. First, it is necessary to achieve a very symmetric and homogeneous tunnel in terms of internal diameter and corneal centration in order to facilitate the introduction of this long arc implant. Second, the specific population of patients where its indication is most favourable are the grade 3 ectasias with low pachymetric values; in these cases, it is mandatory to achieve with high precision the intended depth for the intrastromal tunnel; otherwise, the probability of shallow implantation and late ICRS extrusion is higher. Our investigation group, together with the "*Instituto Oftalmológico Fernandez-Vega*", is conducting a clinical research study to evaluate the results of the new 300-degree arc length. The objective of the study is to evaluate if the same visual, refractive and topographic results can be obtained with this implant as with the 320-degree implant since we consider this late implant more difficult to implant and more prone to late extrusions because its extremities lie closer to the corneal incision.

CHAPTER IX – CONCLUSIONS

The previously published results and the discussion about their impact allow us to present the following conclusions:

1. Predictability of tunnel depth for Intrastromal corneal ring segments implantation between manual and femtosecond laser techniques

- ICRS implantation assisted by a femtosecond laser provides a more precise procedure considering the achieved dissection depth when compared with manual surgery.
- In the manual surgical procedure, the proximal part of the stromal tunnel is significantly shallower (-40.87 ± 69.03 um) than the central (-25.54 ± 71.00 um) and the distal (-26.52 ± 73.22 um) parts.
- In the manual surgical procedure, only 15.24% of eyes reached an achieved depth of implantation within ± 10 um from the intended, while in the femtosecond-laser group, the proportion to achieve it was 67.92%.

2. Comparison of clinical outcomes between manual and femtosecond laser techniques for intrastromal corneal ring segment implantation

- After ICRS surgery with both techniques, there was a statistical significant improvement in uncorrected and corrected distance visual acuity for both groups ($p<0.0001$), and there were no statistically differences between groups regarding visual acuity outcomes ($p>0.3$).
- For both groups, there was a reduction in spherical equivalent after ICRS surgery, and there was no difference between groups regarding the magnitude of spherical equivalent reduction ($p=0.34$) or in the magnitude of the RMS coma-like aberrations reduction ($p=0.2$).
- The vectorial analysis of the corneal astigmatism correction significantly favours the femtosecond group both in terms of the overall vector value and less induction of vector direction change, confirming it as a more predictable procedure.

3. Comparison of complication rates between manual and femtosecond laser-assisted techniques for intrastromal corneal ring segments implantation in keratoconus

- In the manual group, there was a total of 18.11% of complications, as opposed to the femtosecond laser group, with a 3.6% rate. In the manual group, 81.25% of complications were observed in the first three years of clinical implementation of the technique.
- Eyes who suffered a complication had a preoperatively higher mean refractive (p=0.002) and topographic cylinder (p=0.003) and lower UDVA (p=0.005) and CDVA (p=0.002). No association was observed between a higher incidence of complications and younger patients, thinner corneas, or more advanced keratoconus (higher mean keratometry or maximum keratometry values).
- After a second surgical procedure for complication management; visual, refractive, and topographic outcomes significantly improved.

4. Adjustment of intrastromal corneal ring segments after unsuccessful implantation in keratoconic eyes

- ICRS implantation was demonstrated to be a reversible and adjustable surgical procedure for keratoconus treatment.

BIBLIOGRAPHY

1. Freegard TJ. The physical basis of transparency of the normal cornea. Eye (Lond). 1997;11 (Pt 4):465-71.
2. Mishima S. Corneal thickness. Survey of ophthalmology. 1968;13(2):57-96.
3. Maurice D. The cornea and sclera. The Eye.: Academic Press; 1984.
4. Muller LJ, Marfurt CF, Kruse F, Tervo TM. Corneal nerves: structure, contents and function. Experimental eye research. 2003;76(5):521-42.
5. Aguayo JB, McLennan IJ, Graham C, Jr., Cheng HM. Dynamic monitoring of corneal carbohydrate metabolism using high-resolution deuterium NMR spectroscopy. Experimental eye research. 1988;47(2):337-43.
6. Gottsch JD, Chen CH, Aguayo JB, Cousins JP, Strahlman ER, Stark WJ. Glycolytic activity in the human cornea monitored with nuclear magnetic resonance spectroscopy. Archives of ophthalmology. 1986;104(6):886-9.
7. Holden BA, Sweeney DF, Vannas A, Nilsson KT, Efron N. Effects of long-term extended contact lens wear on the human cornea. Investigative ophthalmology & visual science. 1985;26(11):1489-501.
8. Ichijima H, Ohashi J, Cavanagh HD. Effect of contact-lens-induced hypoxia on lactate dehydrogenase activity and isozyme in rabbit cornea. Cornea. 1992;11(2):108-13.
9. Sack RA, Tan KO, Tan A. Diurnal tear cycle: evidence for a nocturnal inflammatory constitutive tear fluid. Investigative ophthalmology & visual science. 1992;33(3):626-40.
10. Rabinowitz YS. Keratoconus. Survey of ophthalmology. 1998;42(4):297-319.
11. Balasubramanian SA, Pye DC, Willcox MD. Are proteinases the reason for keratoconus? Curr Eye Res. 2010;35(3):185-91.
12. Jun AS, Cope L, Speck C, Feng X, Lee S, Meng H, et al. Subnormal cytokine profile in the tear fluid of keratoconus patients. PloS one. 2011;6(1):e16437.
13. Lema I, Brea D, Rodriguez-Gonzalez R, Diez-Feijoo E, Sobrino T. Proteomic analysis of the tear film in patients with keratoconus. Mol Vis. 2010;16:2055-61.
14. Lema I, Duran JA. Inflammatory molecules in the tears of patients with keratoconus. Ophthalmology. 2005;112(4):654-9.

15. Lema I, Sobrino T, Duran JA, Brea D, Diez-Feijoo E. Subclinical keratoconus and inflammatory molecules from tears. The British journal of ophthalmology. 2009;93(6):820-4.

16. Dienes L, Kiss HJ, Perenyi K, Nagy ZZ, Acosta MC, Gallar J, et al. Corneal Sensitivity and Dry Eye Symptoms in Patients with Keratoconus. PloS one. 2015;10(10):e0141621.

17. Rabinowitz YS. The genetics of keratoconus. Ophthalmology clinics of North America. 2003;16(4):607-20, vii.

18. Patel D, McGhee C. Understanding keratoconus: what have we learned from the New Zealand perspective? Clin Exp Optom. 2013;96(2):183-7.

19. Kenney MC, Chwa M, Atilano SR, Tran A, Carballo M, Saghizadeh M, et al. Increased levels of catalase and cathepsin V/L2 but decreased TIMP-1 in keratoconus corneas: evidence that oxidative stress plays a role in this disorder. Investigative ophthalmology & visual science. 2005;46(3):823-32.

20. Chwa M, Atilano SR, Hertzog D, Zheng H, Langberg J, Kim DW, et al. Hypersensitive response to oxidative stress in keratoconus corneal fibroblasts. Investigative ophthalmology & visual science. 2008;49(10):4361-9.

21. McMonnies CW. Mechanisms of rubbing-related corneal trauma in keratoconus. Cornea. 2009;28(6):607-15.

22. Gomes JA, Tan D, Rapuano CJ, Belin MW, Ambrosio R, Jr., Guell JL, et al. Global consensus on keratoconus and ectatic diseases. Cornea. 2015;34(4):359-69.

23. Bawazeer AM, Hodge WG, Lorimer B. Atopy and keratoconus: a multivariate analysis. The British journal of ophthalmology. 2000;84(8):834-6.

