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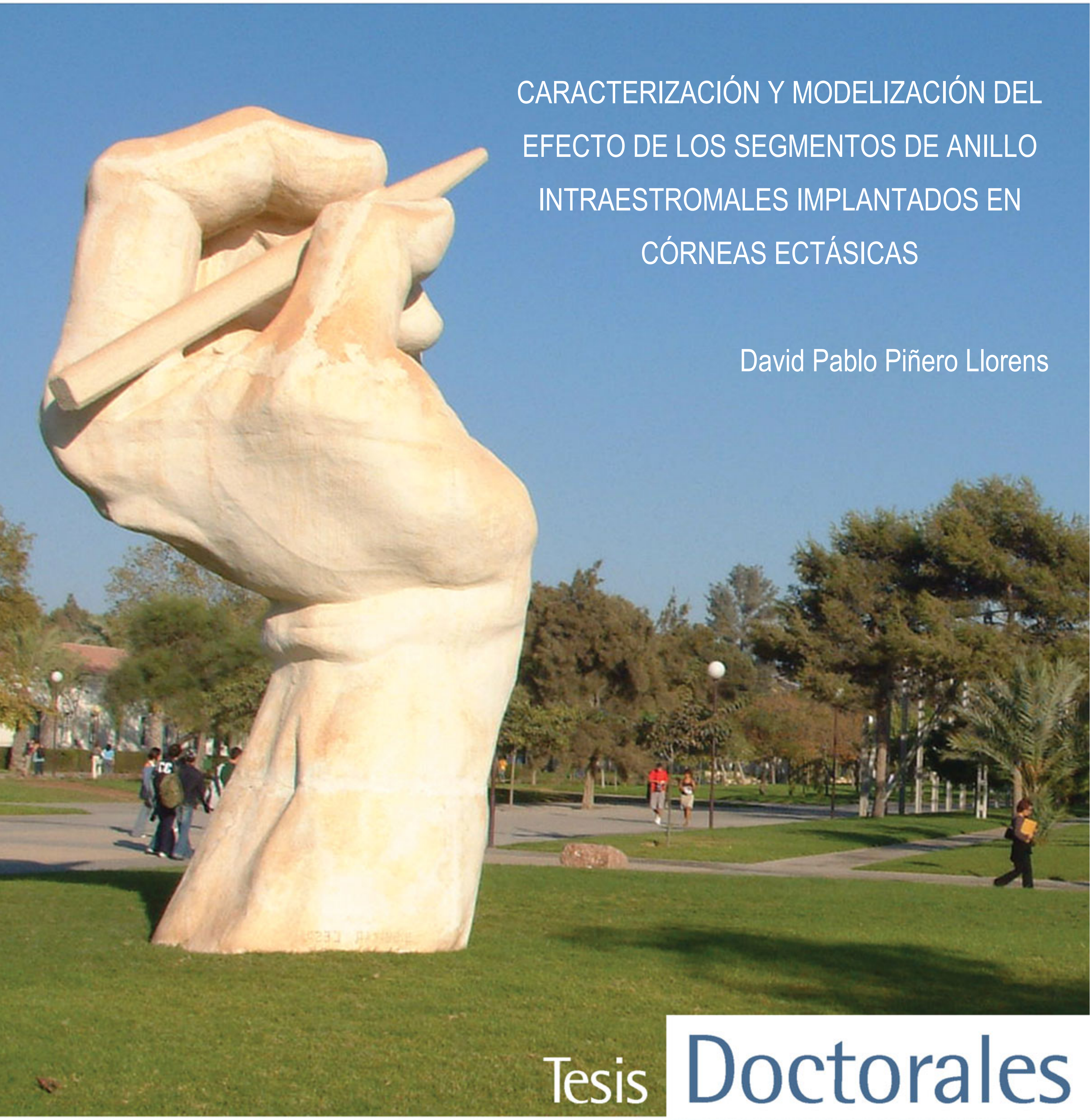

CARACTERIZACIÓN Y MODELIZACIÓN DEL EFECTO DE LOS SEGMENTOS DE ANILLO INTRAESTROMALES IMPLANTADOS EN CÓRNEAS ECTÁSICAS

David Pablo Piñero Llorens

Tesis Doctorales

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TESIS DOCTORAL

CARACTERIZACIÓN Y MODELIZACIÓN DEL EFECTO DE LOS SEGMENTOS DE ANILLO INTRAESTROMALES IMPLANTADOS EN CÓRNEAS ECTÁSICAS

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Julio 2010

Universitat d'Alacant
Universidad de Alicante

Departament de Física, Enginyeria de Sistemes i Teoria del Señal
Departamento de Física, Ingeniería de Sistemas y Teoría de la Señal

Dña. MARÍA INMACULADA PASCUAL VILLALOBOS, Catedrática de Universidad del área de Óptica de la Universidad de Alicante, y

D. JORGE ALIÓ SANZ, Catedrático de Universidad del área de Oftalmología de la Universidad Miguel Hernández:

C E R T I F I C A N: Que la presente memoria titulada *"Caracterización y modelización del efecto de los segmentos de anillo intraestromales implantados en córneas ectásicas"* ha sido realizada bajo su dirección por Don DAVID PABLO PIÑERO LLORENS en el Departamento de Física, Ingeniería de sistemas y Teoría de la Señal de la Universidad de Alicante, y constituye su Tesis Doctoral para optar al Grado de Doctor.

Y para que conste, y en cumplimiento de la legislación vigente, firman el presente certificado en Alicante a quince de mayo de dos mil diez.

Fdo.: María Inmaculada Pascual Villalobos　　　Fdo.: Jorge Alió Sanz

A mi mujer María y a mi hija Núria

Quiero mostrar mi gratitud en primer lugar a los directores de la presente tesis, Jorge Alió e Inmaculada Pascual, por el apoyo y dedicación durante la realización de esta investigación. Sin ellos este trabajo no hubiera sido posible. Os agradezco enormemente la confianza depositada en mí para la realización de esta investigación que tanto he disfrutado.

Quiero agradecer al Instituto Oftalmológico de Alicante Vissum la posibilidad que me ha ofrecido de poder disponer de las instalaciones y los datos clínicos para poder llevar a cabo esta tesis. En particular, agradezco a Laurent Bataille por sus ánimos, confianza y, sobre todo, por tu amistad. También ha sido crucial la aportación realizada por el resto de centros clínicos que han participado en el estudio. Estoy agradecido enormemente a los doctores Miguel Maldonado, Antonio Uceda, Héctor Morbelli, Diego Cuevas, Efekan Coskunseven, Miguel Teus, Rafael Barraquer y Anil Kubaloglu por permitirme incluir sus datos en el análisis retrospectivo realizado en esta tesis. Tampoco quiero olvidar otras personas que también han sido muy importantes para el desarrollo de esta tesis, Bassam El Kady, Esin Sogütlü, Ramón Jiménez y Ralph Michael. A todos, muchísimas gracias.

También doy las gracias a mi familia por el constante apoyo y aliento aportado, ha sido indispensable para seguir adelante. Soy muy afortunado de tener unos hermanos que siempre están ahí. Gracias a ti madre por confiar tanto en mis posibilidades y hacerme ver que siempre puedo ser capaz de avanzar. A ti, María, por ser la mejor motivación y apoyo para seguir investigando, eres increíble y ya sabes que eres la luz de mi alma. También doy las gracias a mi hija Núria por darle sentido a la vida, por darle sentido a todo.

Doy también las gracias a mis compañeros del Departamento de Óptica, Farmacología y Anatomía, así como a mis compañeros de I+D de Vissum por los apoyos (Bianca te debo una). No quiero olvidarme de todos aquellos amigos que han aportado su granito de arena de un modo u otro a este proyecto tan importante para mí.

Muchas gracias a todos…

Lo que con mucho trabajo se adquiere, más se ama.

Aristóteles.

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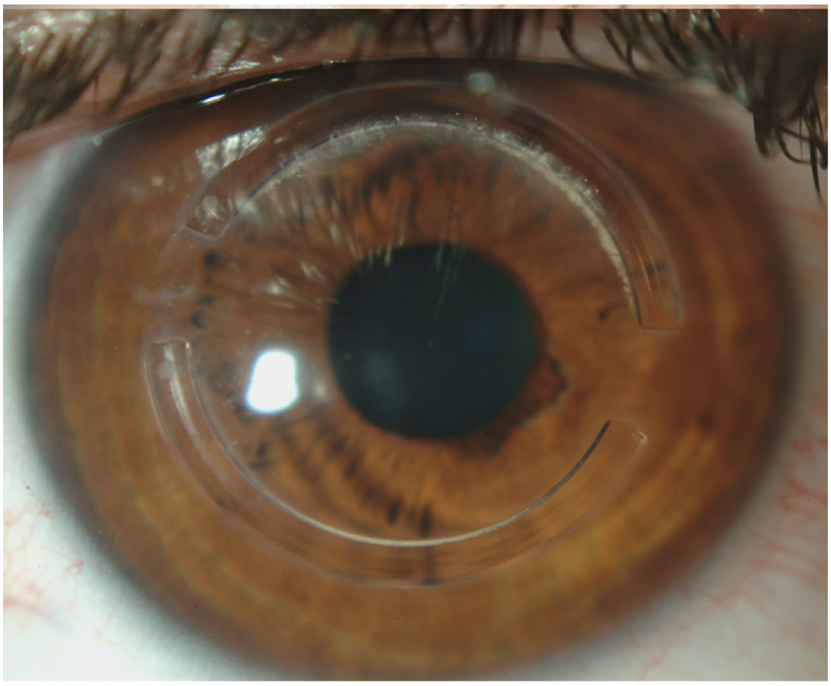


ÍNDICE GENERAL

ÍNDICE DE ABREVIATURAS

A continuación se muestra el listado de abreviaturas empleadas en la presente tesis por orden alfabético.

AE: angle of error, siglas en inglés de ángulo de error (método de Alpins)

AST3: astigmatismo de la superficie corneal anterior determinado mediante topografía en los 3 mm centrales

AST6: astigmatismo de la superficie corneal anterior determinado mediante topografía en los 6 mm centrales

AVCC: agudeza visual con corrección

AVSC: agudeza visual sin corrección

CH: corneal hysteresis, siglas en inglés de histéresis corneal

CLC: crosslinking corneal

CRF: corneal resistance factor, siglas en inglés de factor de resistencia corneal

CSO: Construzione Strumenti Oftalmici (casa comercial que desarrolla uno de los sistemas topográficos empleados en la presente tesis)

D: dioptría

DMP: degeneración marginal pelúcida

DV: difference vector, siglas en inglés de vector diferencia entre TIA y SIA (método de Alpins)

EPL: ectasia post-LASIK

FE: flattening effect, siglas en ingles de efecto aplanamiento (método de Alpins)

ISAI: inferosuperior asymmetry index, siglas en inglés del índice de asimetría supero-inferior correspondiente a la superficie corneal anterior determinado mediante topografía

ICRS: intracorneal ring segments, siglas en inglés de segmentos de anillo intracorneales

KM: poder dióptrico medio correspondiente a la superficie corneal anterior determinado mediante topografía dentro de los 3 mm centrales

K1: poder dióptrico correspondiente a la superficie corneal anterior en el meridiano más plano determinado mediante topografía dentro de los 3 mm centrales

K2: poder dióptrico correspondiente a la superficie corneal anterior en el meridiano más curvo determinado mediante topografía dentro de los 3 mm centrales

LASIK: laser in situ keratomileusis

ME: magnitude of error, siglas en inglés de magnitud del error (método de Alpins)

OCT: optical coherente tomography, siglas en inglés de tomografía óptica de coherencia

ORA: ocular response analyzer, siglas en inglés de un dispositivo especializado para la caracterización de las propiedades biomecánicas de la córnea

QTC: queratocono

Q45: asfericidad media correspondiente a la superficie corneal anterior determinada mediante topografía dentro de los 4,5 mm centrales

Q8: asfericidad media correspondiente a la superficie corneal anterior determinada mediante topografía dentro de los 8 mm centrales

RMS: root mean square, siglas en inglés de error cuadrático medio

SIA: surgically induced astigmatism, siglas en inglés de astigmatismo inducido con la cirugía (método de Alpins)

TIA: targeted induced astigmatism, siglas en inglés de astigmatismo objetivo a inducir (método de Alpins)

TRQ: vector torque (método de Alpins)

Diversas aportaciones se han realizado con el contenido de la presente tesis, tales como comunicaciones orales, en póster, así como las publicaciones en sí que constituyen la tesis. A continuación se muestra el listado de comunicaciones a congresos presentadas:

Comunicaciones orales:

1.- Piñero D, Alió J. Factores predictivos de éxito en el tratamiento del queratocono con segmentos intracorneales. Seminarios de actualización CIMO-CARTUJAVISIÓN. 2010. Sevilla.

2.- Jiménez R, Piñero D, Pascual I, Alió JL. Análisis del astigmatismo corneal mediante el método vectorial de Alpins tras implante de anillos intracorneales en córneas ectásicas. 21 Congreso Internacional de Optometría, Contactología y Óptica Oftálmica. 2010. Madrid.

3.- Montalbán R, Piñero DP, Pascual I. Cambios biomecánicos caracterizados mediante el sistema Ocular Response Analyzer tras el implante de segmentos de anillo intracorneal en queratocono. 21 Congreso Internacional de Optometría, Contactología y Óptica Oftálmica. 2010. Madrid.

4.- Piñero DP, Alió J, Barraquer R, Jiménez R. Relación de las propiedades biomecánicas de la córnea medidas con el sistema ORA y diferentes parámetros visuales, refractivos y aberrométricos en el queratocono. 21 Congreso Internacional de Optometría, Contactología y Óptica Oftálmica. 2010. Madrid.

5.- Piñero DP, Alió J, El Kady B. Diferencias refractivas y aberrométricas en córneas con ectasia incipiente o moderada con dos tipos diferentes de segmentos de anillo intracorneales. 21 Congreso Internacional de Optometría, Contactología y Óptica Oftálmica. 2010. Madrid.

6.- Alió JL, Piñero DP, Barraquer RI, Jiménez R. Corneal biomechanics, refraction, and corneal aberrometry in keratoconus: an integrated diagnostic study. Subspecialty day ISRS/AAO. 2009. San Francisco (USA).

7.- Piñero DP, Barraquer RI, Alió JL. Correlación de las propiedades biomecánicas de la córnea con parámetros visuales, refractivos y aberrométricos en el queratocono. 85 Congreso de la Sociedad Española de Oftalmología. 2009. Santander.

8.- Maldonado MJ, Piñero DP, Uceda A. Resultados refractivos y aberrométricos tras implante de segmentos intracorneales en queratocono: mecánico vs intralase. 85 Congreso de la Sociedad Española de Oftalmología. 2009. Santander.

9.- Piñero D. Personal nomogram based on aberrometry and corneal biomechanics. Keraring Forum 2009. XXVII Congress of the ESCRS. 2009. Barcelona.

10.- Alió J, Piñero D. How can we predict KeraRing outcomes? A scientific-based approach. Keraring Forum 2009. XXVII Congress of the ESCRS. 2009. Barcelona.

11.- Piñero DP, Alió J, Jiménez R. Vectorial analysis of corneal astigmatic changes induced by intracorneal ring segments in ectatic corneas. XXVII Congress of the ESCRS. 2009. Barcelona.

12.- Piñero DP, Alió J, El Kady B. Aberrometric and refractive performance of two types of intracorneal ring segment in early to moderate ectatic disease: Intacs versus KeraRings. XXVII Congress of the ESCRS. 2009. Barcelona.

13.- Piñero DP, Alió JL, El Kady B, Coskunseven E, Morbelli H, Uceda-Montanes A, Maldonado MJ, Cuevas D. Refractive and aberrometric outcomes of intracorneal ring segments for keratoconus: mechanical versus femtosecond-assisted procedure. 17th Congress of the European Society of Ophthalmology. 2009. Amsterdam.

14.- Piñero DP, Alió JL, Morbelli H, Uceda-Montañés A, El Kady B. Refractive and corneal aberrometric changes after intracorneal ring implantation in corneas with pellucid marginal degeneration. 13th ESCRS Winter Refractive Surgery Meeting. 2009. Roma.

15.- Alió JL, Piñero DP, Uceda-Montanes A, El Kady B, Maldonado M. Intracorneal ring implantation for the treatment of post-LASIK ectasia: 2-year follow-up. Subspecialty day ISRS/AAO. 2008. Atlanta.

16.- Piñero D, Bataille L, Alió J. Avances en el manejo de la patología corneal ectásica. III Jornadas de Actualización en Investigación Biomédica. 2008. Valencia.

17.- Uceda A, Morbelli H, Piñero DP, El Kady B, Alió JL, Rodríguez-Prats JL. Uso de anillos intracorneales para el tratamiento de la degeneración corneal pelúcida. 84 Congreso de la Sociedad Española de Oftalmología. 2008. Sevilla.

18.- Alió JL, Piñero DP, Maldonado MJ, El Kady B, Uceda A. Implante de anillos intraestromales para la corrección de miopía residual y tratamiento de la ectasia tras cirugía LASIK: 1 año de seguimiento. 84 Congreso de la Sociedad Española de Oftalmología. 2008. Sevilla.

19.- Piñero DP, Alió J, El Kady B. Intrastromal corneal rings outcomes in advanced cases of ectatic corneal disease. XXVI Congress of the ESCRS. 2008. Berlin.

20.- Piñero DP. ICR implantation in corneas with post-LASIK keratectasia: 2-year follow-up. Keraring: innovations in practice 2008. XXVI Congress of the ESCRS. 2008. Berlin.

Comunicaciones en póster:

1.- Piñero DP, Alió J, Barraquer R, Michael R. Predictive model for the visual outcome alter KeraRing implantation in keratoconus considering corneal biomechanics. ARVO. 2010. Fort Lauderdale (USA).

2.- Maldonado MJ, Piñero D, Murta JN, Teus MA, Barraquer RI, Uceda-Montanes A, Coskunseven E, Morbelli HM, Cuevas D. Intracorneal ring segments in ectatic corneal disease and penetrating keratoplasty: a retrospective analysis of 466 eyes. American Academy of Ophthalmology (AAO) Meeting. 2009. San Francisco (USA).

3.- Jiménez R, Piñero DP, Alió JL. Análisis del cambio del astigmatismo corneal inducido por los segmentos de anillo intracorneales en córneas ectásicas mediante el software ASSORT. XI Jornadas de la Visión de la Comunidad Valenciana. 2009. Alicante.

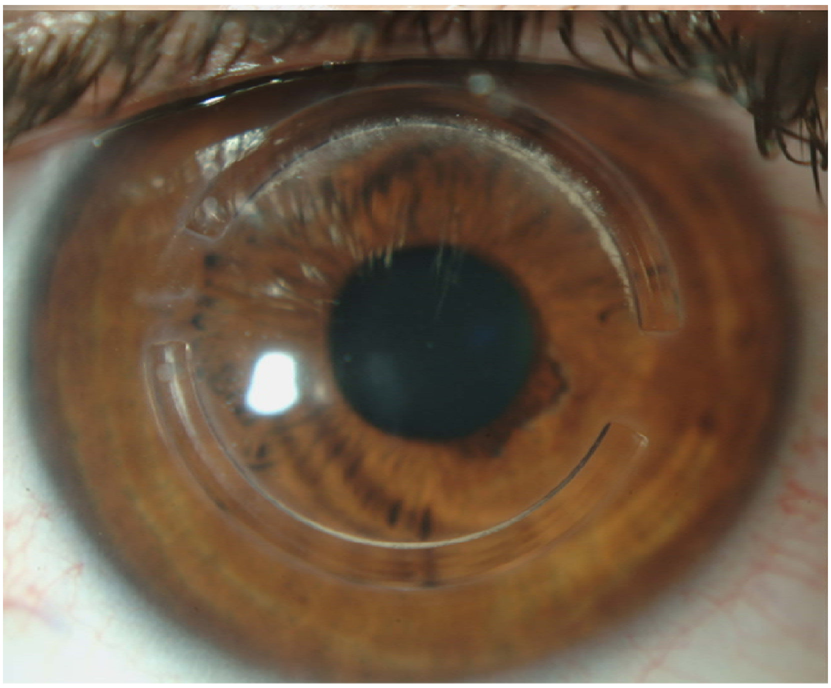
4.- Piñero DP, Alió JL, Morbelli H, Uceda-Montanes A, El Kady B, Coskunseven E. Refractive and corneal aberrometric changes after intracorneal rings implantation in corneas with pellucid marginal degeneration. 17th Congress of the European Society of Ophthalmology. 2009. Amsterdam.

Por otro lado, actualmente están en proceso de revisión dos artículos que continúan la investigación iniciada en la presente tesis:

1.- Piñero DP, Alió J, Barraquer R, Michael R. Corneal biomechanical changes after intracorneal ring segment implantation in keratoconus. Cornea (en revision)

2.- Sogütlü E, Piñero DP, Kubaloglu A, Alió JL. Elevation changes of the posterior corneal surface after intracorneal ring segment implantation in keratoconic corneas. J Cataract Refract Surg (en revision)

CAPÍTULO 0: ARTÍCULOS QUE CONFORMAN LA PRESENTE TESIS



CAPÍTULO 0: ARTÍCULOS QUE CONFORMAN LA PRESENTE TESIS

Un total de nueve artículos publicados en revistas impactadas a nivel internacional conforman la presenta tesis doctoral: un primer artículo de revisión que nos permitió conocer lo desarrollado hasta el momento en el área de investigación de la presente tesis y ocho artículos en los que se ha desarrollado el análisis retrospectivo que constituye en sí la investigación. A continuación se enumeran todos ellos por orden de desarrollo:

1.- Piñero DP, Alió JL. *Intracorneal ring segments in ectatic corneal disease-a review*. Clin Experiment Ophthalmol 2010; 38: 154-67.

2.- Piñero 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: 1675-87.

3.- Piñero DP, Alio JL, Morbelli H, Uceda-Montanes A, El Kady B, Coskunseven E, Pascual I. *Refractive and corneal aberrometric changes after intracorneal ring implantation in corneas with pellucid marginal degeneration*. Ophthalmology 2009; 116: 1656-64.

4.- Piñero DP, Alio JL, Uceda-Montanes A, El Kady B, Pascual I. *Intracorneal ring segment implantation in corneas with post-laser in situ keratomileusis keratectasia*. Ophthalmology 2009; 116:1665-74.

5.- Piñero DP, Alió JL, El Kady B, Pascual I. *Corneal aberrometric and refractive performance of 2 intrastromal corneal ring segment models in early and moderate ectatic disease*. J Cataract Refract Surg 2010; 36: 102–9.

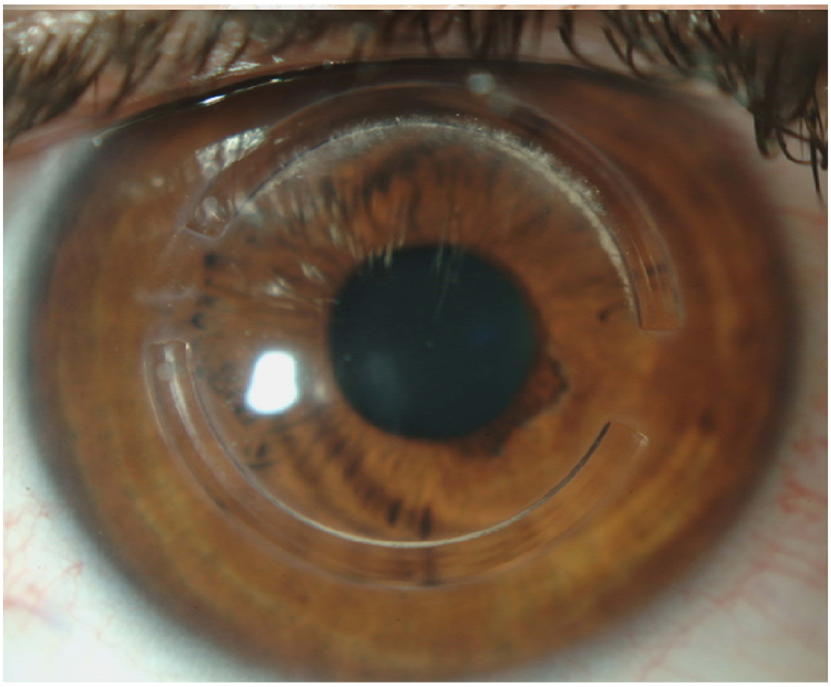
6.- Piñero DP, Alio JL, Barraquer RI, Michael R, Jiménez R. *Corneal biomechanics, refraction, and corneal aberrometry in keratoconus: an integrated study.* Invest Ophthalmol Vis Sci 2010; 51: 1948–55.

7.- Piñero DP, Alio JL, Teus MA, Barraquer RI, Michael R, Jiménez R. *Modification and refinement of astigmatism in keratoconic eyes implanted with intracorneal ring segments*. J Cataract Refract Surg 2010 (accepted for publication).

8.- Piñero DP, Alio JL, Teus MA, Barraquer RI, Uceda-Montañés A. *Modelling the intracorneal ring segment effect in keratoconus using refractive, keratometric and corneal aberrometric data*. Invest Ophthalmol Vis Sci 2010 (in press).

9.- Alió JL, Piñero DP, Sogutlu E, Kubaloglu A. *Intracorneal ring segment reimplantation in keratoconus eyes with previous unsuccessful implants*. J Cataract Refract Surg 2010 (accepted for publication).

CAPÍTULO 1: JUSTIFICACIÓN TEÓRICA DE LA INVESTIGACIÓN



CAPÍTULO 1: JUSTIFICACIÓN TEÓRICA DE LA INVESTIGACIÓN

ÍNDICE:

1.1.- CONCEPTOS GENERALES SOBRE PATOLOGÍA CORNEAL ECTÁSICA

La patología corneal ectásica abarca un grupo de desórdenes o anomalías corneales caracterizadas por un estado inherente de debilidad tectónica corneal o adelgazamiento, que finalmente conduce a la inducción de una protrusión corneal que lleva a un aumento exagerado, ya sea a nivel general o localizado, de la curvatura de la superficie corneal anterior[1,2] (Figura 1). Dicha protrusión, que en la gran mayoría de los casos suele inducir una marcada asimetría del perfil topográfico corneal, es la responsable de la aparición de un astigmatismo irregular que genera una pérdida significativa de la calidad de visión (pérdida de agudeza visual aún con corrección esferocilíndrica en gafa). Puede llegar a ocurrir que la protrusión progrese en el tiempo existiendo el riesgo de perforación. En estos casos tan avanzados es necesario recurrir al transplante de córnea (queratoplastia), siendo el queratocono una causa importante de esta cirugía en el mundo[2,3].

Figura 1.- Perfil cónico corneal que muestra la protrusión existente en una córnea con patología ectásica. En concreto, se trata de una córnea con queratocono, una variante específica de la patología corneal ectásica

La patología corneal ectásica puede ser de carácter primario debido a un problema a nivel de la estructura de colágeno que conforma la arquitectura corneal, tal y como sucede en el queratocono y en la degeneración marginal pelúcida[2]. Pero, por otro lado, también existen los desórdenes ectásicos de carácter secundario o iatrogénico, es decir, inducidos quirúrgicamente[1]. En concreto, esto es lo que sucede (cada vez en menor cantidad debido a los avances en la tecnología diagnóstica preventiva) en algunos pacientes intervenidos de cirugía refractiva con la técnica láser in situ keratomileusis (LASIK) (Figura 2), en los que para la corrección del defecto refractivo existente se lleva a cabo un tallado de la superficie corneal anterior que implica la ablación de una determinada cantidad de tejido corneal, que implica un debilitamiento significativo de la estructura arquitectónica de la córnea y la inducción de una protrusión ectásica que suele ser de carácter progresivo[4,5].

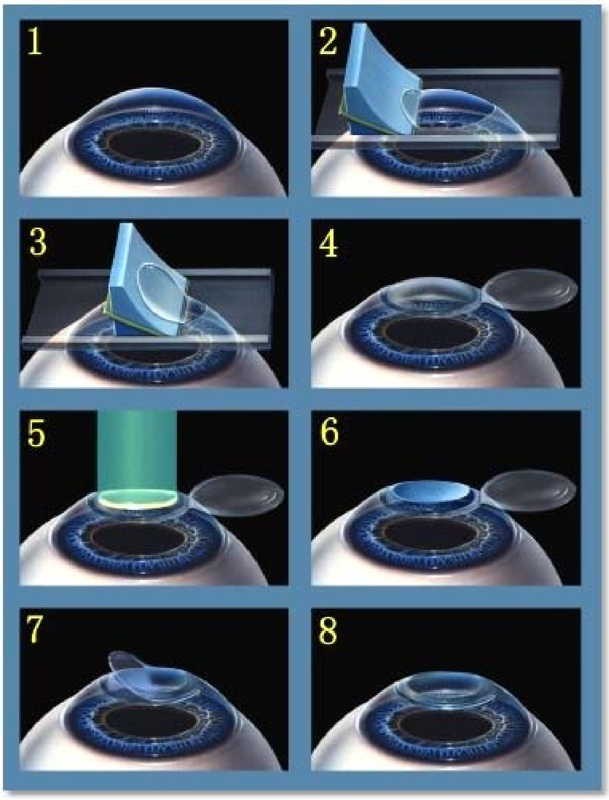


Figura 2.- Diagrama que muestra los pasos de la técnica de cirugía refractiva láser in situ keratomileusis (LASIK):

1. Preparación del campo quirúrgico (esterilización), anestesia tópica
2. Resección de un lentículo de tejido corneal, llamado flap, por medio de un microqueratomo
3. Finalización de la resección dejando un borde del flap sin cortar, el cual actuara como bisagra
4. Levantamiento del flap
5. Ablación de tejido por medio del láser excímer en el lecho estromal expuesto
6. Finalización de la ablación
7. Recolocación del flap
8. Chequeo que el flap está perfectamente posicionado y los bordes coaptados

En lo que se refiere a la patología ectásica primaria, pueden distinguirse diversas variantes en función de una serie de características clínicas: queratocono (Figura 3A), degeneración marginal pelúcida (Figura 3B), queratoglobo (Figura 3C), degeneración marginal de Terrien y queratocono posterior (Figura 3D). En la tabla 1 se muestra de modo esquemático las principales características que definen a algunas de estas variantes ectásicas[6].

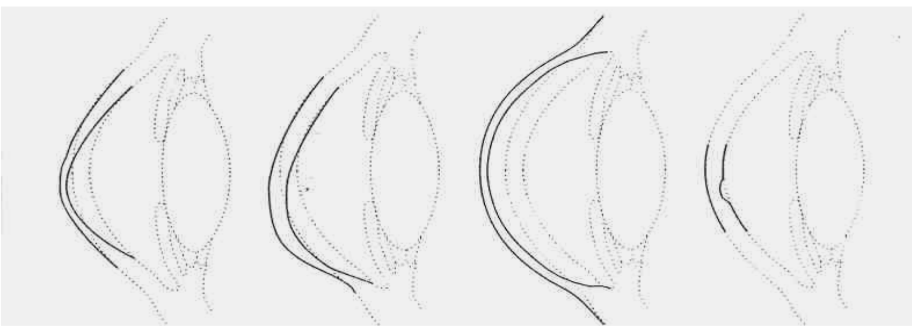


Figura 3.- Diagramas mostrando la configuración del perfil corneal en cuatro tipos diferentes de variantes ectásicas corneales. A. ectasia axial, queratocono. B. ectasia periférica, degeneración marginal pelúcida. C. ectasia generalizada, queratoglobo. D. ectasia axial, queratocono posterior

CARACTERÍSTICA	QUERATOCONO	QUERATOCONO POSTERIOR	QUERATOGLOBO	DEGENERACIÓN MARGINAL PELÚCIDA
Protrusión	Cónica apical en la zona de adelgazamiento	Excavación de la superficie posterior	Generalizada de tipo globular	Periférica, típicamente inferior
Adelgazamiento	Central o paracentral inferior	Central o paracentral	Difuso de todo el estroma, mayor en la periferia	Periférico, usualmente inferior
Lateralidad	Generalmente bilateral	Generalmente unilateral	Generalmente bilateral	Generalmente bilateral
Simetría	Asimétrico	Asimétrico	Simétrico	Asimétrico
Edad de aparición	15-30 años	Generalmente desde el nacimiento	Generalmente desde el nacimiento	Entre los 30 y 40 años, incluso a los 50 años
Evolución	Progresivo, principalmente entre 15-30 años	No progresivo	No progresivo o mínimamente progresivo	Lentamente progresivo
Defecto refractivo	Astigmatismo irregular generalmente miópico o mixto	Astigmatismo irregular, generalmente directo	Astigmatismo irregular, generalmente inverso	Astigmatismo irregular inverso miópico o mixto
Línea férrica	Frecuente. Anillo de Fleischer	Muy rara vez se forma un anillo tipo Fleischer	Nunca	Muy rara vez se forma un anillo tipo Fleischer
Cicatrices	Frecuentes	Frecuentes	Poco frecuentes	Frecuentes
Estrías	Frecuentes (de Vogt)	Nunca	Poco frecuentes	Poco frecuentes
Vascularización	Nunca	Nunca	Poco frecuente, extensión de las arcadas limbares	Nunca
Depósitos lipídicos	Nunca	Nunca	Poco frecuente, depósitos escasos	Nunca
Perforación	Poco frecuente	Muy rara vez	Frecuente, espontánea o por mínimo trauma	Muy rara vez
Hydrops	Poco frecuente	Muy rara vez	Poco frecuente	Poco frecuente

Tabla 1.- Características diferenciales de las alteraciones corneales ectásicas primarias

El queratocono es la más frecuente de todas las anomalías ectásicas primarias de la córnea. Diversas cifras se han estimado para la incidencia del queratocono, aunque la mayoría de las estimaciones se hallan entre 50 y 230 por 100.000 en la población general (aproximadamente 1 por 2000)[2]. En esta anomalía la córnea adopta una forma cónica como consecuencia del adelgazamiento significativo existente a nivel del estroma corneal y la pérdida de estabilidad mecánica (Figura 1). La protrusión y adelgazamiento corneal existentes inducen un alto nivel de irregularidad corneal (astigmatismo irregular), así como de miopía, lo cual conlleva a una pérdida de calidad de visión, que puede ser más o menos severa en función de lo avanzada que se encuentre la ectasia[7]. Es una anomalía progresiva que afecta finalmente a ambos ojos (bilateral), pero puede hallarse afectado inicialmente sólo uno de ellos[8,9]. A nivel de topografía corneal se aprecia un patrón característico: área de encurvamiento corneal rodeada de zonas concéntricas con progresivamente menor poder refractivo y presencia de una significativa asimetría supero-inferior[2] (Figura 4).

La degeneración marginal pelúcida (DMP) es otra de las anomalías ectásicas primarias de la córnea caracterizada por la presencia de una banda de adelgazamiento corneal a nivel periférico, normalmente en forma arqueada o de media luna[2,10]. El área de adelgazamiento suele localizarse inferiormente, extendiéndose desde las 4 a las 8 (simulando posiciones horarias), aunque se han descrito casos de DMP con áreas de adelgazamiento a nivel superior[11]. Esta patología suele ser de carácter asintomático hasta que existe un deterioro significativo de la agudeza visual con y sin corrección como consecuencia del avance de la ectasia. A nivel de topografía corneal se aprecia también un patrón característico conocido como "patrón en alas de mariposa" o "patrón en perilla" (Figura 5): aplanamiento del meridiano vertical que induce un marcado astigmatismo inverso, encurvamiento significativo sobre el área de máximo adelgazamiento que se extiende de forma oblicua y concéntrica al limbo hasta unirse al meridiano horizontal.

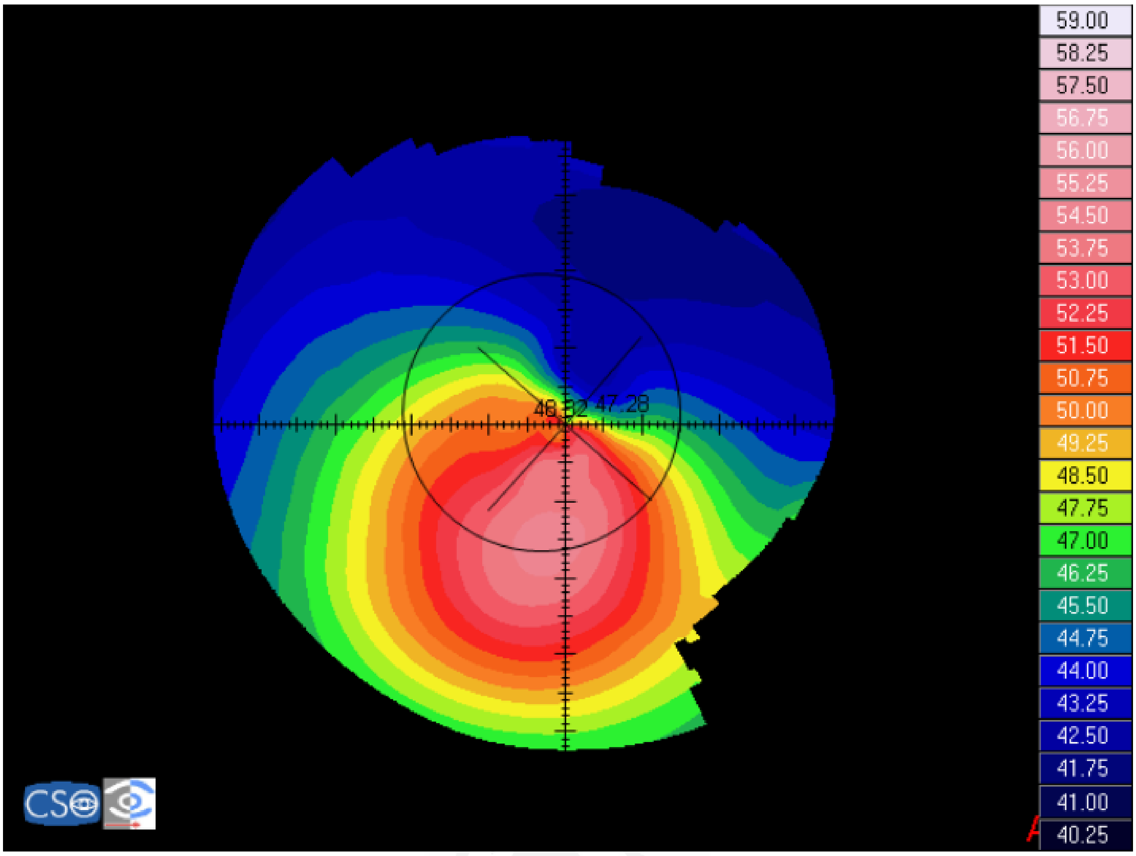


Figura 4.- Patrón topográfico característico del queratocono obtenido mediante un sistema topográfico basado en disco de Plácido (sistema topográfico CSO)

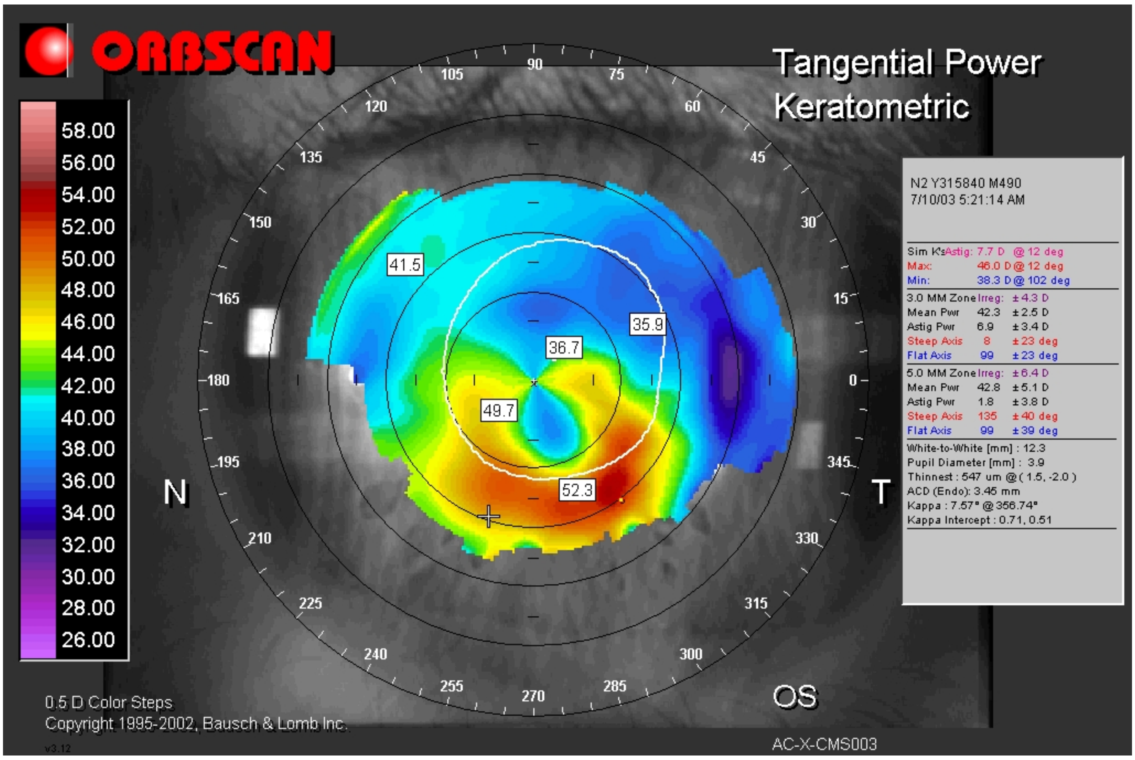


Figura 5.- Patrón topográfico característico de la degeneración marginal pelúcida obtenido mediante un sistema topográfico de barrido de hendidura (sistema topográfico Orbscan IIz).

Por último, tal y como se ha mencionado, existen anomalías ectásicas secundarias, como las que tienen lugar en algunos casos específicos tras la cirugía refractiva LASIK. Esta anomalía se manifiesta a los meses o años tras la cirugía y consiste en un incremento progresivo de la curvatura corneal, normalmente a nivel inferior (Figura 6), con un incremento en el nivel de miopía y astigmatismo, pérdida de agudeza visual sin corrección y en la mayoría de los casos también pérdida de agudeza visual con corrección[5]. La ectasia post-LASIK presenta una incidencia estimada entre 0,04% y 0,6%[13]. Los mecanismos específicos causantes de estas alteraciones corneales resultan hoy todavía desconocidos[5,], aunque parece claro que el debilitamiento de la córnea tras la ablación de tejido con el láser excímer tiene un papel importante en el desarrollo de esta complicación[13-15]. Se han identificado diversos factores de riesgo para el desarrollo de la ectasia post-LASIK, tales como la existencia de un defecto miópico a corregir alto, un escaso espesor del estroma residual tras la ablación[5,13,15-17], un bajo módulo de elasticidad corneal[18] o la existencia de algunas anormalidades topográficas de la córnea[5,13,15-17].

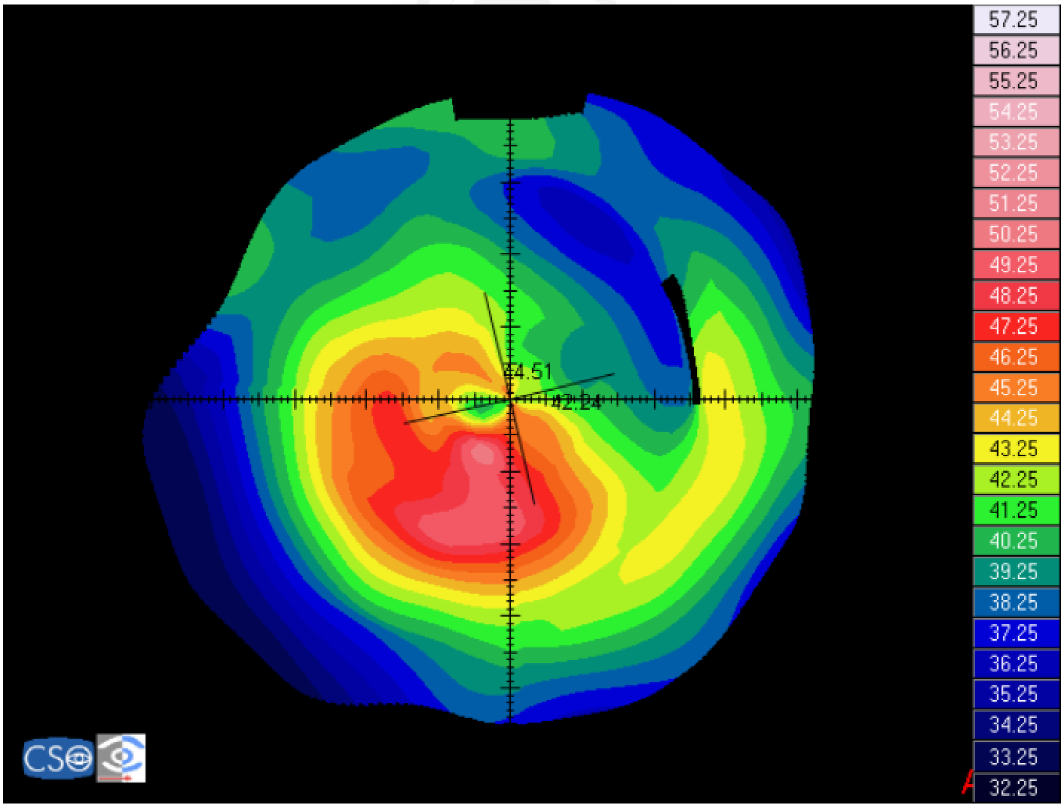


Figura 6.- Patrón topográfico de una córnea con ectasia post-LASIK obtenido mediante un sistema topográfico basado en disco de Plácido (sistema topográfico CSO)

1.2.- LOS SEGMENTOS DE ANILLOS INTRACORNEALES (ICRS) COMO OPCIÓN DE TRATAMIENTO PARA LA PATOLOGÍA CORNEAL ECTÁSICA. ESTADO ACTUAL DEL TEMA

El manejo o tratamiento de los pacientes que presentan cualquier variante de anomalía corneal ectásica tiene dos objetivos: por un lado, la rehabilitación visual ya que la función visual se halla muy deteriorada debido a los cambios que acontecen en la óptica corneal, y por otro lado, el control y paralización del progreso del proceso ectásico. Para la rehabilitación visual, la corrección en gafa sólo resulta apropiada en aquellos casos muy incipientes, es decir, cuando la irregularidad corneal no es lo suficientemente pronunciada como para inducir una disminución de la agudeza visual incluso con la mejor corrección esferocilíndrica. En los casos moderados o avanzados, es necesario recurrir al uso de lentes de contacto o a opciones quirúrgicas para lograr una rehabilitación visual satisfactoria. Se ha comprobado que las lentes de contacto rígidas permeables al gas y también las híbridas son una buena opción de tratamiento en muchos de los casos de ectasia corneal, ya que proporcionan una buena calidad visual debido al efecto de regularización que genera el conjunto lente de contacto-película lagrimal en el primer dioptrio ocular, cubriendo todas las irregularidades existentes[19]. Sin embargo, existen pacientes que pueden presentar una intolerancia al uso de lentes de contacto[20] y otros que alcancen una visión deficiente aún con las lentes de contacto debido justamente a una excesiva irregularidad corneal (descentramientos continuos, mala estabilización de la lente)[21]. En estos casos se debe recurrir a una opción quirúrgica que permita una rehabilitación visual parcial o total.

Dentro de las opciones quirúrgicas, el transplante de córnea o queratoplastia suele ser la última alternativa terapéutica planteada, ya que se trata de una opción muy invasiva, que requiere una larga recuperación y un donante compatible, que proporciona una rehabilitación visual lenta y además existiendo siempre la posibilidad de rechazo al injerto, especialmente en los individuos más jóvenes. Se ha propuesto e investigado el implante de segmentos de anillo intracorneales (intracorneal ring segments, ICRS) como una alternativa terapéutica en la patología corneal ectásica, opción que permite una cierta rehabilitación visual y previene la necesidad de recurrir a un transplante de córnea. Los segmentos de anillo intracorneales (ICRS) son pequeñas piezas de material sintético que son implantadas en lo profundo del estroma corneal con la finalidad de generar modificaciones de la curvatura corneal y, por lo tanto, del estado refractivo ya que la superficie corneal anterior es la estructura más influyente en el estado refractivo global del ojo. En concreto, en el caso de la córnea ectásica el objetivo con estos implantes sería, además de la corrección refractiva esferocilíndrica, la regularización de la superficie corneal anterior y, por tanto, la minimización de las aberraciones ópticas inducidas por este dioptrio.

Además de estas modalidades de tratamiento, cabe mencionar el reciente desarrollo de una nueva alternativa terapéutica para el tratamiento de la patología corneal ectásica: el crosslinking corneal (CLC). El objetivo de este tratamiento es el endurecimiento del tejido corneal, previniendo así su degeneración con la consecuente deformación del mismo. El CLC consiste en la aplicación de una dosis de riboflavina en gotas en el lecho estromal corneal para posteriormente exponer el tejido a radiación ultravioleta A (UVA)[22]. La riboflavina activada induce un incremento de las uniones entre las lamelas de colágeno, produciendo entonces un incremento de la rigidez corneal. Diversos estudios han probado la eficacia de este tratamiento[23,24] e incluso su estabilidad en el tiempo (3 años de seguimiento). Actualmente la controversia reside en si resulta mejor opción la realización del CLC antes o después del implante de los ICRS. Resulta lógico pensar que conviene regularizar la córnea con los ICRS previamente para posteriormente llevar a cabo el endurecimiento del tejido corneal. De todos modos, se trata de un campo en el que actualmente se está llevando a cabo una exhaustiva actividad investigadora.

Debido a que la temática de la presente tesis versa sobre la caracterización y modelización del efecto de los ICRS en la patología corneal ectásica, se llevó a cabo una búsqueda bibliográfica exhaustiva, revisando todos aquellos manuscritos encontrados en la base referencial PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) empleando una serie de palabras clave: “Intracorneal ring segments”, “Intracorneal rings”, “Intrastromal ring segments”, “Intrastromal rings”, “Intacs”, “KeraRing”, y “Ferrara rings”. En total se revisaron más de 90 referencias de las que se extrajo una gran cantidad de información que permitió establecer la situación actual del tema de los ICRS en la patología corneal ectásica. Dicho trabajo se plasmó en una publicación de review en la revista Clinical and Experimental Ophthalmology[25]. Este trabajo supuso el punto de partida de esta tesis y, por tanto, el primer fruto de la misma. Se trata, por tanto, del primer trabajo que se adjunta en la presente tesis.

En el trabajo de review mencionado[25] se revisaron diversos aspectos de los ICRS y su aplicación en la patología ectásica, los cuales se enumeran a continuación:

1.- Concepto de segmento de anillo intracorneal ("Intracorneal ring segment", ICRS) y antecedentes

2.- Tipología de ICRS

3.- Mecanismo de acción de los ICRS

4.- Indicación para el implante de los ICRS en distintas variantes de patología ectásica: queratocono, DMP y ectasia post-LASIK

5.- Nomogramas de implante

6.- Técnicas quirúrgicas de implante de los ICRS

7.- Resultados reportados de los ICRS en distintas variantes de patología ectásica: queratocono, DMP y ectasia post-LASIK

8.- Complicaciones descritas con este tipo de implantes

A continuación se describe de forma esquemática los principales hallazgos de la literatura en referencia a cada una de las áreas mencionadas de estudio de los ICRS.

Concepto de segmento de anillo intracorneal ("Intracorneal ring segment", ICRS) y antecedentes

Como ha sido mencionado anteriormente, los ICRS son pequeñas piezas de material sintético que se implantan en la media periferia de la córnea a nivel estromal profundo con la finalidad de generar cambios de curvatura a nivel central y, por tanto, modificar el estado refractivo del ojo, puesto que el dioptrio corneal es de suma relevancia para la óptica ocular. El concepto surgió inicialmente en el año 1978[25 (ref 1)] con la finalidad de lograr la corrección de la miopía, ya que se comprobó que estos implantes inducían un aplanamiento de la córnea central. Sin embargo, no es hasta la década de los 90 cuando tiene lugar su popularización como consecuencia de la introducción en el mercado del primer modelo comercial a gran escala (Intacs)[25 (ref 4-8)]. A pesar de los resultados iniciales prometedores, la técnica no alcanza el éxito esperado y es rápidamente relegada por la técnica LASIK (laser in situ keratomileusis). Es entonces cuando el implante de los ICRS se plantea como una opción terapéutica en la patología corneal ectásica debido al potencial que tienen estos segmentos de modelar el perfil geométrico de la córnea y al éxito de los primeros resultados reportados (Colin y colaboradores, año 2000)[25 (ref 11)].

Tipología de ICRS

Diversas tipologías de ICRS han sido descritas en la literatura, siendo los principales modelos los que se enumeran a continuación (Figura 7):

-Intacs: arco de circunferencia de 150º, sección hexagonal, diámetro externo de 8,10 mm, un diámetro interno de 6,77 mm y un espesor variable a elegir (0,25-0,45 mm, en pasos de 0,05 mm)

-KeraRing: arco de circunferencia variable (90º, 120º, 160º y 210º), sección triangular, diámetro externo de 5,60 mm, un diámetro interno de 4,40 mm y un espesor variable a elegir (0,15-0,35 mm, en pasos de 0,05 mm)

-Anillos de Ferrara: similares a los KeraRing pero con los bordes redondeados

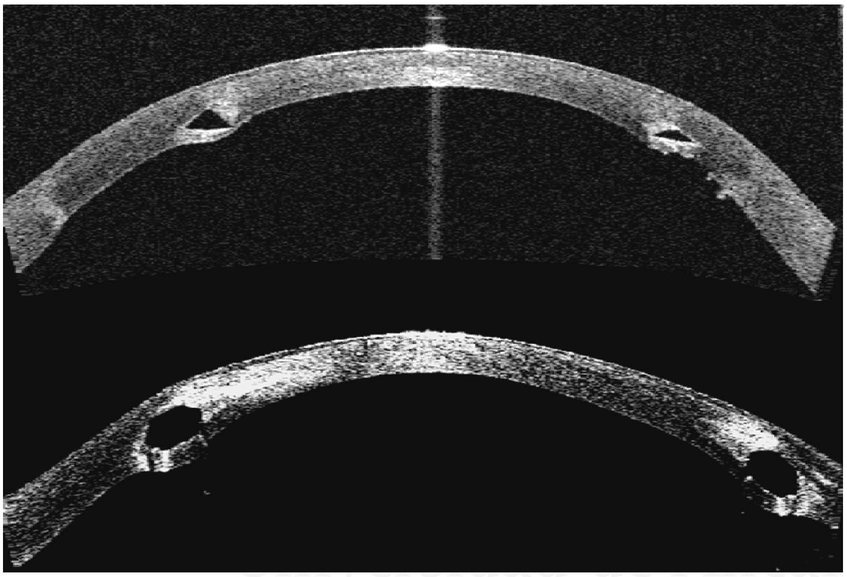


Figura 7.- Imágenes de alta resolución de la córnea, obtenidas mediante el sistema de tomografía de coherencia óptica Visante OCT (Zeiss), en 2 ojos con queratocono: figura superior, córnea con segmentos tipo KeraRings implantados y figura inferior, córnea con segmentos tipo Intacs implantados.