24. Hashemi H, Heydarian S, Hooshmand E, Saatchi M, Yekta A, Aghamirsalim M, et al. The Prevalence and Risk Factors for Keratoconus: A Systematic Review and Meta-Analysis. Cornea. 2020;39(2):263-70.

25. Krachmer JH, Feder RS, Belin MW. Keratoconus and related noninflammatory corneal thinning disorders. Survey of ophthalmology. 1984;28(4):293-322.

26. Lee HK, Jung EH, Cho BJ. Epidemiological Association Between Systemic Diseases and Keratoconus in a Korean Population: A 10-Year Nationwide Cohort Study. Cornea. 2019.

27. Hwang S, Lim DH, Chung TY. Prevalence and Incidence of Keratoconus in South Korea: A Nationwide Population-based Study. American journal of ophthalmology. 2018;192:56-64.

28. Jonas JB, Nangia V, Matin A, Kulkarni M, Bhojwani K. Prevalence and associations of keratoconus in rural maharashtra in central India: the central India eye and medical study. American journal of ophthalmology. 2009;148(5):760-5.

29. Kennedy RH, Bourne WM, Dyer JA. A 48-year clinical and epidemiologic study of keratoconus. American journal of ophthalmology. 1986;101(3):267-73.

30. Georgiou T, Funnell CL, Cassels-Brown A, O'Conor R. Influence of ethnic origin on the incidence of keratoconus and associated atopic disease in Asians and white patients. Eye (Lond). 2004;18(4):379-83.

31. Pearson AR, Soneji B, Sarvananthan N, Sandford-Smith JH. Does ethnic origin influence the incidence or severity of keratoconus? Eye (Lond). 2000;14 (Pt 4):625-8.

32. Rabinowitz YS, Nesburn AB, McDonnell PJ. Videokeratography of the fellow eye in unilateral keratoconus. Ophthalmology. 1993;100(2):181-6.

33. Holland DR, Maeda N, Hannush SB, Riveroll LH, Green MT, Klyce SD, et al. Unilateral keratoconus. Incidence and quantitative topographic analysis. Ophthalmology. 1997;104(9):1409-13.

34. Parker J, Ko WW, Pavlopoulos G, Wolfe PJ, Rabinowitz YS, Feldman ST. Videokeratography of keratoconus in monozygotic twins. Journal of refractive surgery. 1996;12(1):180-3.

35. Wang Y, Rabinowitz YS, Rotter JI, Yang H. Genetic epidemiological study of keratoconus: evidence for major gene determination. American journal of medical genetics. 2000;93(5):403-9.

36. Karimian F, Aramesh S, Rabei HM, Javadi MA, Rafati N. Topographic evaluation of relatives of patients with keratoconus. Cornea. 2008;27(8):874-8.

37. Szczotka-Flynn L, Slaughter M, McMahon T, Barr J, Edrington T, Fink B, et al. Disease severity and family history in keratoconus. The British journal of ophthalmology. 2008;92(8):1108-11.

38. Weed KH, MacEwen CJ, Giles T, Low J, McGhee CN. The Dundee University Scottish Keratoconus study: demographics, corneal signs, associated diseases, and eye rubbing. Eye (Lond). 2008;22(4):534-41.

39. Gordon-Shaag A, Millodot M, Essa M, Garth J, Ghara M, Shneor E. Is consanguinity a risk factor for keratoconus? Optom Vis Sci. 2013;90(5):448-54.

40. Millodot M, Shneor E, Albou S, Atlani E, Gordon-Shaag A. Prevalence and associated factors of keratoconus in Jerusalem: a cross-sectional study. Ophthalmic Epidemiol. 2011;18(2):91-7.

41. Al-Gazali L, Hamamy H. Consanguinity and dysmorphology in Arabs. Hum Hered. 2014;77(1-4):93-107.

42. Al-Gazali L, Hamamy H, Al-Arrayad S. Genetic disorders in the Arab world. BMJ. 2006;333(7573):831-4.

43. Bittles AH, Hussain R. An analysis of consanguineous marriage in the Muslim population of India at regional and state levels. Ann Hum Biol. 2000;27(2):163-71.

44. Bykhovskaya Y, Margines B, Rabinowitz YS. Genetics in Keratoconus: where are we? Eye Vis (Lond). 2016;3:16.

45. Bykhovskaya Y, Li X, Epifantseva I, Haritunians T, Siscovick D, Aldave A, et al. Variation in the lysyl oxidase (LOX) gene is associated with keratoconus in family-based and case-control studies. Investigative ophthalmology & visual science. 2012;53(7):4152-7.

46. Li X, Rabinowitz YS, Tang YG, Picornell Y, Taylor KD, Hu M, et al. Two-stage genome-wide linkage scan in keratoconus sib pair families. Investigative ophthalmology & visual science. 2006;47(9):3791-5.

47. Heon E, Greenberg A, Kopp KK, Rootman D, Vincent AL, Billingsley G, et al. VSX1: a gene for posterior polymorphous dystrophy and keratoconus. Hum Mol Genet. 2002;11(9):1029-36.

48. Moschos MM, Kokolakis N, Gazouli M, Chatziralli IP, Droutsas D, Anagnou NP, et al. Polymorphism Analysis of VSX1 and SOD1 Genes in Greek Patients with Keratoconus. Ophthalmic Genet. 2015;36(3):213-7.

49. Udar N, Atilano SR, Brown DJ, Holguin B, Small K, Nesburn AB, et al. SOD1: a candidate gene for keratoconus. Investigative ophthalmology & visual science. 2006;47(8):3345-51.

50. Baum J. On the location of the cone and the etiology of keratoconus. Cornea. 1995;14(2):142-3.

51. Bron AJ, Rabinowitz YS. Corneal dystrophies and keratoconus. Current opinion in ophthalmology. 1996;7(4):71-82.

52. Bureau J, Fabre EJ, Hecquet C, Pouliquen Y, Lorans G. Modification of prostaglandin E2 and collagen synthesis in keratoconus fibroblasts, associated with an increase of interleukin 1 alpha receptor number. C R Acad Sci III. 1993;316(4):425-30.

53. Jefferies LW, Alexander RA. Connective tissue fibre production in keratoconus. Br J Biomed Sci. 1995;52(1):14-8.

54. Lema I, Duran JA, Ruiz C, Diez-Feijoo E, Acera A, Merayo J. Inflammatory response to contact lenses in patients with keratoconus compared with myopic subjects. Cornea. 2008;27(7):758-63.

55. Wilson SE, He YG, Weng J, Li Q, McDowall AW, Vital M, et al. Epithelial injury induces keratocyte apoptosis: hypothesized role for the interleukin-1 system in the modulation of corneal tissue organization and wound healing. Experimental eye research. 1996;62(4):325-7.

56. Fukuchi T, Yue BY, Sugar J, Lam S. Lysosomal enzyme activities in conjunctival tissues of patients with keratoconus. Archives of ophthalmology. 1994;112(10):1368-74.

57. Sawaguchi S, Twining SS, Yue BY, Chang SH, Zhou X, Loushin G, et al. Alpha 2-macroglobulin levels in normal human and keratoconus corneas. Investigative ophthalmology & visual science. 1994;35(12):4008-14.

58. Sawaguchi S, Yue BY, Sugar J, Gilboy JE. Lysosomal enzyme abnormalities in keratoconus. Archives of ophthalmology. 1989;107(10):1507-10.

59. Torres RM, Merayo-Lloves J, Jaramillo MA, Galvis V. [Corneal biomechanics]. Arch Soc Esp Oftalmol. 2005;80(4):215-23.

60. Vinciguerra R, Ambrosio R, Jr., Elsheikh A, Roberts CJ, Lopes B, Morenghi E, et al. Detection of Keratoconus With a New Biomechanical Index. Journal of refractive surgery. 2016;32(12):803-10.