Mecanismo de acción de los ICRS

Los ICRS actúan como elementos espaciadores entre lamelas corneales (lamela=unidad estructural de colágeno corneal) produciendo un efecto de acortamiento de la longitud del arco central (arc shortening effect) y dando lugar a un aplanamiento de la córnea central (Figura 8), el cual es proporcional al espesor del elemento implantado[25 (ref 15)] en córneas sin ningún tipo de patología. Este fenómeno es debido a las propiedades estructurales de la red de lamelas de colágeno que conforma el estroma corneal: patrón ortogonal en la córnea central y paracentral, y disposición circular o tangencial a 1 mm del limbo[25 (ref 25)]. Sin embargo, esta estructura lamelar tan bien organizada es inexistente o está muy alterada en aquellos casos en los que el tejido corneal ha degenerado, tal y como sucede en el queratocono[25 (ref 24)]. Por lo tanto, el efecto de los ICRS en las corneas ectásicas no tiene por que ser el mismo que acontece cuando se implantan estos segmentos en córneas normales con la finalidad de corregir un defecto miópico. No existen aún en la literatura científica trabajos que traten de desarrollar un modelo matemático adecuado que, considerando las características de la arquitectura de la córnea ectásica, permita optimizar los nomogramas de implantación de los ICRS en córneas ectásicas.

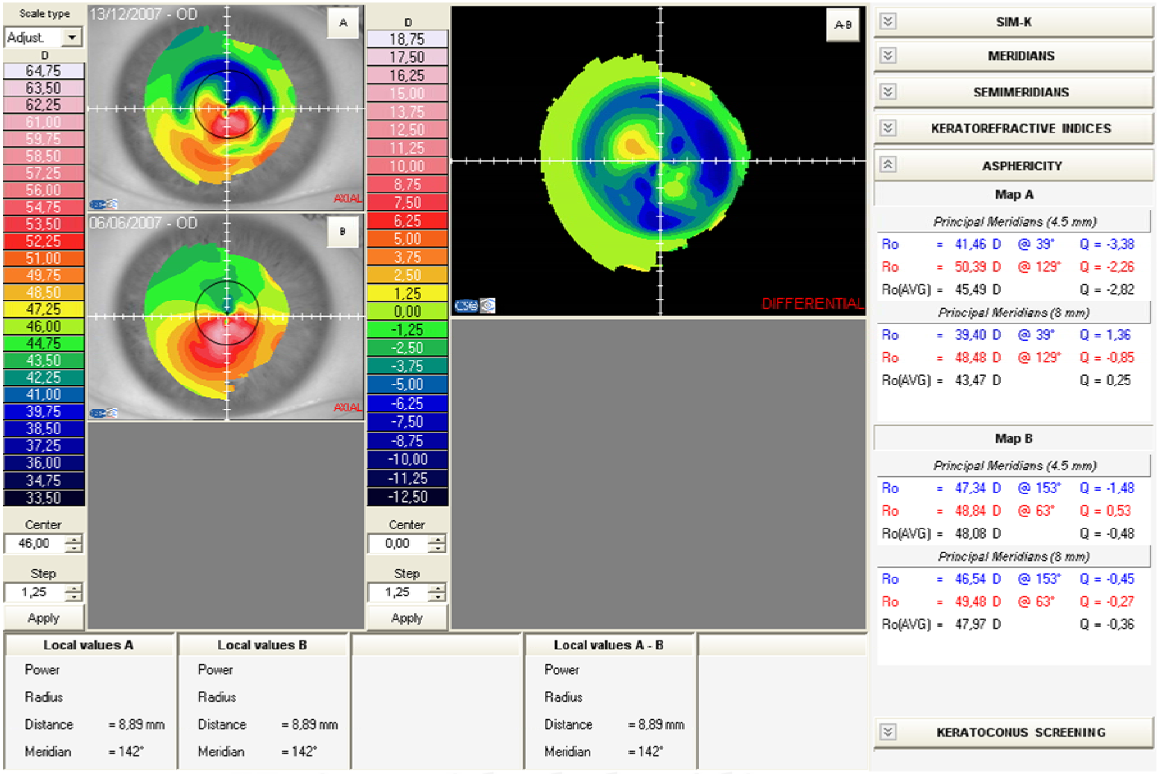


Figura 8.- Mapa diferencial topográfico (derecha) que muestra los cambios entre el patrón topográfico preoperatorio (arriba, derecha) en un ojo con queratocono y el patrón topográfico postoperatorio tras el implante de Intacs (abajo, izquierda).

Indicación para el implante de los ICRS en distintas variantes de patología ectásica: queratocono, DMP y ectasia post-LASIK

Existe una gran cantidad de artículos mostrando resultados de los ICRS en distintas variantes de la patología ectásica. Sin embargo, hay pocos estudios tratando de definir cuáles son las principales condiciones que favorecen la obtención de un buen resultado con los ICRS. A modo de resumen, a continuación se muestran algunas indicaciones reportadas o deducidas de la literatura para la obtención de un resultado favorable con los ICRS.

-Queratocono: menor curvatura corneal central, menor grado de severidad, ausencia de leucomas

-DMP: menor astigmatismo, uso de anillo inferior más delgado

-Ectasia post-LASIK: menor grado de severidad, uso de anillos de Ferrara en casos avanzados

Nomogramas de implante

Diversos nomogramas quirúrgicos han sido propuestos para el implante de ICRS en la córnea ectásica, todo ellos intuitivos y basados en datos clínicos sujetos a una alta subjetividad: refracción esferocilíndrica y apariencia subjetiva del patrón topográfico. No se ha desarrollado aún un nomograma preciso de acuerdo a una modelización matemática que caracterice el efecto de los ICRS. Se han realizado diversas propuestas para el implante de Intacs en queratocono, algunas de ellas basadas en el equivalente esférico y otras en el perfil topográfico corneal, y existiendo en algún caso contradicciones. Por otro lado, también se han desarrollado varios nomogramas para el implante de los anillos de Ferrara y KeraRings, todos ellos, al igual que los Intacs, basados en la refracción esferocilíndrica y en la percepción que tiene el clínico del tipo de patrón topográfico.

Técnicas quirúrgicas de implante de los ICRS

Se han descrito dos procedimientos quirúrgicos diferentes para el implante de los ICRS: procedimiento mecánico y el guiado por láser de femtosegundo[25 (ref 12)]. La diferencia entre ambos procedimientos reside en el modo de crear los túneles corneales donde posteriormente van a ir insertados los segmentos. En el procedimiento mecánico los túneles son creados mediante dos disectores semicirculares que se introducen en un bolsillo lamelar creado para posteriormente ir avanzando con ellos a través del tejido estromal siguiendo un movimiento rotacional, siendo, por tanto, el procedimiento altamente dependiente de la habilidad manual del cirujano. En el caso del procedimiento guiado por láser de femtosegundo, se crean los túneles mediante la fotodisrupción del tejido estromal lograda mediante la aplicación de este tipo de láser. Se han comparado únicamente los resultados visuales y refractivos obtenidos con ambos tipos de tunelización corneal, no obteniéndose diferencias significativas a corto plazo en queratoconos y ectasias post-LASIK[25 (ref 80 y 81)].

No hay un convenio aceptado en lo que respecta a la localización de la incisión para el inicio de la tunelización corneal. Se han propuesto diferentes puntos de referencia, pero no existen estudios que hayan comparado los resultados usando diferentes localizaciones para la incisión.

Resultados reportados de los ICRS en distintas variantes de patología ectásica: queratocono, DMP y ectasia post-LASIK

Existe una gran variedad de artículos que reportan los efectos visuales, refractivos y queratométricos del implante de ICRS en queratocono, DMP y ectasia post-LASIK. A continuación se enumeran de modo esquemático los principales hallazgos.

-Queratocono: aplanamiento corneal central variable (valores medios en la literatura entre 2,14 y 9,60 D), corrección parcial de esfera (efecto entre 0,43 y 5,00 D) y cilindro (efecto entre 0,75 y 2,88 D), mejora de la agudeza visual con y sin corrección esferocilíndrica, cierta regularización corneal (sólo estudiada con KeraRing)

-DMP: reducción del defecto esferocilíndrico, aplanamiento corneal central, gran reducción del astigmatismo corneal

-Ectasia post-LASIK: reducción de la esfera y el cilindro, aplanamiento corneal central, mejora de la agudeza visual con y sin corrección esferocilíndrica

Complicaciones descritas con este tipo de implantes

Algunas complicaciones intraoperatorias han sido descritas con el procedimiento de tunelización corneal mecánico, aunque siempre como eventos puntuales y poco frecuentes, tales como descentramiento de los segmentos, profundidad inapropiada de los túneles corneales o incluso la perforación de la córnea hasta cámara anterior. Respecto a las complicaciones postoperatorias, diversos eventos han sido descritos en la literatura científica, tales como extrusión de los segmentos, neovascularización corneal, infecciones corneales o la presencia de pequeños depósitos en los túneles donde van implantados los segmentos tipo Intacs. Se ha establecido para ojos con queratocono implantados con segmentos tipo Intacs una tasa de un 10% de cirugías posteriores de ajuste (por ejemplo, rotación de segmentos o explante de uno de los 2 segmentos), obteniéndose tras ella normalmente unos buenos resultados, lo que induce a pensar en la potencial reversibilidad y maleabilidad del efecto de estos implantes.

Respecto a los estudios histopatológicos, resulta curioso que hasta el momento sólo exista uno en la literatura, el cual es referenciado en una gran cantidad de trabajos. Samimi et al[25 (ref 92)] comprobaron que los Intacs producían apoptosis de los queratocitos, probablemente a través de un cambio a un fenotipo de colágeno sintético. Estos cambios histológicos parecían ser totalmente reversibles tras el explante de los segmentos, aunque falta una corroboración de esta hipótesis a muy largo plazo.

Como resultado de todo este trabajo documental se pudieron extraer diversas conclusiones sobre el uso de los ICRS para el tratamiento de la patología corneal ectásica. Muchas de dichas conclusiones permitieron establecer algunas de las hipótesis de trabajo de la presente tesis ya que se pudo discernir con mayor claridad cuáles eran las áreas pendientes de desarrollo e investigación en la temática de los ICRS. A continuación se detallan las conclusiones extraídas:

1.- Resulta necesario caracterizar y diferenciar el efecto de las diferentes tipologías de ICRS, sobre todo el efecto de los dos principales tipos, los segmentos con perfil hexagonal y triangular

2.- Resultan necesarios estudios que caractericen el efecto real de los ICRS teniendo en cuenta las peculiaridades de la estructura corneal en las distintas variantes de la patología ectásica.

3.- Resultan necesarios un mayor número de estudios que definan con mayor exactitud y detalle cuáles son los factores predictivos para un buen resultado visual con los ICRS en las diferentes variantes de la patología ectásica corneal.

4.- Resulta necesario el desarrollo de la caracterización del efecto de los ICRS en las distintas variantes de la patología ectásica teniendo en cuenta un mayor número de variables, tales como la aberrometría corneal o el estudio de la biomecánica corneal.

5.- No existen estudios que caractericen los cambios astigmáticos que tienen lugar tras el implante de ICRS en córneas ectásicas considerando el astigmatismo como magnitud vectorial, es decir, sólo se estudian cambios de módulo, lo que limita el conocimiento del impacto visual real del cambio cilíndrico inducido.

6.- Resulta necesario un estudio más detallado y a mayor largo plazo de las posibles limitaciones que induce la técnica de tunelización corneal empleada para el implante de los ICRS, procedimiento mecánico o guiado por láser de femtosegundo.

7.- No existe suficiente evidencia científica que corrobore la reversibilidad y maleabilidad del efecto de este tipo de implantes en patología corneal ectásica.

8.- Queda patente que no se ha desarrollado aún un nomograma preciso de acuerdo a una modelización matemática del efecto de los ICRS, no existiendo hasta el momento una base científica consistente para este tipo de implantes, lo cual supone una limitación para la predictibilidad del procedimiento.

9.- Hay evidencia científica de la eficacia de los ICRS para la rehabilitación visual en la patología corneal ectásica, pero resulta necesario aún un gran número de desarrollos para lograr que el procedimiento sea altamente predecible.

1.3.- LA ABERROMETRÍA CORNEAL ANTERIOR COMO HERRAMIENTA PARA VALORAR EL EFECTO DE LOS ICRS

Las aberraciones oculares juegan un papel primordial en la degradación de la imagen retiniana. Diversos autores han tratado de caracterizar el sistema óptico ocular, así como cada uno de sus elementos refractivos con el fin de conocer la contribución de cada uno de ellos a la formación de la imagen final retiniana. Se ha puesto un especial énfasis en el estudio de la superficie corneal anterior, sobre todo tras la popularización de la cirugía queratorrefractiva. No debemos olvidar que el 70-80% de las aberraciones oculares tienen lugar en este dioptrio ocular, ya que es justo en esta localización donde se halla la máxima diferencia de índices de refracción y, por tanto, la mayor contribución refractiva[26]. Las aberraciones corneales tienen una influencia significativa sobre la imagen final retiniana y su estudio resulta fundamental para una mejor comprensión de los fenómenos visuales experimentados por cada paciente (Figura 9).

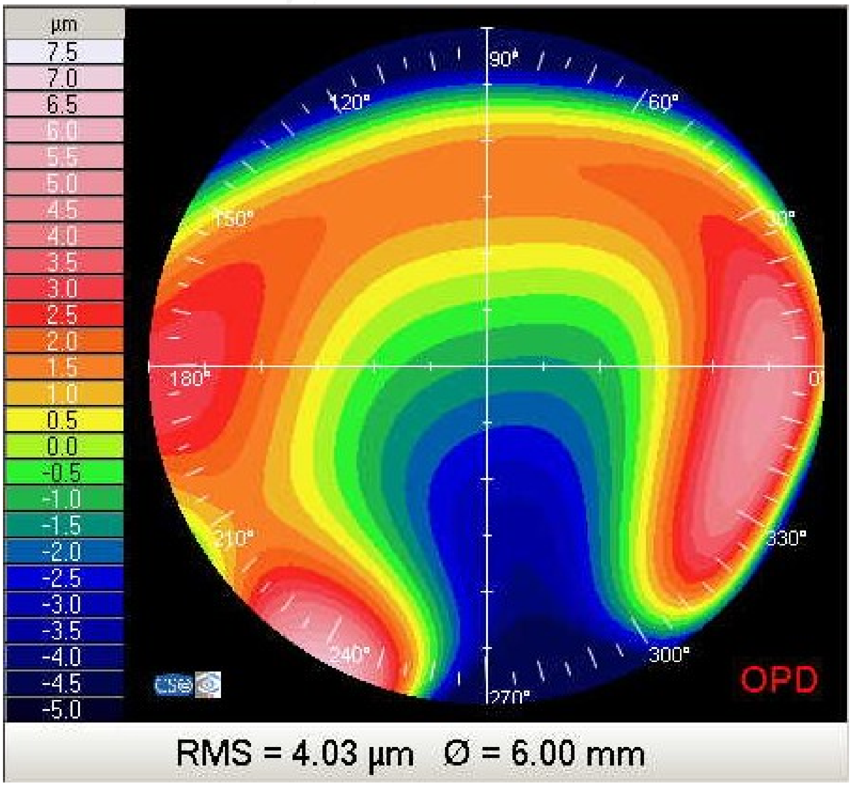


Figura 9.- Mapa aberrométrico total de una córnea. Como se puede apreciar se emplea una escala de colores con la que se caracteriza gráficamente la diferencia del frente de onda corneal con respecto al ideal (libre de aberraciones ópticas).

Diversos autores han tratado de caracterizar las aberraciones debidas a la superficie corneal anterior[27,28], así como su evolución con la edad[29,30]. En todos estos trabajos siempre se han empleado los polinomios de Zernike como expresión matemática para caracterizar el frente de onda corneal. Estos polinomios son considerados el estándar para la caracterización de las aberraciones corneales y oculares[31]. Dicha descomposición de Zernike no consiste más que en una caracterización de la geometría del frente de onda por medio de la suma de funciones polinómicas básicas, las cuales definen pequeños defectos del frente de onda con unas características específicas (coma, aberración esférica, trefoil, etc...) (Figura 10). Cada función básica de Zernike es el resultado del producto de tres términos: radial (n), azimutal (m) y normalizador. La forma estándar de dichas funciones es la siguiente[32]:

$$Z_n^m = N_n^m R_n^{|m|}(\rho)A(m\theta) \qquad (1.1)$$

El entero *n* se denomina índice radial e indica el valor máximo que puede adoptar la variable radial ρ en el término $R_n^{|m|}$. A su vez, el índice *n* siempre es un número positivo. El entero *m*, el cual puede adoptar valores negativos y positivos, se denomina índice azimutal y es multiplicado por la variable angular azimutal (θ) en el término A(mθ).

Los índices radiales más bajos representan a los defectos ópticos más comunes y familiares, denominados defectos de bajo orden. El índice 1 o primer orden (Z_1^1, Z_1^{-1}) se corresponde con los efectos prismáticos a lo largo de los meridianos horizontal y vertical, respectivamente, mientras que el índice radial 2 o segundo orden está compuesto por el desenfoque o error refractivo esférico equivalente (Z_2^0), el astigmatismo cardinal directo o inverso (Z_2^2) y el astigmatismo oblicuo (Z_2^{-2}). A partir de n=3 o tercer orden se habla de defectos ópticos de alto orden o astigmatismo irregular, tales como el coma (Z_3^1, Z_3^{-1}) o la aberración esférica (Z_4^0). A su vez, se emplean coeficientes, denominados coeficientes de Zernike, que indican en qué proporción contribuye cada forma básica a la forma global de la superficie analizada. Hay que tener en cuenta que en la literatura científica normalmente se emplea el término RMS (root mean square), que no es más que el error cuadrático medio para un determinado orden de la descomposición polinomial de Zernike, para una agrupación de aberraciones o para el frente de onda total.

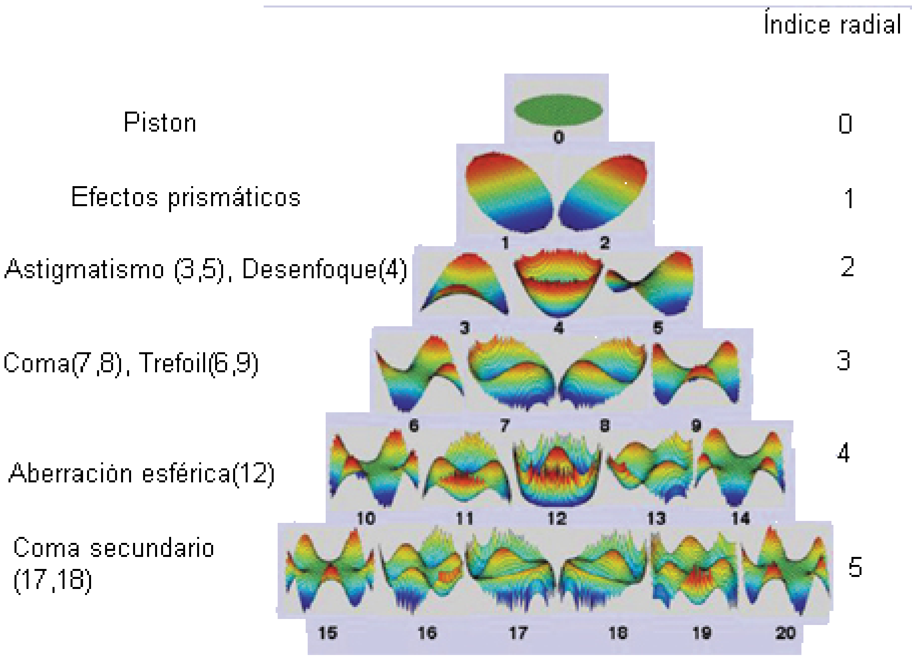


Figura 10.- Diagrama piramidal de Zernike mostrando los defectos ópticos a los que representa cada función básica.

Vinciguerra et al[28] analizaron las aberraciones corneales en un total de 1000 ojos, empleando para ello el topógrafo corneal CSO (CSO, Florencia, Italia). Observaron que se obtenía de promedio un coeficiente de aberración esférica primario (Z_4^0) positivo de 0,52 ± 0,17 µm para un tamaño pupilar de 7 mm, así como un RMS de 0,42 ± 0,23 µm para el defecto comático primario. Wang et al[27] obtuvieron en una muestra de 228 córneas sanas también un Z_4^0 positivo de media, con un valor de 0,28 ± 0,09 µm (rango 0,06-0,54 µm) para un tamaño pupilar de análisis de 6 mm usando el topógrafo Humphrey Atlas. En dicha muestra se obtuvo a su vez un valor medio del RMS para el coma primario de 0,25 ± 0,14 µm (rango 0,02-0,67 µm). Estos dos trabajos concuerdan en el hecho de que existe una gran variabilidad entre individuos.

Existen diversos topógrafos corneales disponibles actualmente en el mercado proporcionando la opción de cálculo de las aberraciones corneales. Dicha opción, se halla incluida en el software específico de cada instrumento. Para poder llevar a cabo este cálculo, se emplean normalmente los datos de elevación proporcionados o estimados por los sistemas topográficos. A partir de esta información, se lleva cabo una reconstrucción del frente de onda corneal, usando para su caracterización matemática la expansión polinomial de Zernike antes mencionada. A partir de los datos de elevación, existen tres métodos para llevar a cabo el cálculo de las aberraciones corneales[33]:

1.- Trazado de rayos: se basa en la ley de Snell y permite reconstruir la geometría de la onda que se propaga a través de la pupila tras la refracción debida a la córnea.

2.- Principio de Fermat: se basa en el hecho de que el camino óptico debe ser el mismo para un rayo marginal y para un rayo axial. Si esto no fuera así, ambos rayos no estarían en fase, siendo dicho desfase debido a la aberración del frente de onda.

3.- Método de aberración de superficie: consiste en calcular directamente la aberración del frente de onda corneal teniendo en cuenta los datos geométricos de la superficie y comparando con la forma ideal de la superficie corneal (libre de aberraciones).

El método de aberración de superficie es el más comúnmente empleado por la mayoría de los dispositivos topográficos corneales existentes actualmente. Para el cálculo de las aberraciones se considera que las diferencias de camino óptico responsables de las aberraciones son producidas por la configuración geométrica de la córnea. De ese modo, se realiza un análisis comparativo entre la superficie corneal real y la libre de aberraciones (óvalo cartesiano). En una córnea real, con una superficie que difiere del óvalo cartesiano, el camino óptico entre puntos imagen y objeto será diferente, y por tanto indicativo de aberración, en comparación al camino recorrido en una córnea con la configuración igual a la del óvalo cartesiano. Esa diferencia en sí es la que se denomina aberración de frente de onda (W)[33]. A continuación se describe en pasos como se obtiene la fórmula que permite el cálculo de W[33] (Figura 11). La definición de los segmentos TQ, QF, TS, SF, SA, AF y SQ viene detallada gráficamente en la Figura 11. Además se empleará la notación "n" para designar al índice de refracción de la córnea.

-Paso 1: Camino óptico en una córnea libre de aberraciones (óvalo cartesiano) = TS + (SF)n.

-Paso 2: Camino óptico en la superficie corneal real = TQ + (QF)n.

-Paso 3: Cálculo de la aberración de frente de onda (W) a partir de la diferencia de camino óptico para la córnea real y el óvalo cartesiano.

$$W = [TS + (SF)n] - [TQ + (QF)n] \qquad (1.2)$$

-Paso 4: Sustituyendo (TS + SQ) por TQ y simplificando la ecuación queda del siguiente modo:

$$W = (SF)n - SQ - (QF)n \qquad (1.3)$$

-Paso 5: Sustituyendo (SA + AF) por SF la ecuación queda del siguiente modo:

$$W = (SA)n + (AF)n - SQ - (QF)n \qquad (1.4)$$

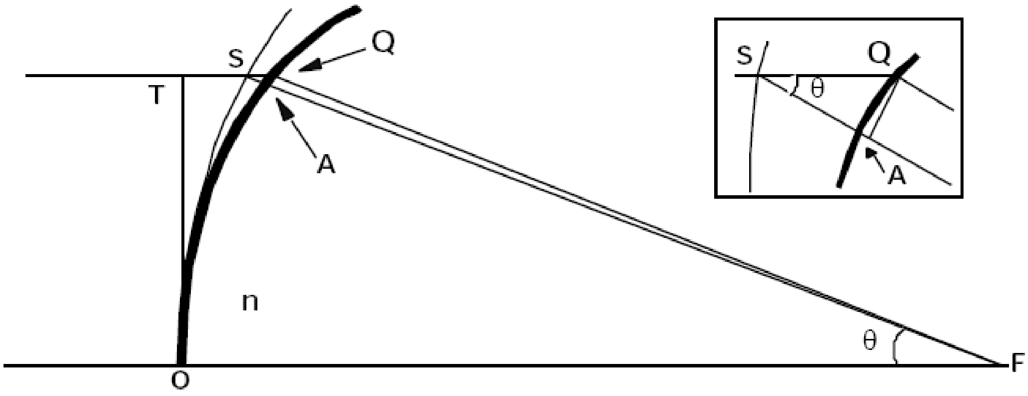


Figura 11.- El método de la aberración de superficie se basa en el principio de Fermat y en la aproximación de que las distancias AF y QF son equivalentes. Para la gran mayoría de córneas, esta aproximación no supone un gran error y permite directamente el cómputo de la aberración de frente de onda a partir de la distancia SQ, es decir, la diferencia entre el óvalo cartesiano (arco OS) y la córnea real (arco OQ). A la derecha existe una imagen en aumento que clarifica la relación existente entre los puntos S, Q y A.

*Notaciones:

O: vértice corneal

F: punto focal

T: punto de corte entre la línea tangente a O y la dirección del rayo de incidencia analizado

S: punto teórico de incidencia del rayo analizado en una superficie ideal libre de aberraciones, el "óvalo cartesiano"

Q: punto de incidencia real del rayo analizado sobre la superficie corneal anterior

A: punto de corte sobre la superficie corneal anterior real del rayo es refractado por la superficie ideal del "óvalo cartesiano en S y va a parar al punto focal F

-Paso 6: Debido a que las distancias QF y AF son muy grandes en comparación a QA, la distancia AF puede aproximarse a QF sin una pérdida significativa de precisión. La ecuación se convierte entonces en la siguiente si además simplificamos:

$$W \approx (SA)n - SQ \qquad (1.5)$$

-Paso 7: El segmento SA es igual a SQ(cosθ), quedando la ecuación del siguiente modo si, a su vez, simplificamos:

$$W = SQ[(\cos\theta)n - 1] \qquad (1.6)$$

-Paso 8: El segmento SQ es conocido como "aberración de superficie" y el ángulo θ equivale a la altura angular del punto de incidencia desde el punto focal paraxial F. Para un rango de tamaños pupilares y curvaturas corneales normales, el valor de cosθ se halla entre 0,99 y 1,00, por lo que se puede llevar a cabo otra aproximación:

$$W \approx SQ(n - 1) \qquad (1.7)$$

El valor del segmento SQ se puede deducir a partir de los datos de elevación corneales, restando los reales a los correspondientes al óvalo cartesiano. Si el índice de refracción corneal es 1,376, la función de aberración de frente de onda corneal es simplemente la que define a la superficie corneal multiplicada por 0,376. Ya que este método tiende a sobrestimar ligeramente las medidas aberrométricas, se suele emplear un n=1,363 para hacer los cálculos, ya que da valores más próximos a los obtenidos con el trazado de rayos[33]. Otros autores, en cambio, emplean el índice de refracción queratométrico (1,3375) para el cálculo[34].

Se han descrito diversas aplicaciones clínicas de la aberrometría corneal obtenida mediante el método de aberración de superficie, tales como el estudio del efecto de las diferentes técnicas de cirugía refractiva corneal o el estudio del impacto óptico de distintas patología corneales. En concreto, el estudio de la aberrometría corneal anterior ha ido adquiriendo importancia en el estudio de la patología corneal ectásica, siendo aplicado en concreto por diversos autores para la detección y gradación del queratocono[35-39]. Se han hallado elevados niveles de coma primario vertical, así como valores altos de RMS para las aberraciones "coma-like" (calculado teniendo en cuenta los defectos de tercer, quinto y séptimo orden) en pacientes con queratocono e incluso en ojos con sospecha de queratocono[35-39] en comparación con los niveles en existentes en córneas sanas.