61. Ambrosio R, Jr., Alonso RS, Luz A, Coca Velarde LG. Corneal-thickness spatial profile and corneal-volume distribution: tomographic indices to detect keratoconus. Journal of cataract and refractive surgery. 2006;32(11):1851-9.

62. Shah S, Laiquzzaman M, Bhojwani R, Mantry S, Cunliffe I. Assessment of the biomechanical properties of the cornea with the ocular response analyzer in normal and keratoconic eyes. Investigative ophthalmology & visual science. 2007;48(7):3026-31.

63. Fontes BM, Ambrosio R, Jr., Velarde GC, Nose W. Ocular response analyzer measurements in keratoconus with normal central corneal thickness compared with matched normal control eyes. Journal of refractive surgery. 2011;27(3):209-15.

64. Ambrosio R, Jr., Valbon BF, Faria-Correia F, Ramos I, Luz A. Scheimpflug imaging for laser refractive surgery. Current opinion in ophthalmology. 2013;24(4):310-20.

65. Lago MA, Ruperez MJ, Martinez-Martinez F, Monserrat C, Larra E, Guell JL, et al. A new methodology for the in vivo estimation of the elastic constants that characterize the patient-specific biomechanical behavior of the human cornea. J Biomech. 2015;48(1):38-43.

66. Pena-Garcia P, Peris-Martinez C, Abbouda A, Ruiz-Moreno JM. Detection of subclinical keratoconus through non-contact tonometry and the use of discriminant biomechanical functions. J Biomech. 2016;49(3):353-63.

67. Wei SS, Li Y, Li J, Liu JG, Ye L, Wan YQ, et al. [Corneal biomechanical properties in keratoconic and normal eyes]. Zhonghua Yan Ke Za Zhi. 2016;52(9):669-73.

68. Roberts CJ, Mahmoud AM, Bons JP, Hossain A, Elsheikh A, Vinciguerra R, et al. Introduction of Two Novel Stiffness Parameters and Interpretation of Air Puff-Induced Biomechanical Deformation Parameters With a Dynamic Scheimpflug Analyzer. Journal of refractive surgery. 2017;33(4):266-73.

69. Zhao Y, Shen Y, Yan Z, Tian M, Zhao J, Zhou X. Relationship Among Corneal Stiffness, Thickness, and Biomechanical Parameters Measured by Corvis ST, Pentacam and ORA in Keratoconus. Front Physiol. 2019;10:740.

70. Woodward MA, Blachley TS, Stein JD. The Association Between Sociodemographic Factors, Common Systemic Diseases, and Keratoconus: An Analysis of a Nationwide Heath Care Claims Database. Ophthalmology. 2016;123(3):457-65 e2.

71. Merdler I, Hassidim A, Sorkin N, Shapira S, Gronovich Y, Korach Z. Keratoconus and allergic diseases among Israeli adolescents between 2005 and 2013. Cornea. 2015;34(5):525-9.

72. Rabinowitz YS. Videokeratographic indices to aid in screening for keratoconus. Journal of refractive surgery. 1995;11(5):371-9.

73. Maeda N, Klyce SD, Smolek MK. Comparison of methods for detecting keratoconus using videokeratography. Archives of ophthalmology. 1995;113(7):870-4.

74. Maeda N, Klyce SD, Smolek MK, Thompson HW. Automated keratoconus screening with corneal topography analysis. Investigative ophthalmology & visual science. 1994;35(6):2749-57.

75. Smolek MK, Klyce SD. Current keratoconus detection methods compared with a neural network approach. Investigative ophthalmology & visual science. 1997;38(11):2290-9.

76. Rabinowitz YS, Rasheed K. KISA% index: a quantitative videokeratography algorithm embodying minimal topographic criteria for diagnosing keratoconus. Journal of cataract and refractive surgery. 1999;25(10):1327-35.

77. de Sanctis U, Aragno V, Dalmasso P, Brusasco L, Grignolo F. Diagnosis of subclinical keratoconus using posterior elevation measured with 2 different methods. Cornea. 2013;32(7):911-5.

78. Gatinel D, Racine L, Hoang-Xuan T. Contribution of the corneal epithelium to anterior corneal topography in patients having myopic photorefractive keratectomy. Journal of cataract and refractive surgery. 2007;33(11):1860-5.

79. Duncan JK, Belin MW, Borgstrom M. Assessing progression of keratoconus: novel tomographic determinants. Eye Vis (Lond). 2016;3:6.

80. Belin MW, Duncan JK. Keratoconus: The ABCD Grading System. Klin Monbl Augenheilkd. 2016;233(6):701-7.

81. Lim L, Wei RH, Chan WK, Tan DT. Evaluation of keratoconus in Asians: role of Orbscan II and Tomey TMS-2 corneal topography. American journal of ophthalmology. 2007;143(3):390-400.

82. Pflugfelder SC, Liu Z, Feuer W, Verm A. Corneal thickness indices discriminate between keratoconus and contact lens-induced corneal thinning. Ophthalmology. 2002;109(12):2336-41.

83. Rabinowitz YS, Rasheed K, Yang H, Elashoff J. Accuracy of ultrasonic pachymetry and videokeratography in detecting keratoconus. Journal of cataract and refractive surgery. 1998;24(2):196-201.

84. Jonsson M, Behndig A. Pachymetric evaluation prior to laser in situ keratomileusis. Journal of cataract and refractive surgery. 2005;31(4):701-6.

85. Ambrosio R, Jr., Caiado AL, Guerra FP, Louzada R, Sinha RA, Luz A, et al. Novel pachymetric parameters based on corneal tomography for diagnosing keratoconus. Journal of refractive surgery. 2011;27(10):753-8.

86. Saad A, Gatinel D. Topographic and tomographic properties of forme fruste keratoconus corneas. Investigative ophthalmology & visual science. 2010;51(11):5546-55.

87. Prakash G, Agarwal A, Mazhari AI, Kumar G, Desai P, Kumar DA, et al. A new, pachymetry-based approach for diagnostic cutoffs for normal, suspect and keratoconic cornea. Eye (Lond). 2012;26(5):650-7.

88. Li Y, Meisler DM, Tang M, Lu AT, Thakrar V, Reiser BJ, et al. Keratoconus diagnosis with optical coherence tomography pachymetry mapping. Ophthalmology. 2008;115(12):2159-66.

89. Avitabile T, Marano F, Uva MG, Reibaldi A. Evaluation of central and peripheral corneal thickness with ultrasound biomicroscopy in normal and keratoconic eyes. Cornea. 1997;16(6):639-44.

90. Temstet C, Sandali O, Bouheraoua N, Hamiche T, Galan A, El Sanharawi M, et al. Corneal epithelial thickness mapping using Fourier-domain optical coherence tomography for detection of form fruste keratoconus. Journal of cataract and refractive surgery. 2015;41(4):812-20.

91. Tan B, Baker K, Chen YL, Lewis JW, Shi L, Swartz T, et al. How keratoconus influences optical performance of the eye. J Vis. 2008;8(2):13 1-0.

92. <KCN.pdf>.

93. Ferrara P, Torquetti L. The New Ferrara ring nomogram: the importance of corneal asphericity in ring selection. Vision Pan-America. 2010:92-5.

94. Read SA, Collins MJ, Carney LG, Franklin RJ. The topography of the central and peripheral cornea. Investigative ophthalmology & visual science. 2006;47(4):1404-15.

95. Yebra-Pimentel E, Gonzalez-Meijome JM, Cervino A, Giraldez MJ, Gonzalez-Perez J, Parafita MA. Corneal asphericity in a young adult population - clinical implications. Archivos de la Sociedad Espanola de Oftalmologia. 2004;79(8):385-92.

96. Savini G, Barboni P, Carbonelli M, Hoffer KJ. Repeatability of automatic measurements by a new Scheimpflug camera combined with Placido topography. Journal of cataract and refractive surgery. 2011;37(10):1809-16.

97. Carney LG, Mainstone JC, Henderson BA. Corneal topography and myopia. A cross-sectional study. Investigative ophthalmology & visual science. 1997;38(2):311-20.

98. Amsler M. Kératocône classique et Kératocône fruste; arguments unitaires. Ophthalmologica. 1946;111(2-3):96-101.

99. Shetty R, D'Souza S, Srivastava S, Ashwini R. Topography-guided custom ablation treatment for treatment of keratoconus. Indian journal of ophthalmology. 2013;61(8):445-50.

100. Santhiago MR, Smadja D, Zaleski K, Espana EM, Armstrong BK, Wilson SE. Flap relift for retreatment after femtosecond laser-assisted LASIK. Journal of refractive surgery. 2012;28(7):482-7.

101. Buhren J, Kuhne C, Kohnen T. Defining subclinical keratoconus using corneal first-surface higher-order aberrations. American journal of ophthalmology. 2007;143(3):381-9.

102. Salmon TO, van de Pol C. Normal-eye Zernike coefficients and root-mean-square wavefront errors. Journal of cataract and refractive surgery. 2006;32(12):2064-74.

103. Aramberri J, editor. Queratocono: pautas para su diagnóstico y tratamiento. First edition ed: Ediciones científicas argentinas; 2010.

104. Torres-Soriano K, Ruiz-Quintero C, Naranjo-Tackman R. Aberraciones de alto orden en ojos con queratocono, medidas mediante análisis de frente de onda Hartmann-Shack. Rev Mex Oftalmol. 2009;83(2):100-5.

105. Maeda N, Fujikado T, Kuroda T, Mihashi T, Hirohara Y, Nishida K, et al. Wavefront aberrations measured with Hartmann-Shack sensor in patients with keratoconus. Ophthalmology. 2002;109(11):1996-2003.

106. Pantanelli S, MacRae S, Jeong TM, Yoon G. Characterizing the wave aberration in eyes with keratoconus or penetrating keratoplasty using a high-dynamic range wavefront sensor. Ophthalmology. 2007;114(11):2013-21.

107. Alio JL, Shabayek MH. Corneal higher order aberrations: a method to grade keratoconus. Journal of refractive surgery. 2006;22(6):539-45.

108. McMahon TT, Szczotka-Flynn L, Barr JT, Anderson RJ, Slaughter ME, Lass JH, et al. A new method for grading the severity of keratoconus: the Keratoconus Severity Score (KSS). Cornea. 2006;25(7):794-800.

109. Gobbe M, Guillon M. Corneal wavefront aberration measurements to detect keratoconus patients. Cont Lens Anterior Eye. 2005;28(2):57-66.

110. Jafri B, Li X, Yang H, Rabinowitz YS. Higher order wavefront aberrations and topography in early and suspected keratoconus. Journal of refractive surgery. 2007;23(8):774-81.

111. Balasubramanian SA, Wasinger VC, Pye DC, Willcox MD. Preliminary identification of differentially expressed tear proteins in keratoconus. Mol Vis. 2013;19:2124-34.

112. Krumeich JH, Daniel J. [Live epikeratophakia and deep lamellar keratoplasty for I-III stage-specific surgical treatment of keratoconus]. Klin Monbl Augenheilkd. 1997;211(2):94-100.

113. Ishii R, Kamiya K, Igarashi A, Shimizu K, Utsumi Y, Kumanomido T. Correlation of corneal elevation with severity of keratoconus by means of anterior and posterior topographic analysis. Cornea. 2012;31(3):253-8.

114. Kanellopoulos AJ, Asimellis G. Revisiting keratoconus diagnosis and progression classification based on evaluation of corneal asymmetry indices, derived from Scheimpflug imaging in keratoconic and suspect cases. Clinical ophthalmology. 2013;7:1539-48.

115. Sahebjada S, Fenwick EK, Xie J, Snibson GR, Daniell MD, Baird PN. Impact of keratoconus in the better eye and the worse eye on vision-related quality of life. Investigative ophthalmology & visual science. 2014;55(1):412-6.

116. Barbero S, Marcos S, Merayo-Lloves J, Moreno-Barriuso E. Validation of the estimation of corneal aberrations from videokeratography in keratoconus. Journal of refractive surgery. 2002;18(3):263-70.

117. Lopes BT, Ramos IC, Dawson DG, Belin MW, Ambrosio R, Jr. Detection of ectatic corneal diseases based on pentacam. Z Med Phys. 2016;26(2):136-42.

118. Shetty R, Ghosh A, Lim RR, Subramani M, Mihir K, Reshma AR, et al. Elevated expression of matrix metalloproteinase-9 and inflammatory cytokines in keratoconus patients is inhibited by cyclosporine A. Investigative ophthalmology & visual science. 2015;56(2):738-50.

119. Yu JG, Bao FJ, Joda A, Fu XA, Zhou S, Wang J, et al. Influence of glucocorticosteroids on the biomechanical properties of in-vivo rabbit cornea. J Mech Behav Biomed Mater. 2014;29:350-9.

120. Jinabhai A, Radhakrishnan H, Tromans C, O'Donnell C. Visual performance and optical quality with soft lenses in keratoconus patients. Ophthalmic Physiol Opt. 2012;32(2):100-16.

121. Griffiths M, Zahner K, Collins M, Carney L. Masking of irregular corneal topography with contact lenses. The CLAO journal : official publication of the Contact Lens Association of Ophthalmologists, Inc. 1998;24(2):76-81.

122. Zadnik K, Barr JT, Edrington TB, Everett DF, Jameson M, McMahon TT, et al. Baseline findings in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study. Investigative ophthalmology & visual science. 1998;39(13):2537-46.

123. Weed KH, Macewen CJ, McGhee CN. The Dundee University Scottish Keratoconus Study II: a prospective study of optical and surgical correction. Ophthalmic Physiol Opt. 2007;27(6):561-7.

124. Marsack JD, Parker KE, Pesudovs K, Donnelly WJ, 3rd, Applegate RA. Uncorrected wavefront error and visual performance during RGP wear in keratoconus. Optom Vis Sci. 2007;84(6):463-70.

125. Negishi K, Kumanomido T, Utsumi Y, Tsubota K. Effect of higher-order aberrations on visual function in keratoconic eyes with a rigid gas permeable contact lens. American journal of ophthalmology. 2007;144(6):924-9.

126. Szczotka LB, Barr JT, Zadnik K. A summary of the findings from the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study. CLEK Study Group. Optometry. 2001;72(9):574-84.

127. Raiskup F, Spoerl E. Corneal crosslinking with riboflavin and ultraviolet A. Part II. Clinical indications and results. Ocul Surf. 2013;11(2):93-108.

128. Daxer A, Misof K, Grabner B, Ettl A, Fratzl P. Collagen fibrils in the human corneal stroma: structure and aging. Investigative ophthalmology & visual science. 1998;39(3):644-8.

129. Bailey AJ. Structure, function and ageing of the collagens of the eye. Eye (Lond). 1987;1 (Pt 2):175-83.

130. Spoerl E, Huhle M, Seiler T. Induction of cross-links in corneal tissue. Experimental eye research. 1998;66(1):97-103.

131. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. American journal of ophthalmology. 2003;135(5):620-7.

132. Jouve L, Borderie V, Sandali O, Temstet C, Basli E, Laroche L, et al. Conventional and Iontophoresis Corneal Cross-Linking for Keratoconus: Efficacy and Assessment by Optical Coherence Tomography and Confocal Microscopy. Cornea. 2017;36(2):153-62.