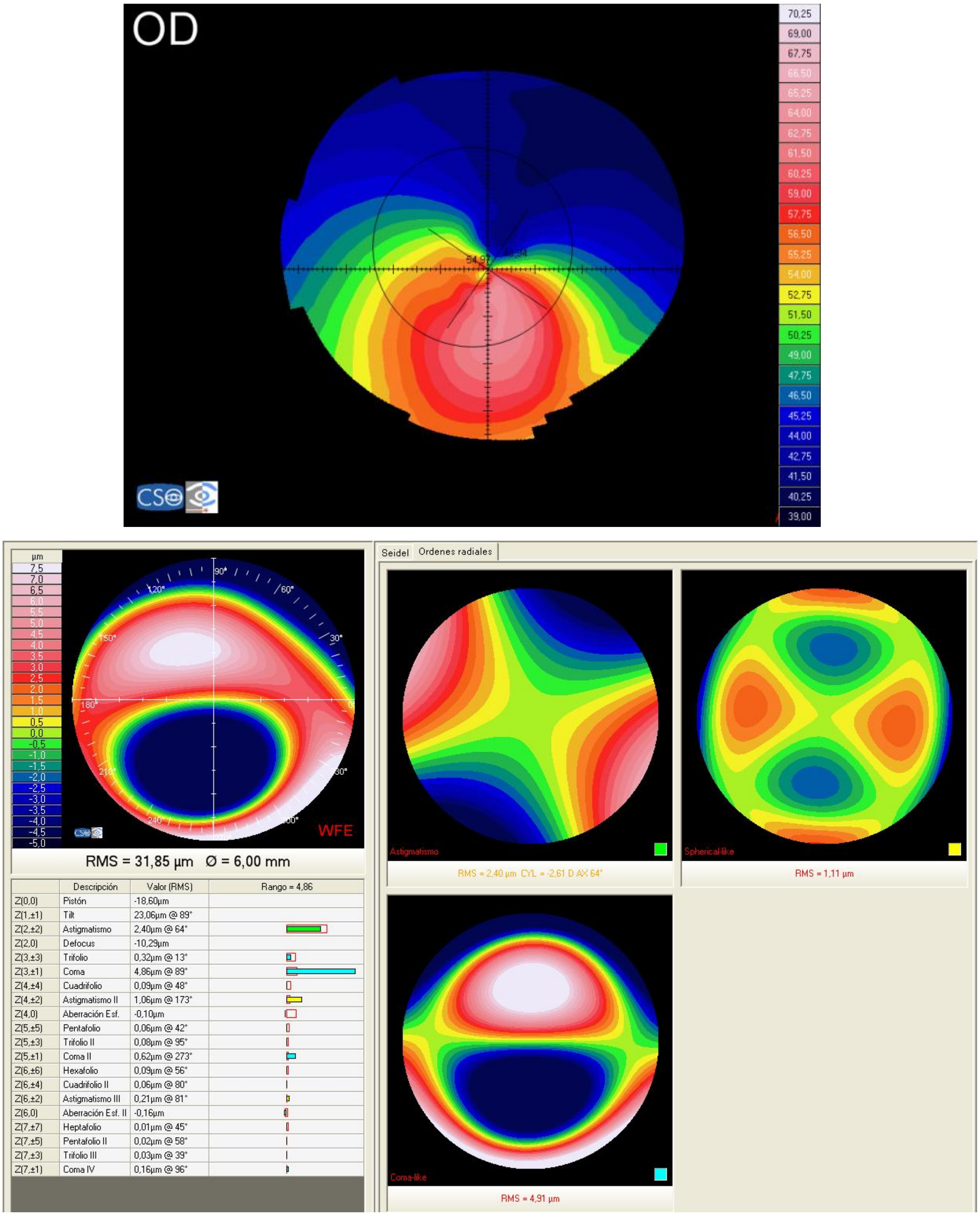


Figura 12.- Queratocono grado 4, según la clasificación de Alió-Shabayek.

A. Mapa topográfico axial

B. Mapa aberrométrico corneal (pupila 6 mm) en el que se muestran los siguientes mapas: mapa aberrométrico total de la córnea (arriba, izquierda), mapa de los componentes astigmáticos de segundo orden (arriba, centro), mapa de los defectos “spherical-like” (cuarto y sexto orden) (arriba, derecha), y mapa de los defectos “coma-like” (tercer, quinto y séptimo orden) (abajo, centro). Estos mapas fueron obtenidos con el sistema topográfico CSO (CSO, Florencia, Italia).

Teniendo en cuenta que el valor RMS “coma-like” era mayor a medida que el queratocono se hallaba más avanzado, se logró establecer en 2006 la primera clasificación de la severidad del queratocono teniendo en cuenta la aberrometría corneal, la clasificación de Alió-Shabayek[37] (Figura 12):

-Queratocono grado 1: ausencia de cicatrices, RMS “coma-like” entre 1,50 y 2,50 µm, queratometría media central menor de 48 D

-Queratocono grado 2: ausencia de cicatrices, RMS “coma-like” entre 2,50 y 3,50 µm, queratometría media central menor de 53 D, grosor corneal mínimo mayor de 400 micras

-Queratocono grado 3: ausencia de cicatrices, RMS “coma-like” entre 3,50 y 4,50 µm, queratometría media central mayor de 53 D, grosor corneal mínimo entre 300 y 400 µm

-Queratocono grado 4: cicatrices corneales centrales, RMS “coma-like” mayor de 4,50 µm, queratometría media central mayor de 55 D, grosor corneal mínimo en torno a 200 µm (Figura 12)

Algunos autores han establecido cierta controversia en el uso de la aberrometría corneal, ya que no caracteriza en sí los defectos oculares globales a pesar de que el primer dioptrio corneal suponga de un 70-80% del poder dióptrico del ojo. Pero hay que tener en cuenta que en ojos altamente aberrados la aberrometría global, obtenida por medio de sensores de frente de onda ocular, no resulta fiable. Actualmente los aberrómetros o sensores de frente de onda ocular o global pueden analizar como máximo un total de 1452 puntos[40]. Este muestreo resulta del todo insuficiente para caracterizar una superficie de alta complejidad que induce grandes cantidades de aberraciones de bajo y alto orden. Por otro lado, también hay que tener en cuenta que el fenómeno de amontonamiento o superposición de los spots luminosos y la asunción de que la pendiente de cada porción de frente de onda analizada con un sensor de frente de onda global es plana, tal y como sucede con los aberrómetros tipo Hartmann-Shack, son aspectos que limitan enormemente la capacidad de análisis de estos dispositivos en la patología ectásica corneal. En contraste, con los sistemas topográficos actuales se pueden llegar a analizar más de 6000 puntos, pudiendo llevarse a cabo un análisis mucho más exhaustivo de la óptica corneal en el área pupilar. De todos modos, Barbero et al[39] hallaron una gran similitud entre los patrones aberrométricos corneal y global en ojos con queratocono, especialmente en los estadíos más incipientes de la patología. En cambio, en ojos con queratocono más avanzado existía una menor coincidencia que los autores atribuyen a los cambios ópticos que acontecen en la cara posterior además de las limitaciones técnicas que presentan los sensores de frente de onda global.

Hasta el momento no existen artículos que reporten en detalle y caractericen los cambios aberrométricos corneales que tienen lugar tras el implante de distintos tipos de ICRS en diferentes variantes de patología corneal ectásica. Como antecedente, sólo hallamos un trabajo de Shabayek y Alió[41] en el que se pudo corroborar como se inducía una disminución significativa del nivel de coma primario en córneas implantadas con segmentos tipo KeraRing y que presentaban de inicio un valor RMS para el coma primario superior a 3 µm. La caracterización de los cambios aberrométricos tras implante de ICRS teóricamente permitiría llevar a cabo una evaluación y monitorización detallada de la regularización de la superficie corneal anterior que tiene lugar con los implantes así como de la mejoría de la calidad visual. Por tanto, esta área debe ser desarrollada con el fin de lograr un mejor conocimiento de lo que acontece con los ICRS en córneas ectásicas. Por ello, se trata de una de las temáticas que se ha investigado a fondo en la presente investigación.

1.4.- ÁREAS PENDIENTES DE DESARROLLO E INVESTIGACIÓN EN EL ÁREA DE LOS ICRS

Tras la revisión bibliográfica mencionada y descrita anteriormente, quedó patente la existencia de diversas áreas pendientes de mayor desarrollo e investigación en el área de los ICRS para el tratamiento de la patología ectásica corneal:

1.- Caracterización completa del efecto real de los ICRS a nivel visual, refractivo, topográfico y aberrométrico corneal en función de las condiciones basales en las diversas variantes de la patología ectásica corneal

2.- Caracterización de las diferencias en el efecto logrado con los ICRS en función del tipo de variante ectásica

3.- Definición detallada y consistente de los diferentes factores predictivos para la obtención de un buen resultado visual tras el implante de ICRS en las distintas variantes de la patología ectásica corneal

4.- Caracterización de las diferencias en el efecto de las dos principales tipologías de ICRS aplicadas en el tratamiento de la patología corneal ectásica: segmentos de perfil triangular (tipo KeraRing) y segmentos de perfil hexagonal (tipo Intacs)

5.- Caracterización completa de las diferencias en el efecto de los ICRS aplicados en el tratamiento de la patología corneal ectásica en función del tipo de tunelización empleada para su inserción: tunelización mecánica y tunelización guiada por láser de femtosegundo

6.- Determinación de la importancia del examen aberrométrico corneal en el estudio del efecto de los ICRS en córneas ectásicas, tratando de establecer las relaciones que puedan existir entre los defectos ópticos de alto orden de la córnea y la alteración biomecánica subyacente en este tipo de córneas

7.- Caracterización del cambio astigmático inducido con los ICRS en córneas ectásicas, pero teniendo en cuenta el carácter vectorial de la magnitud astigmatismo.

8.- Estudio detallado de la reversibilidad y maleabilidad del efecto de los ICRS en las distintas variantes de la patología ectásica corneal

9.- Definición de una modelización matemática empírica que permita la caracterización del efecto de los diversos tipos de ICRS en las diferentes variantes de la patología ectásica corneal teniendo en cuenta parámetros clínicos objetivos.

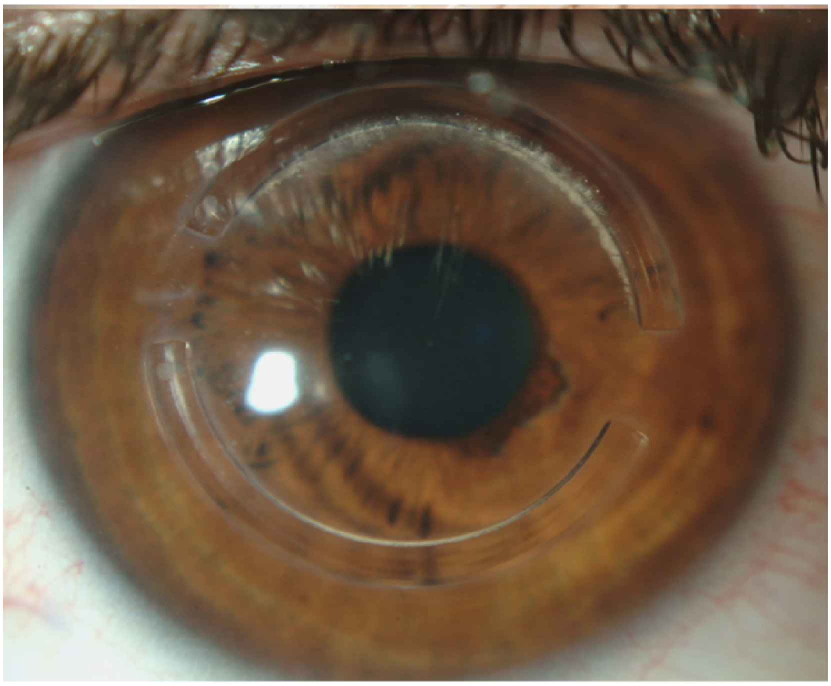
10.- Desarrollo de un nomograma de implante de los ICRS para las diferentes variantes de la patología ectásica corneal con base empírica y teniendo en cuenta parámetros objetivos que permitan una mayor predictibilidad del procedimiento de implante

11.- Determinación de la relación existente entre las peculiaridades estructurales estromales de cada variante de la patología ectásica y las posibles modelizaciones empíricas que puedan obtenerse para caracterizar el efecto de los ICRS en las diversas variantes de patología ectásica corneal

12.- Desarrollo de una modelización avanzada del efecto de los ICRS a partir de un análisis mediante elementos finitos de la estructura de la córnea y su biomecánica.

Varias de estas áreas justificaron el desarrollo y realización de la presente tesis y han permitido el planteamiento de diversas hipótesis de trabajo, tal y como se describirá en detalle en las siguientes secciones del presente documento.

CAPÍTULO 2: HIPÓTESIS Y OBJETIVOS



CAPÍTULO 2: HIPÓTESIS Y OBJETIVOS

ÍNDICE:

2.1.- HIPÓTESIS

El efecto de moldeado corneal de los segmentos de anillo intracorneales (ICRS) empleados en el tratamiento de distintas patologías corneales ectásicas, tales como el queratocono, la degeneración marginal pelúcida o la ectasia post-LASIK, puede modelizarse empíricamente a partir de ciertos parámetros clínicos objetivos, tales como la aberrometría de la superficie corneal anterior, siendo dicha modelización diferente en función del tipo de patología ectásica a tratar y del tipo de segmento empleado, pudiendo obtenerse en cada caso factores predictivos del resultado visual final.

2.2.- OBJETIVOS

A partir de la hipótesis de trabajo planteada, se pretenden alcanzar con la presente tesis los siguientes dos objetivos generales:

1.- Demostrar que el efecto de los dos principales tipos de ICRS es diferente en función del tipo de patología ectásica corneal, existiendo diferentes factores predictivos del resultado visual en cada caso

2.- Modelizar matemáticamente el efecto de los ICRS en una situación particular, el queratocono, la cual es la anomalía ectásica de la córnea de mayor prevalencia, empleando varios parámetros clínicos objetivos, tales como la aberrometría de la superficie corneal anterior.

Se plantean los siguientes objetivos específicos para el cumplimiento del primer objetivo general:

1.- Estudiar los cambios visuales y refractivos, así como los topográficos y aberrométricos correspondientes a la superficie corneal anterior, que tienen lugar tras el implante de las dos principales tipologías de ICRS (Intacs y KeraRing) en 3 variantes diferentes de la patología corneal ectásica: el queratocono, la degeneración marginal pelúcida y la ectasia post-LASIK

2.- Definir los factores predictivos de un buen resultado visual tras el implante de las dos principales tipologías de ICRS (Intacs y KeraRing) en las 3 variantes de patología corneal ectásica antes mencionadas

3.- Caracterizar las diferencias en el efecto inducido a nivel visual y refractivo así como topográfico y aberrométrico de la superficie corneal anterior, tras el implante de ICRS en las 3 variantes de patología corneal ectásica antes mencionadas empleando las dos técnicas existentes de tunelización corneal, mecánica y guiada por láser de femtosegundo

4.- Caracterizar las diferencias en el efecto inducido a nivel visual y refractivo así como topográfico y aberrométrico de la superficie corneal anterior, tras el implante de segmentos tipo Intacs y segmentos tipo KeraRing en las 3 variantes de patología corneal ectásica antes mencionadas

En lo que respecta al segundo objetivo general, se plantean los siguientes objetivos específicos para su cumplimiento:

1.- Desarrollar una modelización matemática empírica que permita la caracterización del efecto del tipo de segmento y la técnica de tunelización que se demostrara más adecuada y efectiva en el queratocono

2.- Analizar la importancia de la inclusión en dicha modelización de la aberrometría corneal anterior y su posible relación indirecta con la alteración biomecánica subyacente

3.- Caracterizar el cambio astigmático inducido por el tipo de segmento y la técnica de tunelización que se demostrara más adecuada y efectiva en el queratocono en el análisis previo realizado mediante análisis vectorial

4.- Caracterizar la potencial reversibilidad y maleabilidad del efecto de los ICRS en el queratocono

A continuación se detalla la distribución de los trabajos incluidos en la presente tesis según el objetivo general con el cual estaban relacionados, sin contar el trabajo 1 que, como se mencionó anteriormente, era un trabajo de revisión que permitió conocer las áreas pendientes de desarrollo e investigación en el área de los ICRS y, a su vez, el planteamiento de la hipótesis de trabajo de la presente tesis.

Trabajos relacionados con el primer objetivo principal de la tesis

-2: Refractive and aberrometric outcomes of intracorneal ring segments for keratoconus: mechanical versus femtosecond-assisted procedures (Ophthalmology)[42]

-3: Refractive and corneal aberrometric changes after intracorneal ring implantation in corneas with pellucid marginal degeneration (Ophthalmology)[43]

-4: Intracorneal ring segment implantation in corneas with post-laser in situ keratomileusis keratectasia (Ophthalmology)[44]

-5: Corneal aberrometric and refractive performance of 2 intrastromal corneal ring segment models in early and moderate ectatic disease (Journal of Cataract and Refractive Surgery)[45]

Trabajos relacionados con el segundo objetivo principal de la tesis

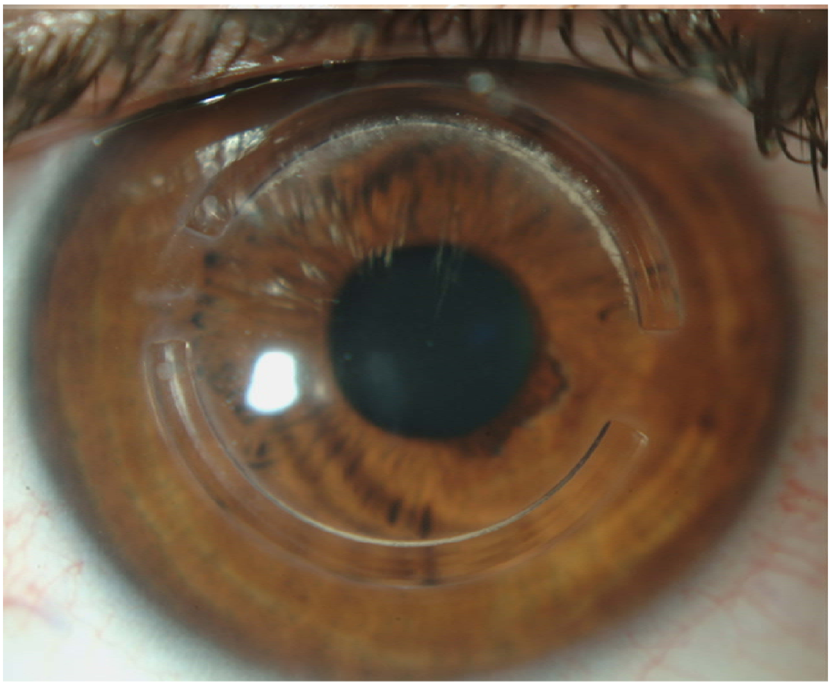
-6: Corneal biomechanics, refraction, and corneal aberrometry in keratoconus: an integrated study (Investigative Ophthalmology and Visual Science)[46]

-7: Modification and refinement of astigmatism in keratoconic eyes implanted with intracorneal ring segments (Journal of Cataract and Refractive Surgery)[47]

-8: Modelling the intracorneal ring segment effect in keratoconus using refractive, keratometric and corneal aberrometric data (Investigative Ophthalmology and Visual Science)[48]

-9: Intracorneal ring segment reimplantation in keratoconus eyes with previous unsuccessful implants (Journal of Cataract and Refractive Surgery)[49]

CAPÍTULO 3: MATERIAL Y MÉTODOS



CAPÍTULO 3: MATERIAL Y MÉTODOS

ÍNDICE:

3.1.- BASES Y FUNDAMENTOS DEL ANÁLISIS RETROSPECTIVO REALIZADO

Para el cumplimiento del primer objetivo general y los específicos asociados de la presente investigación se ha recurrido al análisis retrospectivo de diversas muestras de pacientes con diagnóstico de queratocono, DMP o ectasia post-LASIK y, a su vez, con implante de alguna de las dos principales tipologías de ICRS: Intacs (perfil hexagonal) y KeraRing (perfil triangular). Debido a que la prevalencia de tales patologías ectásicas en la población es significativamente baja[2] se ha decidido realizar un estudio multicéntrico, agrupándose así la casuística de diversos centros y, por tanto, pudiendo lograr un mayor tamaño muestral. En concreto, en la presente investigación se ha incluido casuística de diversos centros integrantes del Subproyecto de Calidad Visual de la Red Temática de Investigación Cooperativa en Salud “Patología Ocular del Envejecimiento, Calidad Visual y Calidad de Vida” (RD07/0062) (Ministerio de Sanidad, Instituto de Salud Carlos III):

-Universidad Miguel Hernández (Alicante). División de Oftalmología en colaboración con la Unidad de Queratocono del Instituto Oftalmológico Vissum Alicante (Vissum Corporación S.L.).

-Fundación Andaluza de Imagen, Color y Óptica (FAICO) en colaboración con el Instituto Oftalmológico Vissum Sevilla (Vissum Corporación S.L.).

-Universidad de Navarra. Departamento de Oftalmología. Clínica Universitaria.

-Universidad de Alcalá, Alcalá de Henares (Madrid) en colaboración con el Instituto Oftalmológico Vissum Madrid (Vissum Corporación S.L.).

-Institut Universitari Barraquer, Universitat Autònoma de Barcelona.

-Fundación para la Investigación Biosanitaria de Andalucía Oriental (FIBAO) en colaboración con el Instituto Oftalmológico Vissum Almería (Vissum Corporación S.L.).

Además de los integrantes de esta Red Cooperativa de Investigación, otros centros adicionales han colaborado en la recopilación de casos de patología ectásica implantados con ICRS:

-Instituto Oftalmológico Vissum Albacete (Vissum Corporación S.L.)

-Departamento Cirugía Refractiva del Dunya Eye Hospital, Estambul (Turquía)

-Kartal Training Hospital, Estambul (Turquía)

El período revisado en cada uno de los centros incluía desde Septiembre de 2000 a Junio de 2008. De dicho período se han extraído los datos visuales, refractivos, topográficos corneales, aberrométricos corneales y de biomecánica corneal de todos aquellos pacientes intervenidos de ICRS y con alguna de las variantes de patología ectásica antes mencionada. La revisión de las historias clínicas ha sido realizada por la misma persona (DPP), así como el paso de la información relevante para nuestra investigación contenida en ellas a la correspondiente base de datos.

La justificación del desarrollo de un análisis retrospectivo viene fundamentada básicamente en la tremenda dificultad de hallar casos con la patología anteriormente mencionada en la población y más que hayan sido implantados con las dos tipologías de ICRS, Intacs o KeraRing, siguiendo exactamente el mismo nomograma. Hay que recordar que el queratocono es considerado como una enfermedad rara (incidencia aproximada de 1/2000)[1] y, a su vez, que las incidencias reportadas de ectasia post-LASIK (entre 0,04 y 0,06%)[13] y DMP (aún desconocida con exactitud debida a la ausencia de estudios al respecto)[1] son significativamente bajas. En concreto, el queratocono ha sido declarado como enfermedad rara por diversas instituciones, tales como ORPHANET (Portal de Información de Enfermedades Raras y Medicamentos Huérfanos, www.orpha.net). Por lo tanto, el desarrollo de un estudio prospectivo, a pesar de ser la opción más adecuada, resultaba totalmente inviable si se quería obtener una muestra relevante de casos para poder llevar a cabo finalmente una modelización. En concreto, se necesitarían décadas para lograr un tamaño muestral necesario para lograr una modelización consistente con suficiente poder estadístico. Esto, en cierto modo, ha resultado ser una cierta limitación puesto que no se ha podido segmentar la población en grupos tanto como se hubiese deseado, pero nos ha permitido obtener ideas claras y avaladas por un análisis estadístico muy exhaustivo de las principales tendencias y factores predictivos. De hecho, los estudios retrospectivos se han establecido como válidos para ese objetivo (estudio de tendencias), así como para definir modelos e hipótesis que poder comprobar posteriormente a nivel prospectivo[50]. Hay que resaltar que en la presente investigación se ha podido obtener una muestra homogénea de casos de queratocono implantados con una geometría específica de ICRS que nos ha permitido la modelización del efecto de los implantes en este tipo de condición ectásica, que resulta ser la más prevalente.

Por lo tanto, se ha desarrollado un análisis retrospectivo detallado, teniendo en cuenta las limitaciones existentes y aplicando los métodos matemáticos de análisis adecuados considerando la heterogeneidad de algunas de las muestras de casos incluidas.

3.2.- MUESTRAS DE PACIENTES ANALIZADAS

En la Tabla 2 se muestra de modo esquemático la contribución de cada uno de los centros participantes a los diferentes estudios que conforman la presente tesis, así como el criterio de inclusión y exclusión seguido en cada uno de ellos para la elección de cada muestra.

La indicación del implante de ICRS se había realizado en todos los casos incluidos en los diferentes estudios que forman parte de esta tesis por la existencia de una agudeza visual mejor corregida reducida y/o una intolerancia al uso de lentes de contacto.

El diagnóstico de queratocono, DMP y ectasia post-LASIK se realizó acorde a los criterios considerados como estándar y reportados en la literatura por diversos autores:

-Queratocono[2]: diagnóstico basado en los hallazgos obtenidos en topografía corneal y en el examen biomicroscópico. Presencia de patrón topográfico asimétrico con encurvamiento inferior (Figura 4), así como de adelgazamiento estromal, protrusión cónica en el ápice corneal, anillo de Fleischer, estrías de Vogt o cicatriz estromal anterior.

-DMP[2,51]: adelgazamiento corneal inferior con ectasia sobre el área de máximo adelgazamiento (examen de lámpara de hendidura), patrón topográfico corneal en "alas de mariposa" (encurvamiento corneal significativo inferior con los meridianos de mayor curvatura radiando hacia el centro de la córnea oblicuamente y abrazando un área de aplanamiento vertical, Figura 5) y marcado astigmatismo refractivo inverso con pérdida de agudeza visual mejor corregida.

-Ectasia post-LASIK[52]: adelgazamiento corneal en el examen con lámpara hendidura, encurvamiento corneal que no se estabiliza (más de 1 D cada 6 meses) (Figura 6), adelgazamiento corneal progresivo constatado por paquimetría ultrasónica, agudeza visual reducida y refracción manifiesta inestable (más de 0,5 D de cambio en el equivalente esférico cada 6 meses).

Tabla 2.- Tabla resumen que muestra los principales datos de las muestras de pacientes consideradas en los estudios que forman parte de la presente tesis.

ESTUDIO	CIRUJANO/S	MUESTRA	CENTRO/S	INCLUSIÓN	EXCLUSIÓN
2	Dr Alió Dr Coskunseven Dr Morbelli Dr Uceda-Montanes Dr Maldonado Dr Cuevas	116 14 6 4 3 3	Alicante Estambul 1 Albacete Sevilla Navarra Almería	Diagnóstico de QTC y tratamiento mediante implante de Intacs o KeraRing	Patología corneal y/u ocular activa
3	Dr Alió Dr Morbelli Dr Uceda-Montanes Dr Coskunseven	10 7 3 1	Alicante Albacete Sevilla Estambul 1	Diagnóstico de DMP y tratamiento mediante implante de Intacs o KeraRing	Patología corneal y/u ocular activa
4	Dr Alió Dr Uceda-Montanes	32 2	Alicante Sevilla	Diagnóstico de EPL y tratamiento mediante implante de Intacs o KeraRing	Patología corneal y/u ocular activa
5	Dr Alió	37: 26 QTC 6 PMD 5 EPL	Alicante	Diagnóstico de QTC, DMP o EPL grado I y II, y tratamiento mediante implante de Intacs o KeraRing	Patología corneal y/u ocular activa
6	Dr Alió Dr Barraquer	58 23	Alicante Barcelona	Diagnóstico de QTC, no tratamiento quirúrgico, medida biomecánica corneal con sistema ORA	Patología corneal y/u ocular activa
7	Dr Alió Dr Teus Dr Barraquer	16 6 13	Alicante Madrid Barcelona	Diagnóstico de QTC, tratamiento mediante implante de KeraRing con láser femtosegundo, medición astigmatismo corneal y refractivo en todas las visitas durante 1 año de seguimiento	Patología corneal y/u ocular activa
8	Dr Alió Dr Teus Dr Barraquer Dr Uceda-Montañés	47 12 12 1	Alicante Madrid Barcelona Sevilla	Diagnóstico de QTC, tratamiento mediante implante de KeraRing de 160º de arco con láser femtosegundo Seguimiento 12 meses completo	Patología corneal y/u ocular activa Reposición o explante del segmento
9	Dr Alió Dr Kubaloglu	18 3	Alicante Estambul 2	Diagnóstico de QTC y retratamiento mediante implante de Intacs o KeraRing tras implante previo con mal resultado o complicación	Patología corneal y/u ocular activa

*Nota: El centro Estambul 1 corresponde al Dunya Eye Hospital y el centro Estambul 2 al Kartal Training Hospital.

Por último, cabe mencionar que en el estudio 8[49] el criterio para decidir la realización de un explante de un ICRS y el posterior reimplante de otros segmentos con diferente criterio se justificaba, tal y como se menciona en la Tabla 2, por la presencia de un mal resultado o una complicación. En concreto, se consideraba un mal resultado cuando el paciente presentaba una agudeza visual postoperatoria mejor corregida muy reducida a nivel postoperatorio que suponía un gran impacto en las actividades diarias del paciente o cuando éste se quejaba de presencia de molestias en visión nocturnas intolerables, tales como halos y glare. En cuanto a las complicaciones, se incluyeron casos de extrusión del segmento y neovascularización de los canales de implante.

3.3.- PROTOCOLO DE EXAMEN Y SEGUIMIENTO DE LOS PACIENTES

En todos los casos se había realizado un examen ocular y visual detallado de inicio, que constaba de las siguientes pruebas diagnósticas: agudeza visual sin corrección (AVSC), agudeza visual mejor corregida (AVCC), refracción manifiesta, examen biomicroscópico con lámpara hendidura, tonometría Goldmann, evaluación del fondo de ojo, paquimetría ultrasónica y análisis topográfico corneal. En aquellos estudios en los que se valoraba el resultado del implante de los ICRS, esta visita de inicio resultaba ser la visita preoperatoria, en la que se recopilaba la información que permitía valorar la viabilidad del proceso quirúrgico.

Un total de tres sistemas topográficos corneales diferentes habían sido empleados en los estudios incluidos en la presente tesis ya que se recopilaron datos de diferentes períodos y de varios centros oftalmológicos diferentes: CMS 100 Topometer (G. Rodenstock Instrument GMBH, Ottobrunn, Alemania), CSO (CSO, Florencia, Italia) y el sistema Orbscan IIz (Bausch & Lomb, Rochester, NY). Los dos primeros sistemas topográficos son sistemas basados en el disco de Plácido, mientras que el sistema Orbscan IIz combina la tecnología tipo Plácido con el barrido de hendidura. Aunque no se han realizado estudios para valorar la concordancia de las medidas topográficas de estos instrumentos específicamente, se ha comprobado que los sistemas tipo Plácido y el sistema Orbscan proporcionan una precisión de medida similar en superficies esféricas calibradas[53]. De todos modos, el uso de sistemas topográficos diferentes resulta una limitación de los análisis retrospectivos llevados a cabo.

En el presente estudio los siguientes parámetros topográficos fueron determinados y recopilados en cada visita con cualquiera de los tres sistemas topográficos mencionados:

-Poder dióptrico corneal en el meridiano más plano dentro de los 3 mm centrales (K1)

-Poder dióptrico corneal en el meridiano más curvo dentro de los 3 mm centrales (K2)

-Poder dióptrico corneal medio dentro de los 3 mm centrales (KM)

-Índice de asimetría supero-inferior (ISAI, inferosuperior asymmetry index), calculado como la diferencia entre el poder dióptrico 3 mm por encima y 3 mm por debajo del centro geométrico de la córnea.

Adicionalmente, en todos aquellos casos que habían sido revisados con el sistema topográfico CSO se pudieron recopilar algunos datos topográficos adicionales, tales como:

-Astigmatismo corneal en los 3 mm centrales (AST3)

-Astigmatismo corneal en los 6 mm centrales (AST6)

-Asfericidad corneal media en los 4,5 mm centrales (Q45)

-Asfericidad corneal media en los 8 mm centrales (Q8)

El análisis de las aberraciones de la cara anterior de la córnea sólo estaba disponible en todos aquellos ojos analizados con el sistema topográfico CSO, ya que este sistema era el único que proporcionaba directamente los datos de aberrometría corneal. El sistema CSO analiza un total de 6144 puntos de la córnea en un área anular circular con un radio interior de 0,33 mm y un radio exterior de 10 mm respecto al vértice corneal. El software de este sistema, EyeTop 2005 (CSO, Florencia, Italia), realiza automáticamente el cálculo de las aberraciones corneales a partir de los datos de elevación obtenidos del perfil corneal, proporcionando estos datos aberrométricos siguiendo el estándar establecido, la descomposición polinomial de Zernike hasta el séptimo orden. Este software se basa en el método de la aberración de superficie para la obtención de las aberraciones corneales, tal y como se explica en el apartado 1.3.

En los estudios incluidos en la presente tesis, todos los coeficientes aberrométricos así como los valores RMS (root mean square, error cuadrático medio) fueron calculados para un tamaño pupilar de 6 mm. En concreto, los siguientes parámetros fueron calculados y recopilados: RMS total, RMS coma primario (calculado para los términos de Zernike $Z_3^{\pm 1}$), RMS "coma-like" (calculado para los términos de Zernike de tercero, quinto y séptimo orden), RMS "spherical-like" (calculado para los términos de Zernike de cuarto y sexto orden) y RMS de alto orden residual (calculado para todos los términos de Zernike excepto los correspondientes a la aberración esférica y coma primarios). A su vez, el coeficiente correspondiente a la aberración esférica primaria (Z_4^0) con su signo fue también calculado y reportado.

En lo que respecta a la biomecánica corneal, sólo valorada en uno de los estudios (estudio 5), se empleó el único sistema comercializado hasta la fecha que permite una caracterización de las propiedades biomecánicas de la córnea in vivo de forma totalmente no invasiva: el sistema Ocular Response Analyzer (ORA) (Reichert, DePew, NY)[54]. Este sistema se basa en un proceso de aplanación bidireccional (Figura 13). En concreto, el sistema lanza un pulso de aire hacia la córnea que induce un aplanamiento de la misma (P1) hasta alcanzar un determinado nivel de concavidad. Tras este primer proceso de aplanación que dura milisegundos, la presión del pulso de aire decrece pasando por un segundo estado de aplanación (P2), mientras se produce el proceso de retorno de la concavidad a la convexidad normal de la córnea (Figura 13). Por lo tanto, durante este proceso se miden dos tipos de presiones diferentes, P1 y P2, y la diferencia entre ellas se denomina histéresis corneal (CH, corneal hysteresis) dada por el sistema ORA. Hay que resaltar que, a pesar de la nomenclatura, el parámetro CH está en relación con las propiedades biomecánicas de la córnea pero no caracteriza en sí bajo ningún concepto un ciclo de histéresis[55]. Además, el sistema proporciona otra parámetro denominado factor de resistencia corneal (CRF, corneal resistance factor), el cual es determinado mediante un algoritmo propio aunque se sabe que es el resultado de una relación lineal entre P1 y P2[54]. Algunos autores, así como el fabricante, establecen que el CRF es un parámetro predominantemente influenciado por las propiedades elásticas del tejido corneal, aunque un mayor desarrollo es necesario para conocer con exactitud el significado físico del parámetro[54,56]. Hasta el momento se ha podido comprobar que los parámetros CH y CRF se hallan significativamente disminuidos en condiciones de inestabilidad biomecánica corneal, tales como el queratocono[55,57]. A su vez, se ha comprobado la reproducibilidad de las medidas con el sistema ORA en córneas sanas sin cirugía previa[58].

En cuanto a los estudios de resultados quirúrgicos, el seguimiento postoperatorio varió en función del tipo de paciente y de los objetivos planteados en el mismo (Tabla 3). En todas las visitas postoperatorias, excepto la de 24-48 horas después de la cirugía, se valoró la agudeza visual, el estado refractivo, la salud del segmento anterior (biomicroscopía), así como el perfil topográfico corneal. Como se ha mencionado anteriormente, en aquellos casos valorados con el sistema CSO, también se pudo estudiar el perfil aberrométrico de la superficie anterior de la córnea.

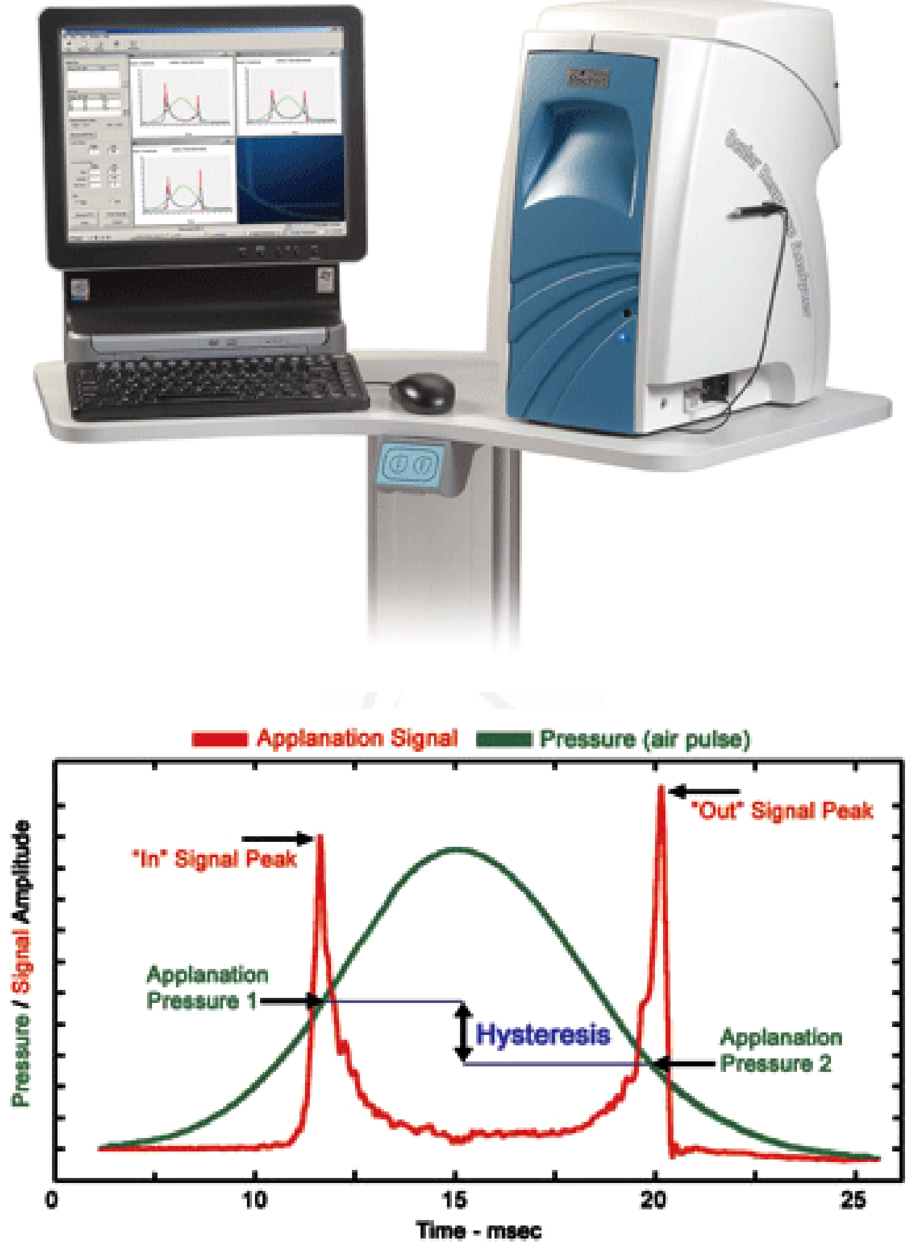


Figura 13.- Imagen del sistema Ocular Response Analyzer (ORA) para la caracterización de la biomecánica de la córnea (arriba) y de la gráfica de monitorización del proceso de aplanación bidireccional proporcionada por el software del sistema (abajo). En la gráfica la línea roja representa la señal de aplanación, mientras que la verde representa la variación del pulso de aire durante el proceso de medida

ESTUDIO	PROTOCOLO	CENTRO/S
1	Preoperatorio 24-48 horas 1,3,6,12 y 24 meses	Alicante Estambul 1 Albacete Sevilla Navarra Almería
2	Preoperatorio 24-48 horas 1,3 y 6 meses	Alicante Albacete Sevilla Estambul 1
3	Preoperatorio 24-48 horas 1,3,6,12 y 24 meses	Alicante Sevilla
4	Preoperatorio 24-48 horas 1,3 y 6 meses	Alicante
5	Un único examen visual	Alicante Barcelona
6	Preoperatorio 24-48 horas 1,3, 6 y 12 meses	Alicante Madrid Barcelona
7	Preoperatorio 3 meses	Alicante Madrid Barcelona Sevilla
8	Preoperatorio 1 mes tras primer implante Pre-explante 1 y 6 meses post-reimplante	Alicante Estambul 2

Tabla 3.- Protocolo de examen y seguimiento llevado a cabo en cada uno de los estudios que conforman la presente tesis

Por último, hay que resaltar que todos los pacientes habían firmado previamente a la cirugía un consentimiento informado acorde a la normativa legal vigente y a lo establecido en la Declaración de Helsinki, que incluía además un consentimiento para el uso posterior de la información clínica de su caso para futuros estudios de carácter retrospectivo. La aprobación de los comités éticos locales de cada institución fue obtenida también para la realización de los diferentes estudios que constituyen la presente tesis.

3.4.- PROCEDIMIENTO QUIRÚRGICO

Todas las cirugías fueron llevadas a cabo por nueve cirujanos oftalmológicos, contribuyendo cada uno de ellos de diverso modo a cada uno de los diversos estudios realizados, tal y como viene indicado en la Tabla 2. Todos los procedimientos quirúrgicos se llevaron a cabo bajo anestesia tópica. Dependiendo del estudio en unos casos se llevó a cabo una tunelización corneal para el implante de los ICRS mediante un disector mecánico y en otros mediante una plataforma comercial de láser de femtosegundo (IntraLase, Intratase Corp, Irving, CA). Las características específicas de cada procedimiento vienen detalladas en los artículos correspondientes[42-49], así como en el artículo de review[25]. A su vez, también viene detallado en el trabajo sobre reimplantes el procedimiento exacto para el explante de los segmentos iniciales y el posterior reimplante de la nueva combinación.

La selección del número de Intacs a implantar así como sus espesores se realizó siguiendo los criterios definidos previamente por Alió y colaboradores[59], el cual se basa en el patrón topográfico corneal (Tabla 4). En lo que respecta a los KeraRing, la modalidad de implante se seleccionó en cada caso teniendo en cuenta el nomograma definido por el fabricante (ver Tabla 5, todos los segmentos KeraRing con una longitud de arco de 160º).

PATRÓN TOPOGRÁFICO CORNEAL	INDICACIÓN
Área de encurvamiento inferior que no alcanza el meridiano 180º (cono inferior)	1 segmento de 0,45 mm de espesor
Área de encurvamiento que se extiende al menos 1 mm por encima y debajo del meridiano 180º (cono central)	2 segmentos: uno inferior de 0,45 mm de espesor y uno superior de 0,25 mm de espesor

Tabla 4.- Nomograma de implante para Intacs definido por Alió y colaboradores[59] para córneas ectásicas: el número de segmentos a implantar y sus espesores se seleccionan teniendo en cuenta el patrón topográfico existente.

Equivalente esférico (D)	*Toda la ectasia se limita a una mitad de la córnea*	*75% de la ectásica en una mitad de la córnea y 25% en la otra mitad*	*Dos tercios del área ectásica en una mitad de la córnea y un tercio en la otra mitad*	*La ectasia se distribuye de igual manera en ambas mitades de la córnea*
>-10 D	25/35	25/35	30/35	35/35
-8 to -10 D	20/30	20/30	25/30	30/30
-6 to -8 D	15/25	15/25	20/25	25/25
-2 to -6 D	0/20	0/20	15/20	20/20

Tabla 5.- Nomograma para el implante de KeraRings propuesto por el fabricante (Mediphakos) (2007). Este nomograma está creado exclusivamente para segmentos de 160º de arco y permite la selección del número de segmentos, así como del espesor de los mismos, a partir del equivalente esférico y el patrón topográfico corneal (distribución de la ectasia). Para definir la distribución de la ectásica la cornea se divide en dos mitades usando el meridiano más curvo como eje de separación. Ejemplo: 25/35=espesor segmento superior/espesor segmento inferior (0,25 mm/0,35 mm). Abreviaturas: D, dioptrías.

Finalmente, la Tabla 6 muestra de modo esquemático los distintos tipos de cirugías e implantes evaluados en cada uno de los diferentes estudios de la presente tesis.

ESTUDIO	TIPOS ICRS	TIPO TUNELIZACIÓN
1	Intacs: 80 ojos (54.79%) KeraRing: 66 ojos (45.21%)	Mecánica: 63 ojos (43.15%) Femtosegundo: 83 ojos (56.85%)
2	Intacs: 3 ojos (14.29%) KeraRing: 18 ojos (85.71%)	Mecánica: 7 ojos (33.33%) Femtosegundo: 14 ojos (66.66%)
3	Intacs: 24 ojos (70.60%) KeraRing: 10 ojos (29.40%)	Mecánica: 20 ojos (58.80%) Femtosegundo: 14 ojos (41.20%)
4	100% KeraRing	100% Femtosegundo
5	No cirugía	No cirugía
6	100% KeraRing	100% Femtosegundo
7	100% KeraRing	100% Femtosegundo
8	Cambio de Intacs a KeraRing: 3 ojos (27.27%) Cambio KeraRing inferior de 160º a 210º: 2 ojos (18.18%) Eliminación segmento superior e inserción 1 nuevo inferior: 3 ojos (27.27%) Inserción anillo inferior más grueso: 2 ojos (18.18%) Rotación segmento: 2 ojos (18.18%)	Mecánica: 11 ojos (52.30%) Femtosegundo: 10 ojos (47.60%) Misma técnica para reimplante excepto en 5 (cambio mecánico a femtosegundo)

Tabla 6.- Tipos de cirugías e implantes evaluados en cada uno de los diferentes estudios de la presente tesis.

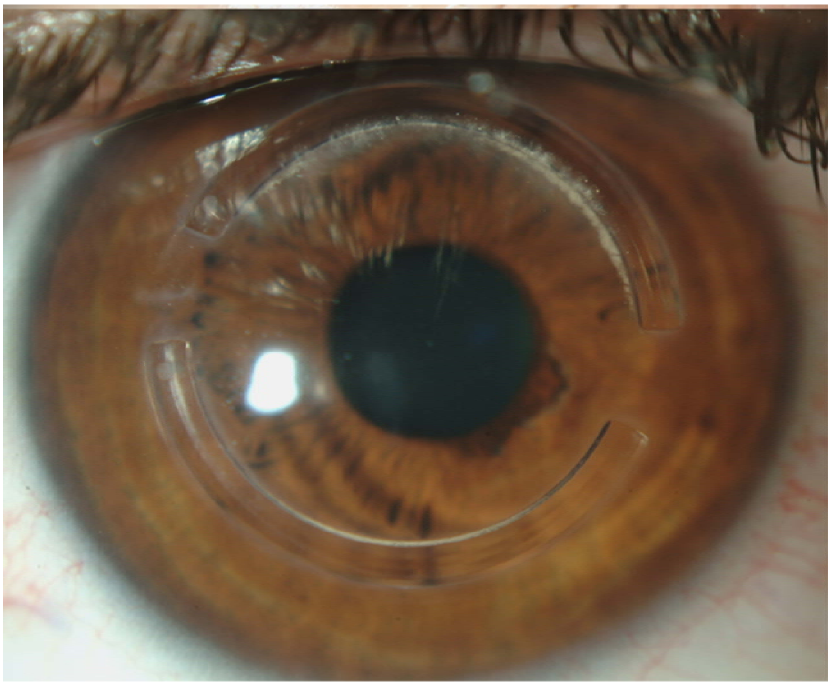
3.5.- ANÁLISIS ESTADÍSTICO DE LOS RESULTADOS Y FORMATO DE PRESENTACIÓN DE LOS MISMOS

Para la realización del análisis estadístico se empleó el software SPSS versión 10.1 para Windows (SPSS, Chicago, Illinois, USA). En primer lugar, se evaluó la normalidad de todas las distribuciones de datos de ambos estudios mediante el test de Shapiro-Wilk. Cuando el uso de estadística paramétrica era posible, se utilizó el test t de Student para muestras pareadas para el análisis comparativo de datos preoperatorios y postoperatorios y el test t de Student para muestras no pareadas para el análisis comparativo de grupos específicos (explantados y no explantados, mecánico y femtosegundo…). Cuando la estadística paramétrica no resultaba aplicable, se empleó el test de rangos de Wilcoxon para el análisis de las diferencias entre datos preoperatorios y postoperatorios y el test Mann-Whitney para la comparativa de grupos específicos. En todos los casos se consideró el nivel de significación estadística para valores de p inferiores a 0,05 (el p-valor es la probabilidad de que una diferencia durante un experimento haya sucedido por casualidad).

Por otro lado, también se determinaron los coeficientes de correlación (Pearson o Spearman dependiendo si la condición de normalidad se cumplía o no) para evaluar el grado de correlación entre diferentes variables de cada estudio. Por último, también se ha llevado a cabo un análisis de regresión lineal múltiple que tratara de correlacionar el espesor del segmento con los cambios inducidos por el ICRS y las condiciones basales de la córnea, comprobando la homocedasticidad del modelo, la ausencia de colinealidad y también la ausencia de correlación entre errores. El análisis estadístico específico viene descrito en detalle en la correspondiente publicación[47].

Por último, en las diferentes tablas y gráficos se ha mostrado en todo momento el valor medio y la correspondiente desviación estándar, con diferente formato de acuerdo a las normas de presentación de datos correspondientes a cada revista [Media ± Desviación estándar; Media (Desviación estándar)]. En ninguno de los casos se llevó a cabo el redondeo de los valores presentados, mostrándose en todo momento dos cifras para el valor medio y la desviación estándar de cada parámetro. Este procedimiento de presentación de datos, a pesar de no seguir los estándares de la teoría de errores en alguno de los casos, fue el formato requerido por el editor en alguna de las publicaciones.

CAPÍTULO 4: RESULTADOS Y DISCUSIÓN



CAPÍTULO 4: RESULTADOS Y DISCUSIÓN

ÍNDICE:

4.1.- RESULTADOS DE LOS TRABAJOS EN RELACIÓN CON EL PRIMER OBJETIVO GENERAL

4.1.1.- Resultados refractivos y aberrométricos corneales tras el implante de ICRS en queratocono: procedimiento mecánico versus procedimiento guiado por láser de femtosegundo *[Piñero 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: 1675-8].*

En este estudio, tal y como se mencionó con anterioridad, se han analizado los cambios visuales, refractivos y aberrométricos corneales que tenían lugar tras el implante de dos tipologías de ICRS en córneas con queratocono. A su vez, también se analizó y evaluó la potencial influencia de la técnica de implantación quirúrgica de los ICRS en los resultados obtenidos: tunelización corneal mediante disección mecánica o con ayuda de láser de femtosegundo. A continuación se enumeran los principales hallazgos y reflexiones extraídas a partir de este primer estudio.

1.- Reducción significativa de esfera y cilindro tras el implante de ICRS con ambas técnicas quirúrgicas, con ligera regresión del efecto corrector a los 12 meses tras el implante sólo en el grupo de córneas en las se llevó a cabo una implantación de los ICRS de forma mecánica. Estos cambios refractivos eran concordantes con los reportados previamente por otros autores[42 (ref 9-13,16-20,35)].

2.- Como consecuencia del efecto refractivo corrector de los ICRS, la AVSC mejoró significativamente tras el implante de los ICRS con ambas técnicas de tunelización, tal y como en otros estudios[42 (ref 9-14,18-20,23,24,26,27,33,35)].

3.- La AVCC sólo experimentó una mejoría significativa en los casos implantados mediante tunelización con láser de femtosegundo. Otros autores también han hallado cambios significativos en la AVCC con técnica mecánica, pero hay que resaltar que en la presente muestra se hallaban incluidos muchos más casos avanzados y moderados (suelen tener peor pronóstico visual) y además la tasa de complicaciones fue algo más elevada en el grupo de tunelización mecánica.

4.- A nivel de curvatura corneal, se pudo comprobar que se producía un aplanamiento corneal central significativo con ambos tipos de técnica quirúrgica, resultando coherente con la reducción miópica también observada y estando en concordancia con lo hallado en trabajos previos[42 (ref 9-20,23,35)]. Al igual que para el efecto corrector refractivo, se pudo apreciar una ligera regresión del efecto de aplanamiento a los 12 meses tras la cirugía en el grupo de córneas con implantación mecánica.

5.- Se pudo comprobar que el efecto del implante de los ICRS a nivel de las aberraciones de la superficie corneal anterior era totalmente dependiente de la técnica de tunelización empleada. En concreto, con el procedimiento mecánico no se detectaron cambios estadísticamente significativos, a pesar de una pequeña reducción inicial a nivel del astigmatismo, el coma primario y las aberraciones “coma-like”. Además se pudo constatar la existencia de un incremento significativo del nivel de algunas aberraciones corneales, tales como el coma primario o las aberraciones “spherical-like”, a los 12 meses tras la cirugía sólo en el grupo de tunelización mecánica. Este hecho constata la gran variabilidad aberrométrica de los implantes de ICRS en nuestro grupo de disección mecánica y, por tanto, la limitación que presentaba al respecto, la cual podría estar en relación con la mayor limitación para la corrección de la AVCC.

6.- En las córneas con implantes de ICRS empleando láser de femtosegundo fue detectada una reducción significativa del valor RMS correspondiente al astigmatismo corneal. Otros índices aberrométricos corneales también fueron reducidos con la cirugía aunque no se halló significación estadística en los mismos, siendo esta tendencia idéntica a la reportada en el único estudio previo valorando los cambios aberrométricos que acontecen tras implante de ICRS[42 (ref 13)]. El hallazgo más relevante fue la ausencia de variabilidad de los resultados aberrométricos corneales durante el período de 24 meses de seguimiento.

7.- Diversos motivos podrían justificar las diferencias detectadas a nivel del efecto visual, refractivo y aberrométrico corneal tras el implante de ICRS en los dos grupos analizados en función de la técnica de implante. Uno de ellos podría ser el uso de dos tipos diferentes de segmentos en ambos grupos, Intacs y KeraRing (diferente sección y diámetro de implante). Otro de los motivos podría ser la diferente proporción de casos de queratocono avanzado incluidos en cada grupo, los cuales suelen tener una mayor probabilidad de complicaciones y un peor pronóstico visual[42 (ref 17,20)]. Por ello se decidió llevar a cabo un análisis adicional de los resultados, comparando casos de la misma severidad e implantados con el mismo tipo de segmento. Dicho análisis sólo fue posible en casos de queratocono incipiente o moderado implantados con Intacs (previa constatación de que ambos subgrupos eran comparables, Intacs vs. KeraRing en queratocono incipiente-moderado) (Figura 14), ya que no existían casos suficientes para realizar estadística consistente en el resto de subgrupos. Esta comparativa mostró que no existían diferencias significativas a nivel visual y de corrección astigmática refractiva entre grupos. Sin embargo, diferencias significativas entre grupos en el nivel de coma primario o de aberraciones “coma-like” fueron detectadas a los 3, 6 y 12 meses tras la cirugía, con los peores resultados en el grupo de disección mecánica (Figura 14). Este resultado constata la tendencia general y, por tanto, deja patente la mayor limitación en el control aberrométrico corneal con el procedimiento de disección mecánica.