133. Padmanabhan P, Rachapalle Reddi S, Rajagopal R, Natarajan R, Iyer G, Srinivasan B, et al. Corneal Collagen Cross-Linking for Keratoconus in Pediatric Patients-Long-Term Results. Cornea. 2017;36(2):138-43.

134. Belin MW, Lim L, Rajpal RK, Hafezi F, Gomes JAP, Cochener B. Corneal Cross-Linking: Current USA Status: Report From the Cornea Society. Cornea. 2018;37(10):1218-25.

135. Sharma N, Maharana P, Singh G, Titiyal JS. Pseudomonas keratitis after collagen crosslinking for keratoconus: case report and review of literature. Journal of cataract and refractive surgery. 2010;36(3):517-20.

136. Pollhammer M, Cursiefen C. Bacterial keratitis early after corneal crosslinking with riboflavin and ultraviolet-A. Journal of cataract and refractive surgery. 2009;35(3):588-9.

137. Perez-Santonja JJ, Artola A, Javaloy J, Alio JL, Abad JL. Microbial keratitis after corneal collagen crosslinking. Journal of cataract and refractive surgery. 2009;35(6):1138-40.

138. Raiskup-Wolf F, Hoyer A, Spoerl E, Pillunat LE. Collagen crosslinking with riboflavin and ultraviolet-A light in keratoconus: long-term results. Journal of cataract and refractive surgery. 2008;34(5):796-801.

139. Caporossi A, Mazzotta C, Baiocchi S, Caporossi T. Long-term results of riboflavin ultraviolet a corneal collagen cross-linking for keratoconus in Italy: the Siena eye cross study. American journal of ophthalmology. 2010;149(4):585-93.

140. O'Brart DP, Kwong TQ, Patel P, McDonald RJ, O'Brart NA. Long-term follow-up of riboflavin/ultraviolet A (370 nm) corneal collagen cross-linking to halt the progression of keratoconus. The British journal of ophthalmology. 2013;97(4):433-7.

141. Wen D, Song B, Li Q, Tu R, Huang Y, Wang Q, et al. Comparison of Epithelium-Off Versus Transepithelial Corneal Collagen Cross-Linking for Keratoconus: A Systematic Review and Meta-Analysis. Cornea. 2018;37(8):1018-24.

142. Meiri Z, Keren S, Rosenblatt A, Sarig T, Shenhav L, Varssano D. Efficacy of Corneal Collagen Cross-Linking for the Treatment of Keratoconus: A Systematic Review and Meta-Analysis. Cornea. 2016;35(3):417-28.

143. Raiskup F, Theuring A, Pillunat LE, Spoerl E. Corneal collagen crosslinking with riboflavin and ultraviolet-A light in progressive keratoconus: ten-year results. Journal of cataract and refractive surgery. 2015;41(1):41-6.

144. Hashemi H, Seyedian MA, Miraftab M, Fotouhi A, Asgari S. Corneal collagen cross-linking with riboflavin and ultraviolet a irradiation for keratoconus: long-term results. Ophthalmology. 2013;120(8):1515-20.

145. Wittig-Silva C, Chan E, Islam FM, Wu T, Whiting M, Snibson GR. A randomized, controlled trial of corneal collagen cross-linking in progressive keratoconus: three-year results. Ophthalmology. 2014;121(4):812-21.

146. Kymionis GD, Portaliou DM, Kounis GA, Limnopoulou AN, Kontadakis GA, Grentzelos MA. Simultaneous topography-guided photorefractive keratectomy followed by corneal collagen cross-linking for keratoconus. American journal of ophthalmology. 2011;152(5):748-55.

147. 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.

148. 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.

149. Elsaftawy HS, Ahmed MH, Saif MY, Mousa R. Sequential Intracorneal Ring Segment Implantation and Corneal Transepithelial Collagen Cross-Linking in Keratoconus. Cornea. 2015;34(11):1420-6.

150. Zhang ZY, Zhang XR. Combination of corneal crosslinking and intrastromal corneal ring segments for the treatment of keratoconus. Journal of cataract and refractive surgery. 2012;38(10):1878-9.

151. Benoist d'Azy C, Pereira B, Chiambaretta F, Dutheil F. Efficacy of Different Procedures of Intra-Corneal Ring Segment Implantation in Keratoconus: a Systematic Review and Meta-Analysis. Transl Vis Sci Technol. 2019;8(3):38.

152. Hersh PS, Issa R, Greenstein SA. Corneal crosslinking and intracorneal ring segments for keratoconus: A randomized study of concurrent versus sequential surgery. Journal of cataract and refractive surgery. 2019;45(6):830-9.

153. Hashemi H, Alvani A, Seyedian MA, Yaseri M, Khabazkhoob M, Esfandiari H. Appropriate Sequence of Combined Intracorneal Ring Implantation and Corneal Collagen Cross-Linking in Keratoconus: A Systematic Review and Meta-Analysis. Cornea. 2018;37(12):1601-7.

154. Koller T, Mrochen M, Seiler T. Complication and failure rates after corneal crosslinking. Journal of cataract and refractive surgery. 2009;35(8):1358-62.

155. Barraquer JI. Modification of refraction by means of intracorneal inclusions. International ophthalmology clinics. 1966;6(1):53-78.

156. Stone W, Jr., Herbert E. Experimental study of plastic material as replacement for the cornea; a preliminary report. American journal of ophthalmology. 1953;36(6 2):168-73.

157. Belau PG, Dyer JA, Ogle KN, Henderson JW. Correction of Ametropia with Intracorneal Lenses. An Experimental Study. Archives of ophthalmology. 1964;72:541-7.

158. Blavatskaia ED, Viazovskii IA, Barsegian LG. [Change in corneal curvature in intralamellar homotransplantation of discs of various diameter and thickness]. Oftalmol Zh. 1967;22(2):123-8.

159. Fleming JF, Wan WL, Schanzlin DJ. The theory of corneal curvature change with the Intrastromal Corneal Ring. The CLAO journal : official publication of the Contact Lens Association of Ophthalmologists, Inc. 1989;15(2):146-50.

160. Nose W, Neves RA, Schanzlin DJ, Belfort Junior R. Intrastromal corneal ring–one-year results of first implants in humans: a preliminary nonfunctional eye study. Refractive & corneal surgery. 1993;9(6):452-8.

161. Ferrara P, Cunha P. Técnica cirúrgica para correcção de miopia; Anel corneano intra-estromal (Myopia correction with intrastromal corneal ring). Rev Bras Oftalmol. 1995;54:577-88.

162. Nose W, Neves RA, Burris TE, Schanzlin DJ, Belfort Junior R. Intrastromal corneal ring: 12-month sighted myopic eyes. Journal of refractive surgery. 1996;12(1):20-8.

163. Colin J, Cochener B, Savary G, Malet F. Correcting keratoconus with intracorneal rings. Journal of cataract and refractive surgery. 2000;26(8):1117-22.

164. Kubaloglu A, Sari ES, Cinar Y, Cingu K, Koytak A, Coskun E, et al. Comparison of mechanical and femtosecond laser tunnel creation for intrastromal corneal ring segment implantation in keratoconus: prospective randomized clinical trial. Journal of cataract and refractive surgery. 2010;36(9):1556-61.

165. Holmes-Higgin DK, Burris TE. Corneal surface topography and associated visual performance with INTACS for myopia: phase III clinical trial results. The INTACS Study Group. Ophthalmology. 2000;107(11):2061-71.

166. Mahmood H, Venkateswaran RS, Daxer A. Implantation of a complete corneal ring in an intrastromal pocket for keratoconus. Journal of refractive surgery. 2011;27(1):63-8.

167. Daxer A, Mahmoud H, Venkateswaran RS. Intracorneal continuous ring implantation for keratoconus: One-year follow-up. Journal of cataract and refractive surgery. 2010;36(8):1296-302.

168. Alio JL, Pinero DP, Daxer A. Clinical outcomes after complete ring implantation in corneal ectasia using the femtosecond technology: a pilot study. Ophthalmology. 2011;118(7):1282-90.

169. Pinero DP, Alio JL, El Kady B, Pascual I. Corneal aberrometric and refractive performance of 2 intrastromal corneal ring segment models in early and moderate ectatic disease. Journal of cataract and refractive surgery. 2010;36(1):102-9.

170. Ferrara G, Torquetti L, Ferrara P, Merayo-Lloves J. Intrastromal corneal ring segments: visual outcomes from a large case series. Clin Exp Ophthalmol. 2012;40(5):433-9.

171. Patel S, Marshall J, Fitzke FW, 3rd. Model for deriving the optical performance of the myopic eye corrected with an intracorneal ring. Journal of refractive surgery. 1995;11(4):248-52.

172. Burris TE, Ayer CT, Evensen DA, Davenport JM. Effects of intrastromal corneal ring size and thickness on corneal flattening in human eyes. Refractive & corneal surgery. 1991;7(1):46-50.

173. Burris TE, Baker PC, Ayer CT, Loomas BE, Mathis ML, Silvestrini TA. Flattening of central corneal curvature with intrastromal corneal rings of increasing thickness: an eye-bank eye study. Journal of cataract and refractive surgery. 1993;19 Suppl:182-7.

174. Siganos D, Ferrara P, Chatzinikolas K, Bessis N, Papastergiou G. Ferrara intrastromal corneal rings for the correction of keratoconus. Journal of cataract and refractive surgery. 2002;28(11):1947-51.

175. Meek KM, Tuft SJ, Huang Y, Gill PS, Hayes S, Newton RH, et al. Changes in collagen orientation and distribution in keratoconus corneas. Investigative ophthalmology & visual science. 2005;46(6):1948-56.

176. Sogutlu E, Pinero DP, Kubaloglu A, Alio JL, Cinar Y. Elevation changes of central posterior corneal surface after intracorneal ring segment implantation in keratoconus. Cornea. 2012;31(4):387-95.

177. Ertan A, Ozkilic E. Effect of age on outcomes in patients with keratoconus treated by Intacs using a femtosecond laser. Journal of refractive surgery. 2008;24(7):690-5.

178. Abad JC, Arango J, Tobon C. Comparison of astigmatism correction using shorter arc length 90 degrees / 120 degrees asymmetric intacs severe keratoconus versus 150 degrees single-segment intacs severe keratoconus in asymmetric keratoconus. Cornea. 2011;30(11):1201-6.

179. Rabinowitz YS, Li X, Ignacio TS, Maguen E. INTACS inserts using the femtosecond laser compared to the mechanical spreader in the treatment of keratoconus. Journal of refractive surgery. 2006;22(8):764-71.

180. Dauwe C, Touboul D, Roberts CJ, Mahmoud AM, Kerautret J, Fournier P, et al. Biomechanical and morphological corneal response to placement of intrastromal corneal ring segments for keratoconus. Journal of cataract and refractive surgery. 2009;35(10):1761-7.

181. Gorgun E, Kucumen RB, Yenerel NM. Influence of intrastromal corneal ring segment implantation on corneal biomechanical parameters in keratoconic eyes. Jpn J Ophthalmol. 2011;55(5):467-71.

182. Barraquer JI. Queratoplastia Refractiva. Estudios e Informaciones Oftalmológicas1949.

183. Torquetti L, Cunha P, Luz A, Kwitko S, Carrion M, Rocha G, et al. Clinical Outcomes After Implantation of 320 degrees -Arc Length Intrastromal Corneal Ring Segments in Keratoconus. Cornea. 2018;37(10):1299-305.

184. Lai MM, Tang M, Andrade EM, Li Y, Khurana RN, Song JC, et al. Optical coherence tomography to assess intrastromal corneal ring segment depth in keratoconic eyes. Journal of cataract and refractive surgery. 2006;32(11):1860-5.

185. Ertan A, Kamburoglu G, Akgun U. Comparison of outcomes of 2 channel sizes for intrastromal ring segment implantation with a femtosecond laser in eyes with keratoconus. Journal of cataract and refractive surgery. 2007;33(4):648-53.

186. Ibares-Frias L, Gallego P, Cantalapiedra-Rodriguez R, Merayo-Lloves J, Martinez-Garcia MC. Clinical, Refractive and Histological Reversibility of Corneal Additive Surgery in Deep Stroma in an Animal Model. Curr Eye Res. 2016;41(9):1192-201.

187. Ibares-Frias L, Gallego P, Cantalapiedra-Rodriguez R, Valsero MC, Mar S, Merayo-Lloves J, et al. Tissue reaction after intrastromal corneal ring implantation in an experimental animal model. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie. 2015;253(7):1071-83.

188. D'Hermies F, Hartmann C, von Ey F, Holzkamper C, Renard G, Pouliquen Y. Biocompatibility of a refractive intracorneal PMMA ring. Fortschr Ophthalmol. 1991;88(6):790-3.

189. Kymionis GD, Siganos CS, Tsiklis NS, Anastasakis A, Yoo SH, Pallikaris AI, et al. Long-term follow-up of Intacs in keratoconus. American journal of ophthalmology. 2007;143(2):236-44.

190. Ruckhofer J, Bohnke M, Alzner E, Grabner G. Confocal microscopy after implantation of intrastromal corneal ring segments. Ophthalmology. 2000;107(12):2144-51.

191. Ferrer C, Alio JL, Montanes AU, Perez-Santonja JJ, del Rio MA, de Toledo JA, et al. Causes of intrastromal corneal ring segment explantation: clinicopathologic correlation analysis. Journal of cataract and refractive surgery. 2010;36(6):970-7.

192. Ruckhofer J, Stoiber J, Alzner E, Grabner G, Multicenter European Corneal Correction Assessment Study G. One year results of European Multicenter Study of intrastromal corneal ring segments. Part 2: complications, visual symptoms, and patient satisfaction. Journal of cataract and refractive surgery. 2001;27(2):287-96.

193. Zare MA, Hashemi H, Salari MR. Intracorneal ring segment implantation for the management of keratoconus: safety and efficacy. Journal of cataract and refractive surgery. 2007;33(11):1886-91.

194. 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.

195. Coskunseven E, Kymionis GD, Tsiklis NS, Atun S, Arslan E, Siganos CS, 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.

196. Barbara R, Barbara A, Naftali M. Depth evaluation of intended vs actual intacs intrastromal ring segments using optical coherence tomography. Eye (Lond). 2016;30(1):102-10.

197. Kouassi FX, Buestel C, Raman B, Melinte D, Touboul D, Gallois A, et al. Comparison of the depth predictability of intra corneal ring segment implantation by mechanical versus femtosecond laser-assisted techniques using optical coherence tomography (OCT Visante). Journal francais d'ophtalmologie. 2012;35(2):94-9.

198. Kamburoglu G, Ertan A, Saraçbasi O. Measurement of Depth of Intacs Implanted Via Femtosecond Laser Using Pentacam. Journal of refractive surgery. 2009;25:377-82.

199. Gorgun E, Kucumen RB, Yenerel NM, Ciftci F. Assessment of intrastromal corneal ring segment position with anterior segment optical coherence tomography. Ophthalmic surgery, lasers & imaging : the official journal of the International Society for Imaging in the Eye. 2012;43(3):214-21.