8.- Posibles factores en relación con el mejor control aberrométrico corneal tras el implante de ICRS con el procedimiento de tunelización guiado por láser de femtosegundo: menor trauma quirúrgico, mayor control de la complicada biomecánica de la córnea con queratocono, menor dependencia de la habilidad manual del cirujano (se evita una gran fuente de variabilidad) y creación de una tunelización en un mismo plano que permite un mejor posicionamiento de los segmentos.

9.- Se halló una correlación significativa y fuerte de la AVCC postoperatoria (6 y 12 meses) con algunos parámetros aberrométricos corneales sólo en el grupo de ojos implantados con ICRS mediante disección mecánica: RMS alto orden, coma primario, aberraciones “coma-like” y aberraciones “spherical-like”. Hay que tener en cuenta que el procedimiento mecánico presentaba una mayor limitación en el control aberrométrico corneal, siendo por tanto el resultado visual con esta técnica muy sensible al nivel de aberraciones corneales existente de partida.

10.- La tasa de complicaciones como la extrusión del segmento, la neovascularización de los canales y la presencia de “corneal melting” era algo mayor en aquellos ojos con implante de ICRS mediante disección mecánica, aunque las diferencias entre grupos no alcanzaron significación estadística. Esta tendencia a una mayor presencia de complicaciones pudo ser un factor adicional que contribuyera a la mayor limitación aberrométrica corneal observada con el procedimiento mecánico.

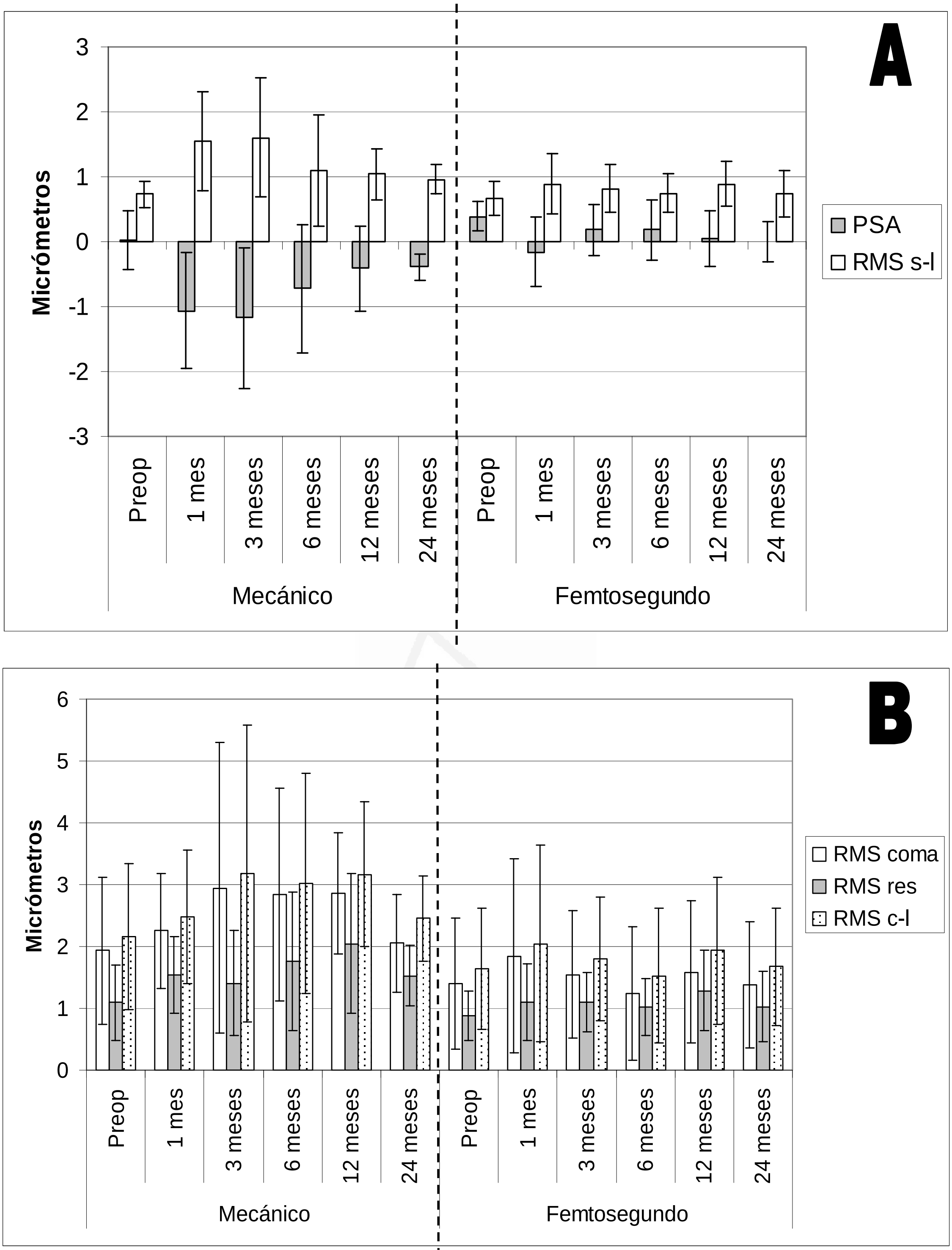


Figura 14.- Comparativa de los resultados aberrométricos tras implante de Intacs en ojos con queratocono incipiente o moderado en función de la técnica de implante: tunelización mecánica (izquierda) y tunelización asistida con láser de femtosegundo (derecha). A. Cambios en la aberración esférica primaria (PSA, barras grises) y las aberraciones "spherical-like" (RMS s-l, barras blancas). B. Cambios en el coma primario (RMS coma, barras blancas), en las aberraciones de alto orden residuales RMS res, barras blancas) y las aberraciones "coma-like" (RMS c-l, barras punteadas)

4.1.2.- Resultados refractivos y aberrométricos corneales tras el implante de ICRS en DMP *[Piñero DP, Alio JL, Morbelli H, Uceda-Montanes A, El Kady B, Coskunseven E, Pascual I. Refractive and corneal aberrometric changes after intracorneal ring implantation in corneas with pellucid marginal degeneration. Ophthalmology 2009; 116: 1656-64].*

En este estudio, tal y como se mencionó con anterioridad, se han analizado los cambios visuales, refractivos y aberrométricos corneales que tenían lugar tras el implante de dos tipologías de ICRS en córneas con DMP. A continuación se enumeran los principales hallazgos y reflexiones extraídas a partir de este estudio.

1.- Reducción estadísticamente significativa del cilindro tras el implante de ICRS en córneas con DMP. Resulta compleja la comparación con estudios previos, ya que hasta el momento sólo se han reportado casos clínicos aislados o pequeñas muestras de casos (máximo 8)[43 (ref 8-14)]. De todos modos, nuestro hallazgo es concordante con las tendencias previamente reportadas[43 (ref 8-14)]. Hay que resaltar que se logró de media una reducción del cilindro refractivo de aproximadamente un 50%.

2.- También se pudo constatar la existencia de un cambio significativo de la esfera. En concreto, se apreció una tendencia clara a la hipermetropía postoperatoria. Este resultado puede parecer coherente ya que en la DMP el defecto predominante es el astigmatismo, con una gran mayoría de casos con esferas positivas o próximas a cero. Si se induce un aplanamiento corneal central en casos como estos, el cambio refractivo hacia una mayor hipermetropía parecería totalmente justificado. Sin embargo, esta teoría no fue constatada en nuestra muestra, ya que hubo casos de astigmatismo miópico con una importante esfera positiva postoperatoria. Por lo tanto, quedó constancia de la falta de predictibilidad de los ICRS empleando el nomograma estándar para la corrección de la esfera en las córneas con DMP. Podría ser causa de este hecho un posible efecto de desalineación de la corrección astigmática, lo cual tendría un impacto relevante e impredecible en la esfera.

3.- Tal y como se esperaba y en concordancia con trabajos previos[43 (ref 8-14)], se pudo apreciar un aplanamiento corneal central significativo. En concreto, sólo se redujo significativamente el poder dióptrico más curvo de la córnea, lo que concuerda con la reducción significativa del astigmatismo tanto a nivel refractivo como corneal.

4.- Se apreció una reducción significativa de las aberraciones corneales coma-like y de alto orden residual, que justificaría el gran porcentaje de casos que experimentó ganancia de líneas de AVCC (55.55% de los casos) (Figura 15).

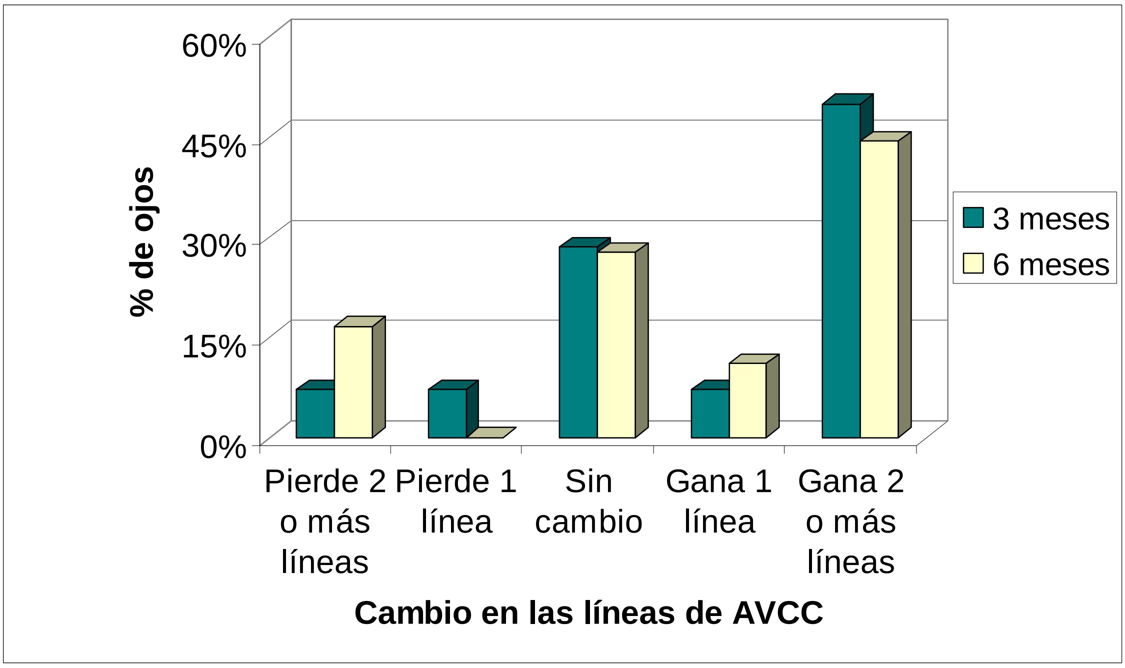


Figura 15.- Cambios a nivel postoperatorio de la AVCC expresados en formato de líneas

5.- Comparación de resultados en función de la técnica de implantación: hipermetropización significativa al mes tras la cirugía con el procedimiento de tunelización mecánico, mientras que la esfera se redujo con el procedimiento asistido por láser de femtosegundo. Hay que tener en cuenta que preoperatoriamente existían diferencias estadísticamente significativas a nivel de la esfera entre ambos grupos de ojos, existiendo un mayor porcentaje de casos con esfera positiva preoperatoriamente en el grupo de ojos intervenidos con el procedimiento de disección mecánica. En lo que respecta al cilindro, éste fue efectivamente reducido con ambas técnicas quirúrgicas, no existiendo diferencias estadísticamente significativas entre ellas. La comparación de datos aberrométricos no se pudo realizar ya que todos los casos examinados con el sistema topográfico CSO habían sido intervenidos con el procedimiento de tunelización asistido con láser de femtosegundo.

6.- Se obtuvo una correlación inversa, fuerte y estadísticamente significativa entre el valor RMS correspondiente al astigmatismo corneal preoperatorio y la AVCC a los 6 meses, así como entre la aberración esférica primaria preoperatoria y la AVCC a los 6 meses. En contraste, no se halló correlación entre el nivel preoperatorio de coma primario y la AVCC postoperatoria. Por lo tanto, el nivel de astigmatismo y aberración esférica primaria corneal actuaban como factores limitantes del resultados visual.

7.- El explante de los segmentos se llevó a cabo en un total de 4 ojos (19,0%). En todos los casos el explante se había indicado por la existencia de un empeoramiento visual progresivo durante el seguimiento. Se obtuvieron diferencias en el límite de la significación estadística entre los casos de explante y los de no explante para el valor cilíndrico manifiesto preoperatorio. Esto refuerza la idea de la mayor limitación de estos implantes en córneas con elevado nivel de toricidad.

4.1.3.- Implante de ICRS en corneas con ectasia tras cirugía refractiva LASIK *[Piñero DP, Alio JL, Uceda-Montanes A, El Kady B, Pascual I. Intracorneal ring segment implantation in corneas with post-laser in situ keratomileusis keratectasia. Ophthalmology 2009; 116:1665-74].*

En este estudio, tal y como se mencionó con anterioridad, se han analizado los cambios visuales, refractivos y aberrométricos corneales que tenían lugar tras el implante de dos tipologías de ICRS en córneas con ectasia post-LASIK. A continuación se enumeran los principales hallazgos y reflexiones extraídas a partir de este estudio.

1.- Se apreció una reducción no significativa estadísticamente ni a nivel de la esfera (cambio medio a los 6 meses: 0,52 D) ni del equivalente esférico (cambio medio a los 6 meses: 0,93 D) tras la cirugía. Esto contrasta con lo reportado previamente por otros autores, que sí apreciaron un cambio estadísticamente significativo a nivel del equivalente esférico tras el implante de ICRS[44 (ref 18,22)]. Dos motivos podrían justificar tal diferencia: la inclusión de casos ectásicos de mayor severidad en la presente muestra y el uso de otros nomogramas diferentes en alguno de los estudios previos. Por otro lado, también se apreció una regresión del limitado efecto corrector de la esfera al final del seguimiento, lo que sugiere la incapacidad de estos implantes para la paralización del proceso ectásico.

2.- Reducción progresiva significativa del cilindro refractivo (cambio medio a los 6 meses: 0,83 D, a los 24 meses: 1,56 D), al igual que en series previas[44 (ref 19,20)].

3.- No se detectaron cambios significativos en la AVSC, pero sí una mejora significativa en la AVCC (mejora de 2 líneas o más en la AVCC en el 38,89% de los casos a los 6 meses y en un 60% de los casos a los 24 meses). Mejoras similares también habían sido reportadas por otros autores en series previas[44 (ref 13,17-24)].

4.- Se observó un aplanamiento corneal central significativo en el período postoperatorio inicial (cambio medio de 1,54 D), con una regresión posterior del mismo (cambio medio de 1,74 D) (Figura 16). Esta regresión era concordante con el incremento miópico detectado durante el período final del seguimiento.

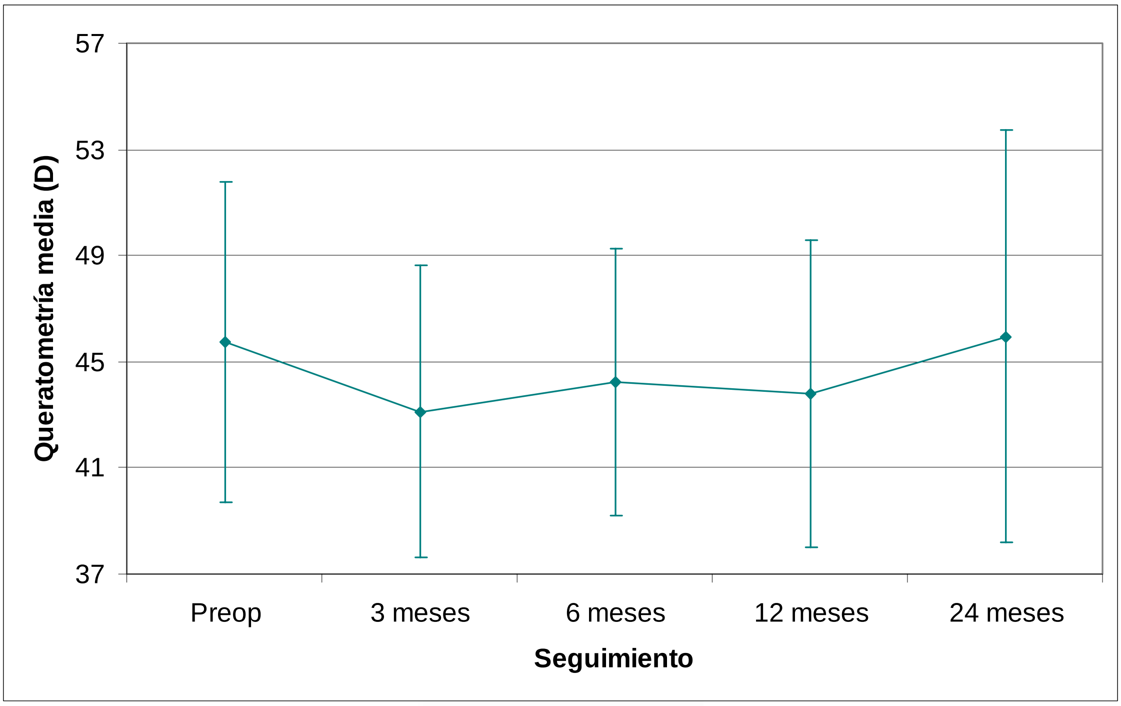


Figura 16.- Cambios a nivel de la queratometría media durante el seguimiento de 24 meses tras el implante de ICRS

5.- A los 6 meses tras la cirugía sólo se apreció una reducción estadísticamente significativa en el valor RMS correspondiente a las aberraciones "coma-like". También se apreciaron reducciones en los valores RMS para el astigmatismo y para el coma primario, pero estos cambios no alcanzaron significación estadística. Esta mejoría a nivel aberrométrico corneal justificaba en parte la mejoría significativa de la AVCC. A su vez, se pudo observar una tendencia hacia la negativización de la aberración esférica primaria.

6.- Se comprobó que existía una correlación estadísticamente significativa entre la AVCC a los 6 meses tras la cirugía y los niveles preoperatorios de aberración esférica primaria (r=0,71), coma primario (r=-0,92) y aberraciones "coma-like" (r=-0,92). Por tanto, la presencia de aberración comática y esférica primaria positiva a nivel preoperatorio era un factor limitante del resultado visual con los ICRS.

7.- Los valores RMS en el postoperatorio inmediato para las aberraciones corneales "spherical-like", "coma-like" y de alto orden residual eran superiores en el grupo de ojos en los que se empleó el procedimiento mecánico de implantación, siendo únicamente significativa la diferencia entre grupos para el valor RMS correspondiente a las aberraciones "spherical-like". También se pudo comprobar que existía una tendencia no significativa hacia la aberración esférica negativa en el grupo de ojos intervenidos empleando la tunelización mecánica. Por lo tanto, al igual que sucedía en los casos de queratocono, la técnica quirúrgica para el implante de los ICRS parece jugar un papel clave en el control aberrométrico logrado con los ICRS en la ectasia post-LASIK. Se postulan las mismas causas para este hecho que en el caso de las córneas con queratocono.

8.- No se hallaron diferencias estadísticamente significativas a nivel preoperatorio ni 1 mes tras la cirugía entre córneas implantadas con Intacs y córneas implantadas con KeraRing. Hay que tener en cuenta que el tamaño muestral con cada tipo de implante era limitado y esto podría ser una importante limitación para este resultado.

9.- Se llevó a cabo el explante de los segmentos en un total de 6 ojos (17,6%). En 3 de esos ojos el explante se indicó por la existencia de problemas visuales postoperatorios (pérdida de AVCC y/o insatisfacción por parte del paciente con la calidad de visión alcanzada con los implantes). En cambio, en los otros 3 casos el explante se llevó a cabo por problemas de migración o extrusión de los segmentos, todos ellos intervenidos con el procedimiento de tunelización mecánica. La esfera y el cilindro medio resultaron superiores en el grupo de ojos sin explante, aunque las diferencias no alcanzaron significación estadística. En lo que respecta a la aberrometría corneal, todos los coeficientes aberrométricos preoperatorios resultaron más elevados en el grupo de ojos con explante, aunque las diferencias no alcanzaron significación estadística probablemente debido al pequeño tamaño muestral del grupo de ojos con explante (sólo 6).

4.1.4.- Comparativa de resultados refractivos y aberrométricos corneales con dos tipologías diferentes de ICRS en córneas con ectasia incipiente o moderada *[Piñero DP, Alió JL, El Kady B, Pascual I. Corneal aberrometric and refractive performance of 2 intrastromal corneal ring segment models in early and moderate ectatic disease J Cataract Refract Surg 2010; 36: 102–9].*

En este estudio, tal y como se mencionó con anterioridad, se ha realizado un estudio comparativo de los resultados visuales, refractivos y aberrométricos corneales en córneas ectásicas implantadas con Intacs y KeraRing en un período de seguimiento de 6 meses. Ambos grupos contenían casos de ectasia incipiente y/o moderada de características visuales, refractivas, queratométricas y aberrométricas corneales comparables. A su vez, similares porcentajes de queratocono, DMP y ectasia post-LASIK estaban presentes en ambos grupos (mayor porcentaje de casos de queratocono). A continuación se enumeran los principales hallazgos y reflexiones extraídas a partir de este estudio.

1.- Tal y como cabía esperar de acuerdo a los tres estudios previos de esta tesis y a los realizados por otros autores[45 (ref 2,4,5,9,10,12)], se pudo constatar la existencia de una mejora de la situación refractiva (esfera y cilindro) tras el implante de ambos tipos de ICRS (Figura 17). Sólo la mejoría a nivel del cilindro refractivo no fue estadísticamente significativa en el grupo de córneas implantadas con Intacs. Otros autores, en cambio, en estudios previos sí apreciaron una mejoría significativa a nivel del astigmatismo refractivo tras el implante de Intacs[45 (ref 2,9-12,19,43)] (Figura 17). La principal razón para esta discrepancia son las diferencias existentes en las muestras analizadas. Hay que tener en cuenta que la mayoría de los estudios previos incluían casos de queratocono grado III y IV, en los que el nivel de astigmatismo preoperatorio es elevado y probablemente se pueda lograr un mayor efecto reductor a pesar de la aparente limitación correctora cilíndrica de los segmentos tipo Intacs.

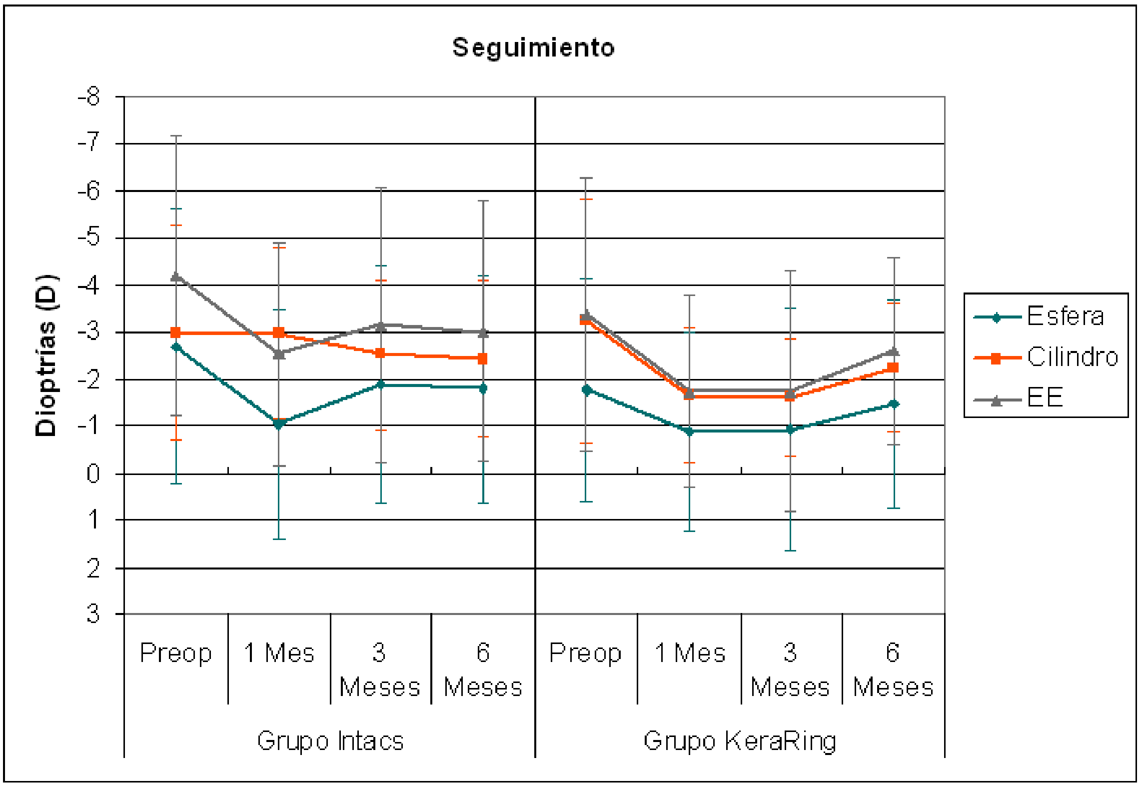


Figura 17.- Cambios a nivel refractivo en los dos grupos analizados: grupo I (córneas implantadas con Intacs) y grupo K (córneas implantadas con KeraRing)

2.- Motivos para la limitación de la corrección astigmática con Intacs: posición de los segmentos con respecto al centro de la córnea y tipo de geometría. Hay que tener en cuenta que los segmentos tipo Intacs se posicionan más lejos del centro geométrico de la córnea que los tipo KeraRing, lo cual supone una limitación para el efecto de los mismos. Esta limitación fue puesta de manifiesto en una simulación numérica previamente reportada, empleando un modelo geométrico[45 (ref 38)]. Sin embargo, dicha simulación presentaba algunas limitaciones, no incluyendo todas las tensiones que tienen lugar en la red estromal de colágeno tras el implante de los ICRS.

3.- La AVSC mejoró significativamente en el grupo de córneas implantadas con KeraRing, mientras que no fue así en el grupo implantado con Intacs, lo cual resulta coherente teniendo en cuenta la mayor corrección astigmática lograda con los segmentos tipo KeraRing.

4.- Tal y como se esperaba, teniendo en cuenta los tres estudios previos de la presente tesis y trabajos previos de otros autores[45 (ref 2,4-12,15,22,29,33,44)], se observó un aplanamiento corneal central significativo con ambos tipos de implante, el cual justifica el cambio observado a nivel de la esfera.

5.- Pudo constatarse la existencia de un comportamiento aberrométrico de la córnea diferente tras el implante de ambas tipologías de ICRS. En concreto, los segmentos tipo Intacs indujeron una negativización significativa de la aberración esférica primaria al mes tras la cirugía, mientras que los segmentos tipo KeraRing indujeron un cambio pequeño, no significativo y hacia signo positivo. Dicha diferencia significativa al mes desapareció progresivamente durante el resto del seguimiento. Posiblemente la geometría del segmento sea el factor condicionante de esta diferencia, ya que es el responsable de la inducción de distinto tipo de tensiones en la estructura estromal. Como resultado curioso, cabe mencionar la similitud apreciada en los cambios aberrométricos a nivel de la aberración comática con ambos tipos de segmentos.