200. Carrasquillo KG, Rand J. Intacs for keratoconus and post-lasik ectasia - mechanical versus femtoscond laser assisted channel creation. Cornea. 2007;26:956-62.

201. Pinero DP, Alio JL, El Kady B, Coskunseven E, Morbelli H, Uceda-Montanes A, et al. Refractive and aberrometric outcomes of intracorneal ring segments for keratoconus: mechanical versus femtosecond-assisted procedures. Ophthalmology. 2009;116(9):1675-87.

202. Rabinowitz Y. INTACS inserts using the femtosecond laser compared to the mechanical spreader in the treatment of keratoconus. Journal of refractive surgery. 2006.

203. Chhadva P, Yesilirmak N, Cabot F, Yoo SH. Intrastromal Corneal Ring Segment Explantation in Patients With Keratoconus: Causes, Technique, and Outcomes. Journal of refractive surgery. 2015;31(6):392-7.

204. Alio JL, Pinero DP, Esin S, Anin K. Implantation of new intracorneal ring segments after segment explantation for unsuccesful outcomes in eyes with keratoconus. Journal of cataract and refractive surgery. 2010;36(36):1303-10.

205. Torquetti L, Ferrara G, Almeida F, Cunha L, Ferrara P, Merayo-Lloves J. Clinical outcomes after intrastromal corneal ring segments reoperation in keratoconus patients. International journal of ophthalmology. 2013;6(6):796-800.

206. Ertan A, Colin J. Intracorneal rings for keratoconus and keratectasia. Journal of cataract and refractive surgery. 2007;33(7):1303-14.

207. Asbell PA, Ucakhan OO, Abbott RL, Assil KA, Burris TE, Durrie DS, et al. Intrastomal corneal ring segments: reversibility of refractive effect. Journal of refractive surgery. 2001;17(1):25-31.

208. Chan SM, Khan HN. Reversibility and exchangeability of intrastromal corneal ring segments. Journal of cataract and refractive surgery. 2002;28(4):676-81.

209. Alio JL, Artola A, Ruiz-Moreno JM, Hassanein A, Galal A, Awadalla MA. Changes in keratoconic corneas after intracorneal ring segment explantation and reimplantation. Ophthalmology. 2004;111(4):747-51.

210. Brenner LF, Alio JL, Vega-Estrada A, Baviera J, Beltran J, Cobo-Soriano R. Indications for intrastromal corneal ring segments in ectasia after laser in situ keratomileusis. Journal of cataract and refractive surgery. 2012;38(12):2117-24.

211. Moshirfar M, Edmonds JN, Behunin NL, Christiansen SM. Current options in the management of pellucid marginal degeneration. Journal of refractive surgery. 2014;30(7):474-85.

212. Lisa C, Garcia-Fernandez M, Madrid-Costa D, Torquetti L, Merayo-Lloves J, Alfonso JF. Femtosecond laser-assisted intrastromal corneal ring segment implantation for high astigmatism correction after penetrating keratoplasty. Journal of cataract and refractive surgery. 2013;39(11):1660-7.

213. Torquetti L, Ferrara G, Almeida F, Cunha L, Araujo LP, Machado A, et al. Intrastromal corneal ring segments implantation in patients with keratoconus: 10-year follow-up. Journal of refractive surgery. 2014;30(1):22-6.

214. Vega-Estrada A, Alio JL, Brenner LF, Burguera N. Outcomes of intrastromal corneal ring segments for treatment of keratoconus: five-year follow-up analysis. Journal of cataract and refractive surgery. 2013;39(8):1234-40.

215. Ziaei M, Barsam A, Shamie N, Vroman D, Kim T, Donnenfeld ED, et al. Reshaping procedures for the surgical management of corneal ectasia. Journal of cataract and refractive surgery. 2015;41(4):842-72.

216. Izquierdo L, Jr., Mannis MJ, Mejias Smith JA, Henriquez MA. Effectiveness of Intrastromal Corneal Ring Implantation in the Treatment of Adult Patients With Keratoconus: A Systematic Review. Journal of refractive surgery. 2019;35(3):191-200.

217. Fernandez-Vega Cueto L, Lisa C, Poo-Lopez A, Madrid-Costa D, Merayo-Lloves J, Alfonso JF. Intrastromal Corneal Ring Segment Implantation in 409 Paracentral Keratoconic Eyes. Cornea. 2016;35(11):1421-6.

218. Alfonso JF, Fernandez-Vega Cueto L, Baamonde B, Merayo-Lloves J, Madrid-Costa D, Montes-Mico R. Inferior Intrastromal Corneal Ring Segments in Paracentral Keratoconus With No Coincident Topographic and Coma Axis. Journal of refractive surgery. 2013;29(4):266-72.

219. Alfonso JF, Lisa C, Merayo-Lloves J, Fernandez-Vega Cueto L, Montes-Mico R. Intrastromal corneal ring segment implantation in paracentral keratoconus with coincident topographic and coma axis. Journal of cataract and refractive surgery. 2012;38(9):1576-82.

220. Boimer C, Lee K, Sharpen L, Mashour RS, Slomovic AR. Evolving surgical techniques of and indications for corneal transplantation in Ontario from 2000 to 2009. Can J Ophthalmol. 2011;46(4):360-6.

221. Reddy JC, Hammersmith KM, Nagra PK, Rapuano CJ. The role of penetrating keratoplasty in the era of selective lamellar keratoplasty. International ophthalmology clinics. 2013;53(2):91-101.

222. Reinhart WJ, Musch DC, Jacobs DS, Lee WB, Kaufman SC, Shtein RM. Deep anterior lamellar keratoplasty as an alternative to penetrating keratoplasty a report by the american academy of ophthalmology. Ophthalmology. 2011;118(1):209-18.

223. Sharma N, Agarwal P, Titiyal JS, Kumar C, Sinha R, Vajpayee RB. Optimal use of donor corneal tissue: one cornea for two recipients. Cornea. 2011;30(10):1140-4.

224. Han DC, Mehta JS, Por YM, Htoon HM, Tan DT. Comparison of outcomes of lamellar keratoplasty and penetrating keratoplasty in keratoconus. American journal of ophthalmology. 2009;148(5):744-51 e1.

225. Ardjomand N, Hau S, McAlister JC, Bunce C, Galaretta D, Tuft SJ, et al. Quality of vision and graft thickness in deep anterior lamellar and penetrating corneal allografts. American journal of ophthalmology. 2007;143(2):228-35.

226. Kelly TL, Williams KA, Coster DJ, Australian Corneal Graft R. Corneal transplantation for keratoconus: a registry study. Archives of ophthalmology. 2011;129(6):691-7.

227. Thompson RW, Jr., Price MO, Bowers PJ, Price FW, Jr. Long-term graft survival after penetrating keratoplasty. Ophthalmology. 2003;110(7):1396-402.

228. Kubaloglu A, Sari ES, Unal M, Koytak A, Kurnaz E, Cinar Y, et al. Long-term results of deep anterior lamellar keratoplasty for the treatment of keratoconus. American journal of ophthalmology. 2011;151(5):760-7 e1.

229. van Dijk K, Parker J, Tong CM, Ham L, Lie JT, Groeneveld-van Beek EA, et al. Midstromal isolated Bowman layer graft for reduction of advanced keratoconus: a technique to postpone penetrating or deep anterior lamellar keratoplasty. JAMA Ophthalmol. 2014;132(4):495-501.

230. Cheng YY, Visser N, Schouten JS, Wijdh RJ, Pels E, van Cleynenbreugel H, et al. Endothelial cell loss and visual outcome of deep anterior lamellar keratoplasty versus penetrating keratoplasty: a randomized multicenter clinical trial. Ophthalmology. 2011;118(2):302-9.

231. Javadi MA, Motlagh BF, Jafarinasab MR, Rabbanikhah Z, Anissian A, Souri H, et al. Outcomes of penetrating keratoplasty in keratoconus. Cornea. 2005;24(8):941-6.

232. Jaycock PD, Jones MN, Males J, Armitage WJ, Cook SD, Tole DM, et al. Outcomes of same-sizing versus oversizing donor trephines in keratoconic patients undergoing first penetrating keratoplasty. Ophthalmology. 2008;115(2):268-75.

233. Bahar I, Kaiserman I, Srinivasan S, Ya-Ping J, Slomovic AR, Rootman DS. Comparison of three different techniques of corneal transplantation for keratoconus. American journal of ophthalmology. 2008;146(6):905-12 e1.

234. Jensen LB, Hjortdal J, Ehlers N. Longterm follow-up of penetrating keratoplasty for keratoconus. Acta Ophthalmol. 2010;88(3):347-51.

235. Chamberlain WD, Rush SW, Mathers WD, Cabezas M, Fraunfelder FW. Comparison of femtosecond laser-assisted keratoplasty versus conventional penetrating keratoplasty. Ophthalmology. 2011;118(3):486-91.

236. Pramanik S, Musch DC, Sutphin JE, Farjo AA. Extended long-term outcomes of penetrating keratoplasty for keratoconus. Ophthalmology. 2006;113(9):1633-8.

237. Geerards AJ, Vreugdenhil W, Khazen A. Incidence of rigid gas-permeable contact lens wear after keratoplasty for keratoconus. Eye Contact Lens. 2006;32(4):207-10.

238. Sutton G, Hodge C, McGhee CN. Rapid visual recovery after penetrating keratoplasty for keratoconus. Clin Exp Ophthalmol. 2008;36(8):725-30.

239. Tuft SJ, Fitzke FW, Buckley RJ. Myopia following penetrating keratoplasty for keratoconus. The British journal of ophthalmology. 1992;76(11):642-5.

240. Brahma A, Ennis F, Harper R, Ridgway A, Tullo A. Visual function after penetrating keratoplasty for keratoconus: a prospective longitudinal evaluation. The British journal of ophthalmology. 2000;84(1):60-6.

241. Brierly SC, Izquierdo L, Jr., Mannis MJ. Penetrating keratoplasty for keratoconus. Cornea. 2000;19(3):329-32.

242. Lim L, Pesudovs K, Goggin M, Coster DJ. Late onset post-keratoplasty astigmatism in patients with keratoconus. The British journal of ophthalmology. 2004;88(3):371-6.

243. Lains I, Rosa AM, Guerra M, Tavares C, Lobo C, Silva MF, et al. Irregular Astigmatism After Corneal Transplantation–Efficacy and Safety of Topography-Guided Treatment. Cornea. 2016;35(1):30-6.

244. Fontana L, Parente G, Sincich A, Tassinari G. Influence of graft-host interface on the quality of vision after deep anterior lamellar keratoplasty in patients with keratoconus. Cornea. 2011;30(5):497-502.

245. Funnell CL, Ball J, Noble BA. Comparative cohort study of the outcomes of deep lamellar keratoplasty and penetrating keratoplasty for keratoconus. Eye (Lond). 2006;20(5):527-32.

246. Busin M, Zambianchi L, Arffa RC. Microkeratome-assisted lamellar keratoplasty for the surgical treatment of keratoconus. Ophthalmology. 2005;112(6):987-97.

247. Eldaly ZH, Abdelsalam MA, Hussein MS, Nassr MA. Comparison of Laser In Situ Keratomileusis Flap Morphology and Predictability by WaveLight FS200 Femtosecond Laser and Moria Microkeratome: An Anterior Segment Optical Coherence Tomography Study. Korean J Ophthalmol. 2019;33(2):113-21.

248. Liu Q, Zhou YH, Zhang J, Zheng Y, Zhai CB, Liu J. Comparison of corneal flaps created by Wavelight FS200 and Intralase FS60 femtosecond lasers. International journal of ophthalmology. 2016;9(7):1006-10.

249. de Sanctis U, Lavia C, Nassisi M, D'Amelio S. Keraring Intrastromal Segment Depth Measured by Spectral-Domain Optical Coherence Tomography in Eyes with Keratoconus. Journal of ophthalmology. 2017;2017:4313784.

250. Naftali M, Jabaly-Habib H. Depth of intrastromal corneal ring segments by OCT. European journal of ophthalmology. 2013;23(2):171-6.

251. Torky MA, Al Zafiri YA, Khattab AM, Farag RK, Awad EA. Visumax femtolasik versus Moria M2 microkeratome in mild to moderate myopia: efficacy, safety, predictability, aberrometric changes and flap thickness predictability. BMC Ophthalmol. 2017;17(1):125.

252. Binder PS, Lin L, van de Pol C. Intracorneal Inlays for the Correction of Ametropias. Eye Contact Lens. 2015;41(4):197-203.

253. Maurice D, editor Nutritional aspects of corneal grafts and prostheses. Corneo-Plastic Surgery: Proceedings of the Second International Corneo-plastic Conference; 1969 1969; Oxford, United Kingdom: Pergamon Press.

254. Larrea X, De Courten C, Feingold V, Burger J, Buchler P. Oxygen and glucose distribution after intracorneal lens implantation. Optom Vis Sci. 2007;84(12):1074-81.

255. Giacomin NT, Mello GR, Medeiros CS, Kilic A, Serpe CC, Almeida HG, et al. Intracorneal Ring Segments Implantation for Corneal Ectasia. Journal of refractive surgery. 2016;32(12):829-39.

256. Samimi S, Leger F, Touboul D, Colin J. Histopathological findings after intracorneal ring segment implantation in keratoconic human corneas. Journal of cataract and refractive surgery. 2007;33(2):247-53.

257. Hong JW, Liu JJ, Lee JS, Mohan RR, Mohan RR, Woods DJ, et al. Proinflammatory chemokine induction in keratocytes and inflammatory cell infiltration into the cornea. Investigative ophthalmology & visual science. 2001;42(12):2795-803.

258. Fini ME. Keratocyte and fibroblast phenotypes in the repairing cornea. Prog Retin Eye Res. 1999;18(4):529-51.

259. Twa MD, Ruckhofer J, Kash RL, Costello M, Schanzlin DJ. Histologic evaluation of corneal stroma in rabbits after intrastromal corneal ring implantation. Cornea. 2003;22(2):146-52.

260. Torquetti L, Ferrara P. Reasons for intrastromal corneal ring segment explantation. Journal of cataract and refractive surgery. 2010;36(11):2014; author reply -5.

261. Ferrara P, Torquetti L. Clinical outcomes after implantation of a new intrastromal corneal ring with a 210-degree arc length. Journal of cataract and refractive surgery. 2009;35(9):1604-8.

262. Bautista-Llamas MJ, Sanchez-Gonzalez MC, Lopez-Izquierdo I, Lopez-Munoz A, Gargallo-Martinez B, De-Hita-Cantalejo C, et al. Complications and Explantation Reasons in Intracorneal Ring Segments (ICRS) Implantation: A Systematic Review. Journal of refractive surgery. 2019;35(11):740-7.

263. Alio JL, Shabayek MH, Belda JI, Correas P, Feijoo ED. Analysis of results related to good and bad outcomes of Intacs implantation for keratoconus correction. Journal of cataract and refractive surgery. 2006;32(5):756-61.

264. Alfonso JF, Fernandez-Vega-Cueto L, Lisa C, Monteiro T, Madrid-Costa D. Long-Term Follow-up of Intrastromal Corneal Ring Segment Implantation in Pediatric Keratoconus. Cornea. 2019;38(7):840-6.