4.2.- RESULTADOS DE LOS TRABAJOS EN RELACIÓN CON EL SEGUNDO OBJETIVO GENERAL

4.2.1.- Biomecánica corneal, refracción y aberrometría corneal en queratocono: estudio integrado *[Piñero DP, Alio JL, Barraquer RI, Michael R, Jiménez R. Corneal biomechanics, refraction, and corneal aberrometry in keratoconus: an integrated study. Invest Ophthalmol Vis Sci 2010; 51: 1948–55].*

Queda patente de acuerdo a los 4 primeros estudios de la presente tesis la relevancia del perfil aberrométrico de la superficie corneal anterior como factor pronóstico y limitante del resultado visual obtenido con los ICRS en córneas ectásicas. Estos implantes parecen tener un efecto más limitado e incluso nulo en aquellas córneas afectas de mayor cantidad de aberraciones ópticas. Una hipótesis de trabajo que planteamos en este punto de la tesis fue la posibilidad de que dichas alteraciones aberrométricas y, por tanto, de la regularidad de la superficie corneal anterior, fueran la consecuencia, y por tanto signo, de la alteración biomecánica inherente de la córnea. En otras palabras, la existencia de una gran debilidad tectónica supondría la susceptibilidad del tejido corneal a las presiones inducidas sobre él por parte del contenido intraocular o los párpados, viéndose deformado con mayor facilidad por éstas y presentando, por tanto, una irregularidad más significativa. Como de inicio se iba a plantear la modelización del efecto de los ICRS en un tipo específico de anomalía ectásica, se decidió estudiar esta hipótesis exclusivamente para el queratocono, que resulta ser la anomalía ectásica de mayor prevalencia en la población.

El problema de la presente investigación residía en como valorar la biomecánica corneal y si disponíamos de una muestra de datos retrospectiva con medidas clínicas de biomecánica corneal. Tras una extensa y exhaustiva búsqueda bibliográfica en PubMed, pudimos comprobar que existían diversos estudios que habían intentado definir y probar metodologías para la caracterización de la biomecánica corneal, siendo todas ellas difíciles de aplicar en la práctica clínica debido a su gran invasividad (por ejemplo, inyección de solución salina en cámara anterior o técnicas de indentación corneal)[46 (ref 13,18-22)]. Hasta la fecha, sólo existe un dispositivo comercializado para la medición de las propiedades biomecánicas de la córnea in vivo de modo no invasivo, el sistema Ocular Response Analyzer (ORA), el cual ya fue descrito en detalle en el apartado Material y métodos. Se basa en un proceso de aplanación bidireccional de la córnea y proporciona dos parámetros de medida, CH y CRF. Estos parámetros se hallan significativamente alterados en córneas con una conocida alteración biomecánica[46 (ref 9,10,13,23-27)], pero no se conoce aún con exactitud su significado físico y su relación con las propiedades mecánicas estándar empleadas para la caracterización de los sistemas elásticos (módulo de Young). A pesar de esta limitación de concepto, se recurrió a la recopilación de datos medidos con el sistema ORA, ya que eran las únicas medidas en relación con la biomecánica corneal que estaban disponibles.

A continuación se enumeran los principales hallazgos y reflexiones extraídas a partir de este estudio.

1.- Se obtuvo una correlación negativa moderada entre CRF y curvatura media corneal. Hay que tener en cuenta que la queratometría media siempre ha sido considerada como un criterio básico para caracterizar la severidad del queratocono[46 (ref 6)] (Figura 18).

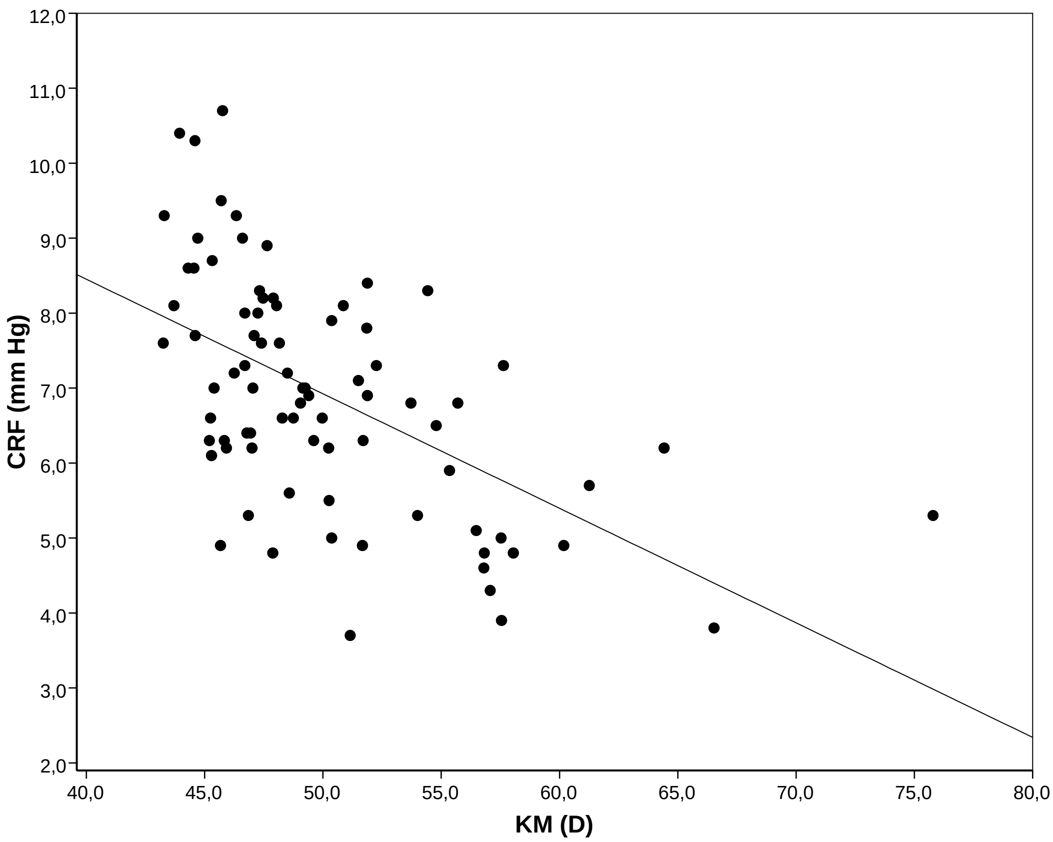


Figura 18.- Diagrama de dispersión que muestra la relación existente entre CRF y KM. La línea recta de ajuste fue obtenida por medio del método de los mínimos cuadrados (R^2: 0,316)

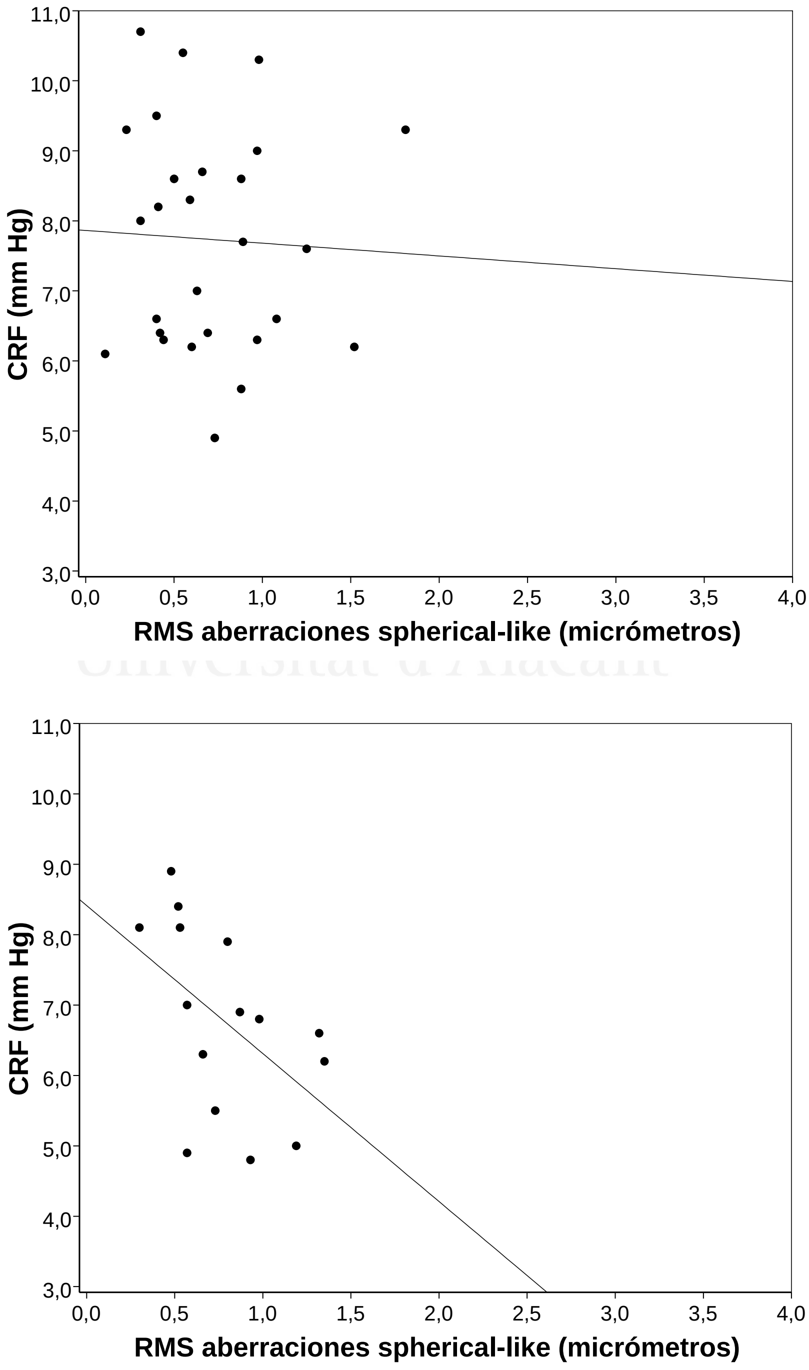
2.- Se hallaron correlaciones estadísticamente significativas aunque débiles entre el parámetro CRF y diferentes coeficientes aberrométricos corneales (alto orden, coma primario, “spherical-like” y “coma-like”). Todas estas correlaciones eran de signo negativo, por lo que indicaban que cuanto mayor era la magnitud de las aberraciones, menor era el valor del parámetro CRF. Además hay que tener en cuenta que existía una especial variabilidad de los datos aberrométricos en los casos con CRF moderado (6-7 mm Hg), lo que contribuía a debilitar las correlaciones entre aberrometría y CRF. En estudios previos se ha podido constatar que cuanto mayor era la severidad de la patología de acorde a las alteraciones refractivas, queratométricas, paquimétricas y biomicroscópicas, mayores eran las cantidades de aberraciones ópticas de la superficie corneal anterior, especialmente las aberraciones “coma-like”[46 (ref 5-8)].

3.- El parámetro CH no correlacionaba significativamente con ningún parámetro refractivo, queratométrico, paquimétrico o aberrométrico corneal. Por tanto, parece ser un parámetro con una mayor limitación para la caracterización de los cambios que tienen lugar en la córnea queratocónica y, por tanto, con una menor capacidad diagnóstica. Este hecho concuerda con lo establecido por un modelo biomecánico previo que trataba de describir el efecto de la viscosidad y la elasticidad del tejido corneal en los parámetros CH y CRF[46 (ref 17)]: el valor de CH en queratocono resultaba muy variable ya que en córneas con esta patología un valor bajo de CH podía representar a una córnea con un alto o bajo módulo de elasticidad, dependiendo del nivel de viscosidad asociado al material.

4.- El análisis de regresión lineal múltiple puso de manifiesto que el 40% de la varianza en el valor de CRF podía ser explicada mediante la potencia queratométrica más plana y el nivel de aberraciones corneales “spherical-like”. Por lo tanto, se pudo establecer una relación entre el parámetro biomecánico CRF y el nivel de alteración queratométrica central y aberrométrica de la superficie corneal anterior. Se ha establecido que debido a su definición y forma de cálculo el parámetro CRF podría estar más influenciado por el componente elástico del tejido corneal.

5.- No se hallaron correlaciones significativas entre los parámetros biomecánicos obtenidos con el sistema ORA y los datos visuales y refractivos. Hay que tener en cuenta que no siempre el status refractivo va a ser un indicativo de la alteración biomecánica subyacente y además la refracción subjetiva en el queratocono resulta en muchos casos de baja fiabilidad ya que en aquellas situaciones en las que existe una pérdida significativa de la calidad visual debido al incremento aberrométrico corneal resulta muy difícil para el paciente definir el punto de máximo enfoque[46 (ref 28)].

6.- Al comparar los valores biomecánicos obtenidos entre grupos de córneas con diferente grado de severidad del queratocono de acuerdo al sistema de gradación de Amsler-Krumeich y Alió-Shabayek (ligera o grado I, moderada o grado II y severa o grado III-IV), diferencias significativas entre grupos se hallaron para los parámetros biomecánicos CH y CRF. Sólo para el parámetro CRF se hallaron diferencias estadísticamente significativas entre todos los pares de grupos, con valores progresivamente menores a medida que era mayor la severidad de la enfermedad.



A

B

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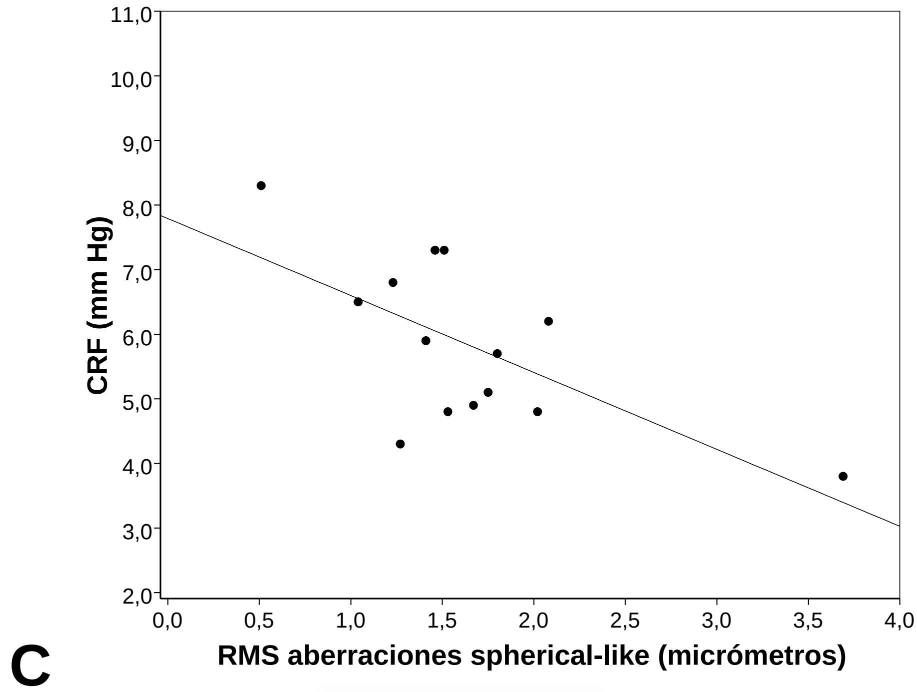


Figura 19.- Diagrama de dispersión que muestra la relación existente entre CRF y el valor RMS para las aberraciones corneales spherical-like en función de la severidad del queratocono: A, ligera; B, moderada; C, severa. La línea recta de ajuste fue obtenida por medio del método de los mínimos cuadrados (A, R^2< 0,01; B, R^2: 0,25; C, R^2: 0,43).

7.- Se halló una correlación inversa, fuerte y estadísticamente significativa entre la magnitud de las aberraciones corneales “spherical-like” y el parámetro CRF en córneas con queratocono severo (Figura 19). Sin embargo, esta correlación inversa resultó moderada y muy débil en los grupos de córneas con severidad moderada y ligera, respectivamente (Figura 19). No se puede establecer una explicación sencilla y concreta para este hecho ya que el proceso ectásico de la córnea es un proceso multifactorial, existiendo diversas variables interactuando. Lo que está claro es que la alteración biomecánica de la córnea representada por un valor CRF bajo convierte a la córnea en una estructura más susceptible a presiones externas, tales como la ejercida por el contenido intraocular o los párpados.

***4.2.2.- Modificación y ajuste del astigmatismo en ojos con queratocono implantados con ICRS** [Piñero DP, Alio JL, Teus MA, Barraquer RI, Michael R, Jiménez R. Modification and refinement of astigmatism in keratoconic eyes implanted with intracorneal ring segments. J Cataract Refract Surg 2010 (accepted for publication)].*

Una vez conocida la relación entre aberrometría corneal anterior y biomecánica de la córnea y previamente al desarrollo de la modelización matemática del efecto de los ICRS se procedió al análisis vectorial de los cambios astigmáticos que tenían lugar tras el implante de ICRS en queratocono. Teniendo en cuenta las limitaciones puestas de manifiesto en los trabajos previos de la presente tesis por parte de la técnica de tunelización mecánica y de los segmentos tipo Intacs, se decidió realizar el estudio vectorial de los cambios astigmáticos tras el implante de KeraRing mediante tunelización guiada por láser de femtosegundo. Hasta el momento, en nuestros trabajos previos así como en el resto de la literatura científica sobre los ICRS, no se había realizado un análisis de los cambios astigmáticos corneales, considerando el carácter vectorial de la variable astigmatismo. En concreto, en este trabajo se ha empleado el método vectorial de Alpins[47 (ref 23,24)] para analizar dichos cambios, el cual está ampliamente descrito en el artículo correspondiente. Para evitar el factor subjetividad de la refracción, sobre todo en los casos de queratocono más avanzado, se han analizado específicamente los cambios a nivel del astigmatismo corneal central. Hay que tener en cuenta la relevancia óptica del mismo en los casos de queratocono y que tanto la incisión como la posición de los segmentos se planifican a partir de este astigmatismo. A continuación se enumeran los principales hallazgos y reflexiones extraídas a partir de este estudio.

1.- Los cambios visuales, refractivos, queratométricos y aberrométricos corneales apreciados tras el implante de KeraRing en esta muestra de ojos con queratocono eran semejantes a los obtenidos en el primer y cuarto estudio de la presente tesis y, a su vez, concordantes también con la literatura científica previa acerca del tema.

2.- Reducción estadísticamente significativa del astigmatismo corneal en concordancia con la reducción significativa del astigmatismo refractivo, pero existiendo una clara tendencia a la infracorrección.

3.- Con el método de Alpins se analizaron diversos vectores y parámetros escalares, que son los siguientes: vector cambio astigmático objetivo (targeted induced astigmatism, TIA), vector astigmatismo inducido con la cirugía (surgically induced astigmatism, SIA), vector diferencia entre TIA y SIA (difference vector, DV), la magnitud del error calculada como la diferencia aritmética entre los módulos de los vectores SIA y TIA (magnitude of error, ME), el ángulo de error formado entre los vectores TIA y SIA (angle of error, AE), vector factor de aplanamiento calculado como la cantidad de astigmatismo reducido en el meridiano adecuado (flattening effect, FE) y vector torque calculado como el cambio astigmático inducido debido al desalineamiento del efecto corrector (torque, TRQ). A continuación se enumeran los principales hallazgos de este análisis vectorial:

-La magnitud del vector SIA fue significativamente inferior a la del vector TIA. Por lo tanto, se produjo una infracorrección del astigmatismo corneal que se mantuvo durante todo el seguimiento (infracorrección media de 1,82 D a los 12 meses tras la cirugía).

-El módulo del vector DV superaba la dioptría en la mayoría de los casos, siendo la orientación de dicho vector muy variable en función de cada caso e incluso entre visitas consecutivas en un mismo caso (Figura 20). Este hecho ponía de manifiesto que existían otros parámetros que debían ser considerados en futuros nomogramas, tales como índices descriptores de la biomecánica corneal ya que el uso de los datos refractivos y topográficos no parecía ser suficiente para lograr una predictibilidad del resultado aceptable. Además la variación en algunos casos del vector DV durante el seguimiento podría suponer la existencia de cambios biomecánicos en estas córneas aún tras el implante de los ICRS, ya que éstos en sí no modifican la propiedades de la estructura del colágeno corneal en toda su extensión.

-La ME media fue negativa, lo que corroboraba la tendencia a la infracorrección del implante de KeraRing con el nomograma empleado. Aún así, existieron casos que mostraron la tendencia justamente opuesta, lo que volvía a corroborar la falta de predictibilidad del actual nomograma y la necesidad de incluir variables nuevas en futuros desarrollos.

-El vector SIA y FE debían ser coincidentes si el efecto corrector del astigmatismo se hubiera realizado en el eje adecuado. Sin embargo, en la presente muestra este hecho no sucedió, confirmando la inadecuada orientación del efecto de los implantes KeraRing en estas córneas con queratocono durante todo el período de seguimiento.

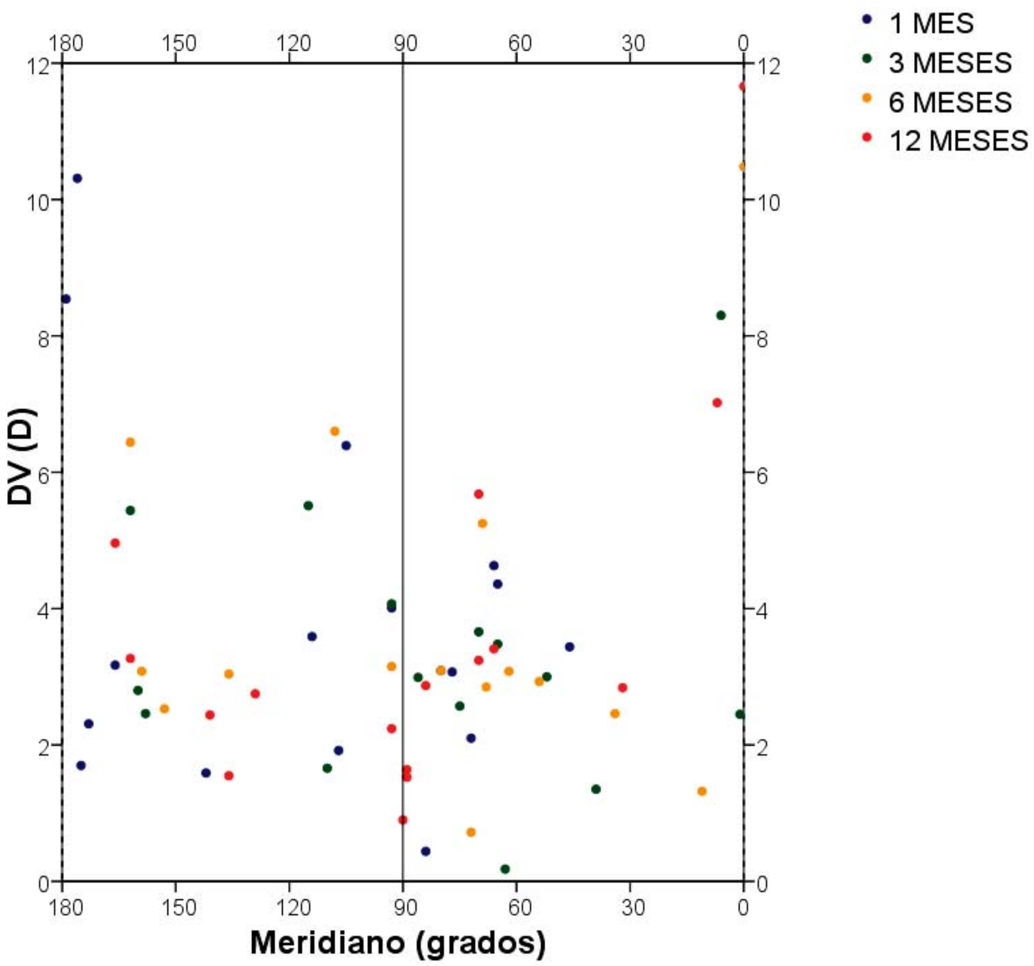


Figura 20.- Diagrama mostrando el módulo y orientación del vector DV para los casos analizados durante el seguimiento de 12 meses

-Por otro lado, el vector TRQ debía ser nulo si el efecto astigmático corrector se hubiera realizado en el eje adecuado. Sin embargo, como cabía esperar teniendo en cuenta los resultados para el vector FE, esto no fue así, sino que se mantuvo durante el seguimiento con un valor de módulo próximo a la unidad. Tal y como sucedió con otros vectores, también se pudo apreciar una gran variabilidad, con valores próximos a cero y valores mayores de 2 D. En cambio, sí que se pudo apreciar una tendencia constante en todos los casos y durante todo el seguimiento: el signo positivo de este vector. Este hecho representa que dicho vector presentaba una orientación a 45º de la orientación del SIA siguiendo la dirección de las agujas del reloj. Por lo tanto, dejó patente la inadecuación de la posición del implante, ya que no se estaba teniendo en cuenta algunas propiedades estructurales de la córnea queratocónica que necesitan ser conocidas en detalle.

-Por último, el AE fue de media negativo, lo que indicaba una desalineamiento del efecto corrector en dirección de las agujas del reloj con respecto al eje objetivo. Al igual que con el resto de parámetros, la variabilidad del AE resultó ser muy significativa.

4.- Correlación inversa significativa entre astigmatismo corneal preoperatorio y la ME (r=-0,74, 12 meses) (Figura 21) y, a su vez, correlación directa también significativa entre el módulo del vector DV y el astigmatismo corneal preoperatorio (r=0.64, 12 meses). Esto implicaba que la presencia de un mayor astigmatismo corneal suponía la presencia de un mayor nivel de infracorrección. Es posible que la córnea queratocónica con elevada toricidad presentara una organización específica de la malla de colágeno que limitara el efecto de los segmentos con el nomograma empleado.

5.- Correlación positiva y estadísticamente significativa entre los módulos de los vectores SIA y FE y dos coeficientes aberrométricos corneales, el valor RMS para las aberraciones de alto orden residual y el valor RMS para las aberraciones "spherical-like". Estas correlaciones sólo se mantuvieron al inicio del seguimiento ya que al final del mismo se volvieron débiles y sin significación estadística asociada. A mayor SIA, mayor cantidad de aberraciones de alto orden era inducida inicialmente, pero luego este efecto se diluía, posiblemente debido a cambios biomecánicos que compensaban o eliminaban dicha correlación.

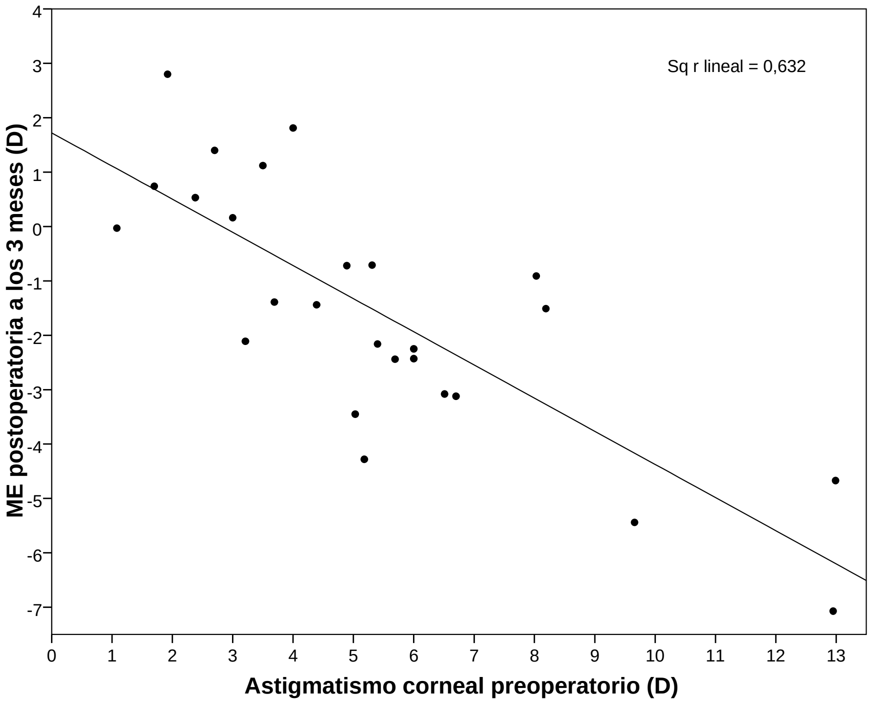


Figura 21.- Diagrama de dispersión mostrando la relación existente entre el astigmatismo corneal preoperatorio y la magnitud de error (ME) en la corrección del mismo. La línea recta de ajuste fue obtenida por medio del método de los mínimos cuadrados (R^2: 0,63)

4.2.3.- Modelización del efecto de los ICRS en queratocono empleando datos refractivos, queratométricos y aberrométricos corneales *[Piñero DP, Alio JL, Teus MA, Barraquer RI, Uceda-Montañés A. Modelling the intracorneal ring segment effect in keratoconus using refractive, keratometric and corneal aberrometric data. Invest Ophthalmol Vis Sci 2010 (accepted for publication)].*

Teniendo en cuenta las limitaciones puestas de manifiesto en los trabajos previos de la presente tesis por parte de la técnica de tunelización mecánica y de los segmentos tipo Intacs, se decidió realizar la modelización matemática del efecto de los segmentos KeraRing implantados mediante tunelización guiada por láser de femtosegundo. Dicha modelización sólo se llevó a cabo para una determinada longitud de arco del segmento (160º), ya que como se ha mencionado anteriormente, los segmentos tipo KeraRing están disponibles en varios tipos de longitud de arco. En futuros estudios se tratará de incluir en el modelo este tipo específico de variable.

En la modelización llevada a cabo se ha tratado de relacionar el espesor de los segmentos superior e inferior con el efecto refractivo y aberrométrico logrado, así como con la condiciones de partida de la córnea. Para llevar a cabo este proceso, se han tenido en cuenta las siguientes notaciones:

-Segmento superior se considera todo aquel segmento cuyo centro geométrico se halle localizado en la mitad superior de la cornea

-Segmento inferior se considera todo aquel segmento cuyo centro geométrico se halle localizado en la mitad inferior de la cornea

-Se considera el espesor de un segmento cero cuando uno de los dos segmentos, el superior o el inferior, no ha sido implantado.

Hay que tener en cuenta que para el desarrollo de esta modelización se han tenido en cuenta los cambios visuales, refractivos y aberrométricos corneales que tuvieron lugar tres meses tras el implante de los segmentos con el fin de caracterizar el efecto del segmento en sí mismo y evitar el efecto de posibles cambios biomecánicos posteriores como consecuencia del progreso del proceso ectásico[48 (ref 2,34)].

A continuación se enumeran los principales hallazgos y reflexiones extraídas a partir de este estudio.

1.- Diferentes correlaciones estadísticamente significativas fueron detectadas entre los espesores de los segmentos y ciertas medidas clínicas como el cambio en la queratometría media o el cambio en las aberraciones corneales de alto orden, aunque todas ellas fueron débiles o moderadas. A su vez, también se comprobó que existían correlaciones estadísticamente significativas aunque limitadas entre el cambio inducido en la queratometría media y en la refracción y ciertos parámetros preoperatorios, como la AVSC, la AVCC, la queratometría media o la esfera. Este análisis de correlaciones dejó patente que varios factores estaban implicados e influenciaban en el efecto logrado con los segmentos KeraRing de 160º de arco. Por lo tanto, era necesario el uso de un análisis que tratara de relacionar las diferentes variables implicadas y por ello se llevó a cabo un análisis de regresión lineal múltiple.

2.- En primer lugar, se obtuvieron dos modelos relacionando los espesores de los segmentos superior e inferior con los cambios específicos logrados postoperatoriamente y con la condiciones de partida de la córnea sólo considerando aquellos datos que se hallaban disponibles en todos los casos de la muestra, datos visuales refractivos y queratométricos.

-Modelo 1= R^2: 0,84, p<0,01

$$SST\ (\mu m) = 102.84 - 13.48 \times CYL_p - 21.27 \times DifKM - 0.65 \times DifIST \qquad (4.1)$$

-Modelo 2= R^2: 0,62, p<0,01)

$$IST\ (\mu m) = 102.84 - 13.48 \times CYL_p - 21.27 \times DifKM + 0.35 \times DifIST \qquad (4.2)$$

, donde SST es el espesor del segmento superior, IST el espesor del segmento inferior, CYL_p el cilindro refractivo preoperatorio, DifKM el cambio en la queratometría media tras la cirugía, y DifIST la diferencia entre los espesores de los segmentos superior e inferior.

3.- En segundo lugar, se obtuvieron otros dos modelos pero introduciendo también los datos aberrométricos corneales, los cuales sólo estaban disponibles en una porción más pequeña de la muestra, pero aún así se obtuvieron modelos más consistentes.

-Modelo 3= R^2: 0,91, p<0,01

$$SST\ (\mu m) = 132.20 - 12.14 \times CYL_p - 20.47 \times DifKM + 24.37 \times DifRMSHOA - 0.74 \times DifIST \qquad (4.3)$$

-Modelo 4= R^2: 0,64, $p<0{,}01$

$$IST(\mu m) = 132.20 - 12.14 \times CYL_p - 20.47 \times DifKM + 24.37 \times DifRMSHOA + 0.26 \times DifIST \quad (4.4)$$

, donde SST es el espesor del segmento superior, IST el espesor del segmento inferior, CYL_p el cilindro refractivo preoperatorio, DifKM el cambio en la queratometría media tras la cirugía, DifRMSHOA el cambio en el valor RMS para las aberraciones corneales de alto orden, y DifIST la diferencia entre los espesores de los segmentos superior e inferior.

4.- La bondad de ajuste de los 4 modelos de regresión lineal múltiple fue constatada mediante el análisis estadístico correspondiente (estudio de la homocedasticidad, ausencia de multicolinealidad, normalidad de la distribución de los residuales).

5.- En los 4 modelos obtenidos se ha podido confirmar que el nivel de astigmatismo preoperatorio limita el efecto de los segmentos, hecho que pudimos constatar en el estudio anterior de la presente tesis y que postulamos que debía ser la consecuencia del complejo entramado estromal presente en la córnea con queratocono y elevada toricidad. Por otra parte, la diferencia de espesor entre los segmentos superior e inferior resultaba ser un factor crucial adicional, sugiriendo en todo momento que la combinación más óptima era la colocación de un segmento inferior más grueso que el superior.

6.- Otro hecho curioso observado fue que cuanto mayor era el espesor de los segmentos se lograba una menor reducción queratométrica, pero una mayor corrección aberrométrica corneal de alto orden. Por lo tanto, quedaba patente el diferente comportamiento de estos segmentos en la córnea queratocónica en comparación con la normal[48 (ref 26,27)], el cual estaba justificado por las diferencias estructurales a nivel estromal de la córnea afecta de queratocono[48 (ref 28)].

7.- El análisis de residuales de los cuatro modelos puso de manifiesto las limitaciones de los modelos propuestos. En concreto, aquellos casos con residuales asociados mayores de 50 μm en la estimación de los espesores presentaban niveles más elevados de astigmatismo corneal y aberraciones corneales de alto orden. En uno de los estudios previos de la presente tesis habíamos constatado que aquellos casos de queratocono más avanzado y con la mayor alteración biomecánica presentaban niveles más elevados de astigmatismo y aberraciones corneales de alto orden (Figura 22). Por lo tanto, aquellos casos en los que existe una mayor alteración biomecánica el uso de los modelos desarrollados en este estudio es menos preciso, puesto que en dichos casos una modelización más compleja sería necesaria.

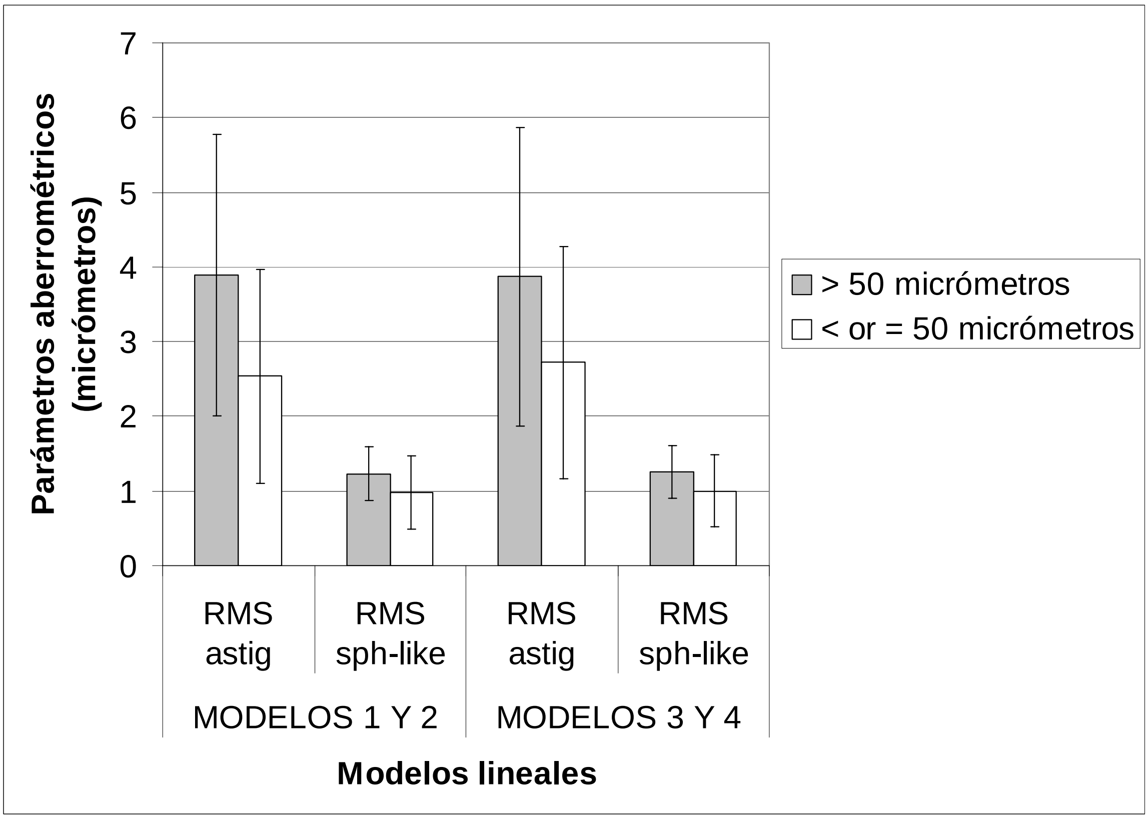


Figura 21.- Diferencias a nivel del astigmatismo corneal (RMS astig) y las aberraciones corneales "spherical-like" (RMS sph-like) entre casos con residuales no tipificados mayores de 50 μm (barras grises) y casos con residuales por debajo o igual a 50 μm (barras blancas) para los cuatros modelos

4.2.4.- Reimplante de ICRS en ojos con queratocono tras el fracaso de implantes previos *[Alió JL, Piñero DP, Sogutlu E, Kubaloglu A. Intracorneal ring segment reimplantation in keratoconus eyes with previous unsuccessful implants. J Cataract Refract Surg 2010 (accepted for publication)].*

En este estudio, tal y como se mencionó con anterioridad, se ha analizado la potencial reversibilidad y maleabilidad del efecto de los ICRS en el queratocono. Para ello, se ha analizado el resultado visual, refractivo y aberrométrico corneal del reimplante de segmentos en aquellos casos en los que habían fracasado implantes previos debido a diversas causas: extrusión de los segmentos, neovascularización de los canales de implante, mala calidad visual postoperatoria y molestias en visión nocturna. Teóricamente, teniendo en cuenta el carácter viscoelástico del tejido corneal, se podría volver a inducir un remodelado del perfil corneal anterior en aquellos casos en lo que un modelado previo no ha sido satisfactorio. A continuación se enumeran los principales hallazgos y reflexiones extraídas a partir de este estudio.

1.- Reducción estadísticamente significativa de la esfera y cilindro refractivo tras el reimplante, el cual era concordante con la mejora significativa también observada en la AVSC.

2.- Hubo una tendencia a la mejora de la AVCC tras el reimplante, pero dicho cambio no alcanzó significación estadístico.

3.- Quedó patente un incremento astigmático corneal con el primer implante. Tras el reimplante, se constató una tendencia al aplanamiento corneal aunque los cambios no alcanzaron significación estadística. Un factor que pudo afectar a este hecho fue las grandes diferencias existentes en el intervalo entre el explante del segmento y el reimplante (de 1 a 12 meses), pudiendo existir casos en los que no hubo tiempo a una recuperación completa de la geometría corneal tras el explante.

4.- Respecto a la aberrometría corneal, se pudo constatar la existencia de una reducción significativa de las aberraciones corneales “coma-like” tras el reimplante, la cual pudo contribuir a la ligera mejora de la AVCC.

5.- En lo que respecta a la comparativa del resultado final en función de la causa de reimplante, no se hallaron diferencias significativas en los resultados visuales y refractivos. Sin embargo, en aquellos casos en los que previamente había acontecido una extrusión del implante se pudo constatar la tendencia a una mayor curvatura central (Figura 22) y mayores cantidades de aberraciones corneales de alto orden, aunque las diferencias no alcanzaron significación estadística, probablemente debido a los limitados tamaños muéstrales.

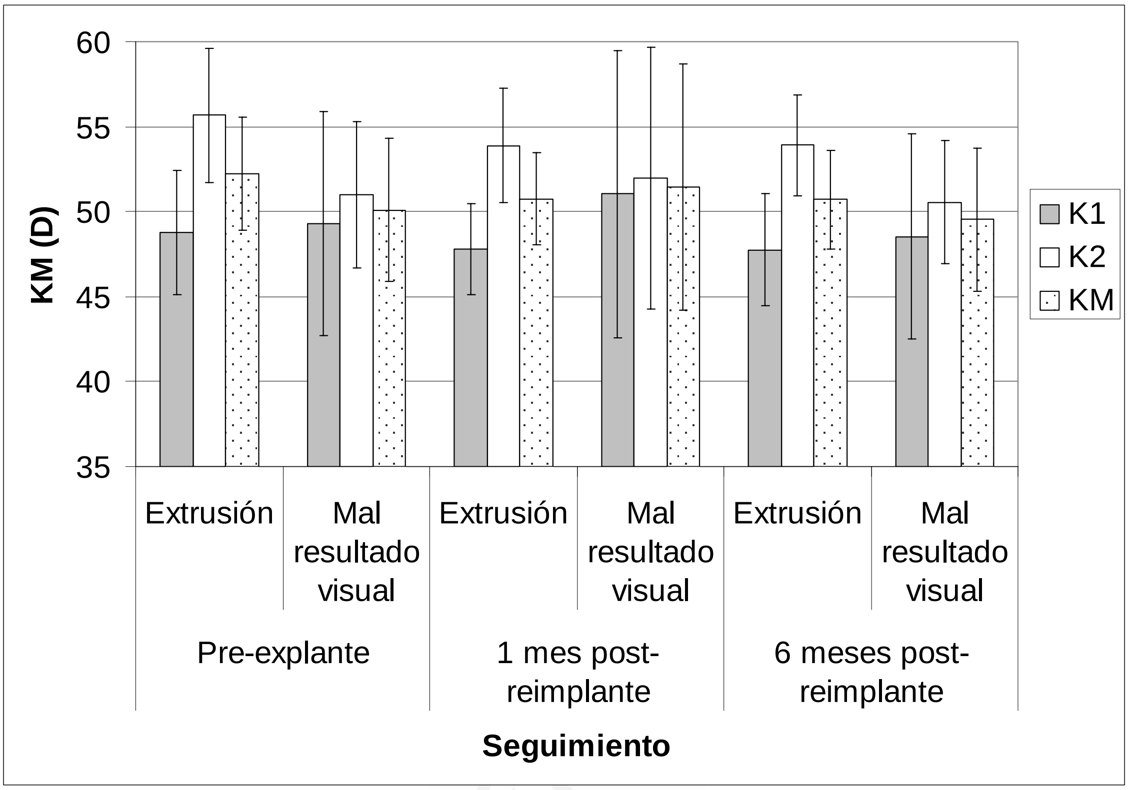
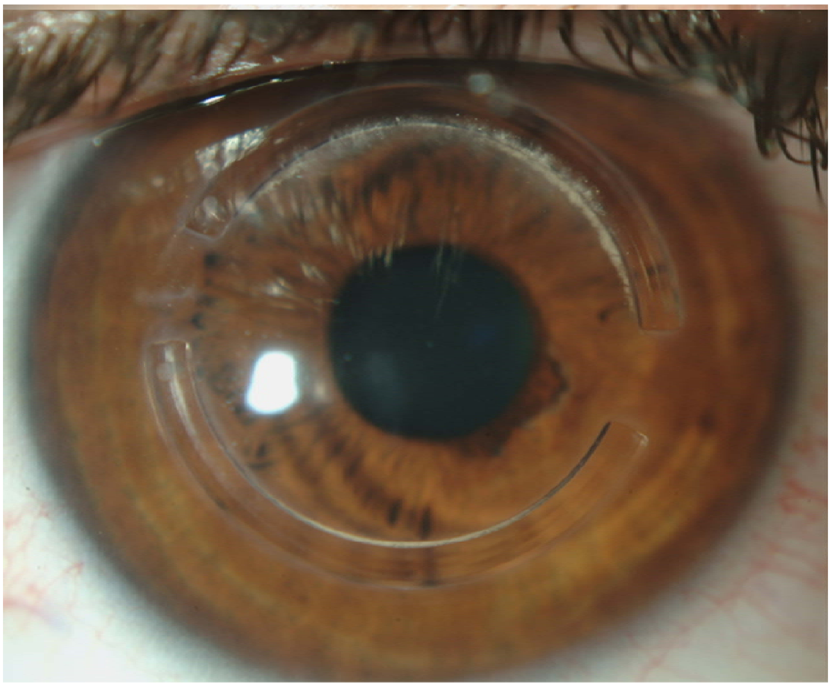


Figura 22.- Diferencias a nivel de los valores queratométricos centrales de la superficie corneal anterior durante el seguimiento entre dos grupos específicos de pacientes: pacientes con reimplante debido a la extrusión de los segmentos previos y pacientes con reimplante debido a un mal resultado visual con implantes previos

CAPÍTULO 5: CONCLUSIONES Y FUTURAS PERSPECTIVAS



CAPÍTULO 5: CONCLUSIONES Y FUTURAS PERSPECTIVAS

A continuación se van a detallar las dos principales conclusiones extraídas de esta tesis, teniendo en cuenta los dos objetivos principales planteados:

1.- El efecto de las dos principales tipologías de ICRS, Intacs de perfil hexagonal y KeraRing de perfil triangular, es diferente y con distintos factores predictivos del resultado visual en tres variantes específicas de la patología ectásica corneal: queratocono, degeneración marginal pelúcida y ectasia post-LASIK.

2.- Las variaciones de curvatura y aberrométricas corneales de alto orden que se consiguen tras el implante de segmentos KeraRing de 160º de arco en córneas con queratocono, las cuales son potencialmente reversibles y modificables, se hallan en relación con el espesor de los segmentos implantados, el grado de astigmatismo preoperatorio y la diferencia de espesor entre segmentos, aunque en los casos de queratocono más avanzado dicha relación está limitada por la alteración biomecánica subyacente.

Las conclusiones específicas extraídas a partir de la primera conclusión general son las siguientes:

1.- Tras el implante de las dos principales tipologías de ICRS (Intacs y KeraRing) en tres variantes diferentes de la patología corneal ectásica, queratocono, degeneración marginal pelúcida y ectasia post-LASIK, tiene lugar una mejora a nivel visual y refractivo como consecuencia del aplanamiento corneal central y la disminución de las aberraciones corneales de alto orden, aunque estos cambios difieren en magnitud y tendencia en función de la variante de la patología ectásica.

2.- La aberrometría corneal preoperatoria es útil para identificar el pronóstico visual tras el implante de las dos principales tipologías de ICRS (Intacs y KeraRing) en las tres variantes de patología corneal ectásica antes mencionadas, aunque existen diferencias en los coeficientes aberrométricos a considerar en función del tipo de ectasia.

3.- El uso de la disección mecánica para la tunelización previa a la inserción de los ICRS limita el potencial control aberrométrico de la superficie corneal anterior que se puede lograr con estos segmentos, especialmente en las córneas afectas de queratocono. Por lo tanto, resulta muy recomendable el uso siempre de la tecnología de femtosegundo para la creación de los túneles donde van insertados los ICRS, ya que se logra mayor precisión en la disección.

4.- Empleando la tunelización guiada por láser de femtosegundo en córneas con patología ectásica incipiente o moderada, los segmentos tipo Intacs de perfil hexagonal implantados a un diámetro de 6.0 mm permiten una menor corrección astigmática y, a su vez, inducen una mayor cantidad de aberración esférica primaria negativa en el postoperatorio inicial en comparación con los segmentos tipo KeraRing implantados a un diámetro de 5.0 mm.

Las conclusiones específicas extraídas a partir de la segunda conclusión general son las siguientes:

1.- Las variaciones de curvatura y aberraciones de alto orden de la superficie corneal anterior que tienen lugar tras el implante de segmentos KeraRing de 160º de longitud de arco a un diámetro de 5.0 mm se pueden predecir y calcular a partir de un modelo de regresión lineal múltiple, existiendo mayor error de predicción en aquellos ojos con queratocono que presentan una superficie corneal anterior altamente aberrada.

2.- La presencia de una superficie altamente aberrada en el queratocono se asocia a una alteración biomecánica mayor, caracterizada ésta mediante un proceso no invasivo de aplanamiento corneal bidireccional. Por ese motivo, la modelización del efecto de los ICRS en estos casos resulta mucho más compleja, puesto que será necesario el uso de modelos mucho más complejos.

3.- Los segmentos KeraRing de 160º de longitud de arco implantado de acorde al nomograma del fabricante en córneas con queratocono inducen una infracorrección del astigmatismo corneal, existiendo también un desalineamiento del efecto corrector en dirección de las agujas del reloj con respecto al eje objetivo. En futuros modelos a desarrollar se deberá tener en cuenta este desalineamiento del efecto corrector astigmático con el fin de optimizar los nomogramas de implante.

4.- El reimplante de ICRS en córnea con queratocono y que sufrieron previamente el explante o modificación de un implante previo debido a un mal resultado resulta efectivo y satisfactorio, sugiriendo la posibilidad de remodelización de la superficie corneal anterior con estos implantes a pesar de haber tenido lugar una modelización previa con segmentos y/o tunelización inadecuadas.

En lo que respecta a las futuras perspectivas de seguimiento de las presentes investigaciones existen varios proyectos, algunos de ellos ya en marcha:

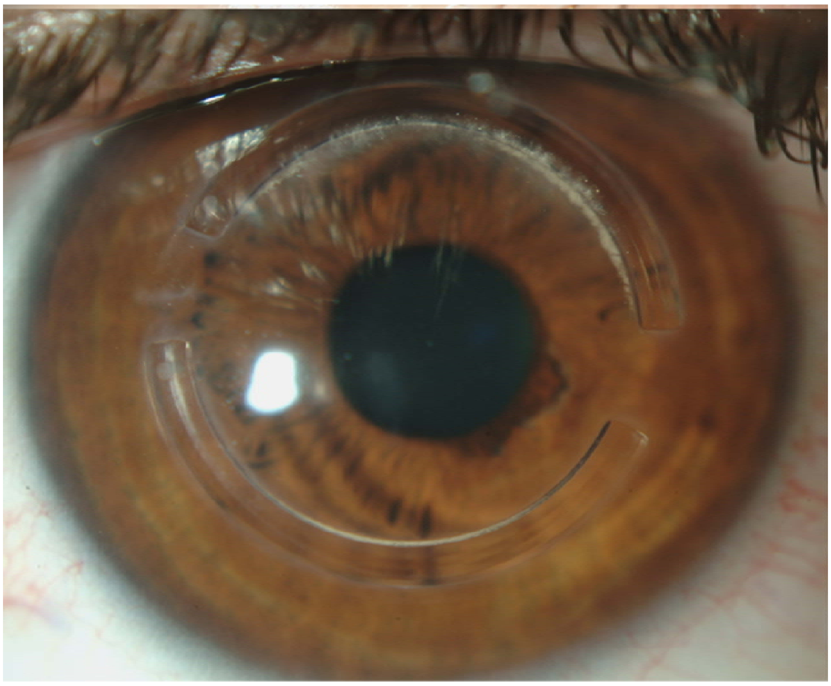
1.- Aplicación de la modelización obtenida como nomograma de implante en casos de queratocono de forma prospectiva con el fin de valorar la eficacia real de la misma y su potencial aplicabilidad. Actualmente ya se han implantado algunos casos con este modelo y el resultado hasta el momento ha sido muy satisfactorio, aunque siempre escogiendo casos incipientes o moderados.

2.- Desarrollo de modelizaciones más completas incluyendo la longitud de arco, no sólo el espesor del segmento, como un factor adicional a tener en cuenta. Actualmente se están recopilando datos de implantes con diferentes longitudes de arco (90º, 120º y 210º) con el fin de tener un tamaño muestral lo suficientemente grande como para lograr la potencia estadística requerida.

3.- Analizar el cambio inducido por los ICRS en la cara posterior de la córnea ectásica y el impacto que dichos cambios pueden tener en el resultado visual final.

4.- Desarrollo de una nueva metodología no invasiva para la caracterización de la biomecánica de la córnea con el fin de poder introducir el factor biomecánico en la modelización, ya incluyendo desarrollos matemáticos mucho más complejos (elemento finitos).

CAPÍTULO 6: REFERENCIAS



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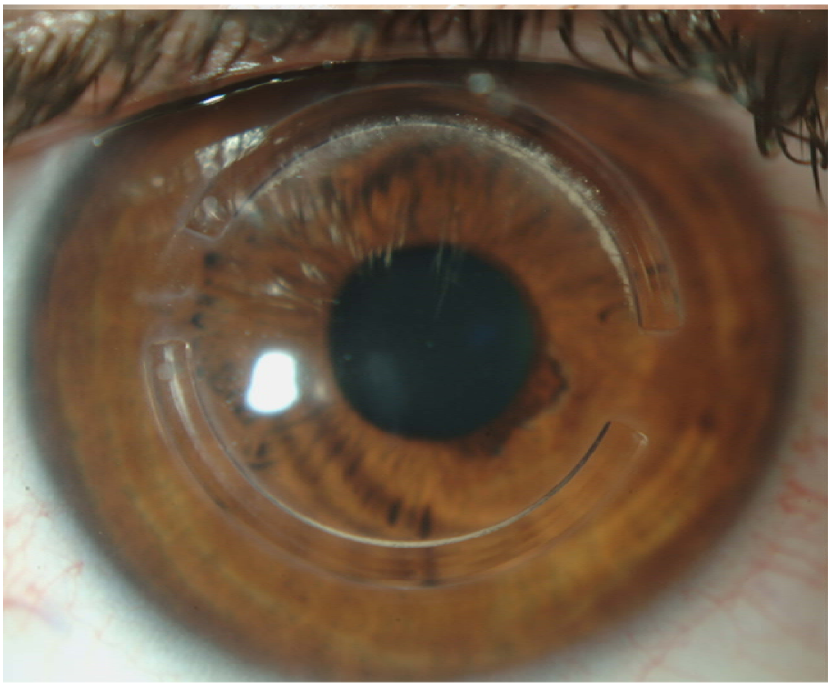
APÉNDICE



Clinical and Experimental Ophthalmology 2010; 38: 154–167 doi: 10.1111/j.1442-9071.2010.02197.x

Review

Intracorneal ring segments in ectatic corneal disease – a review

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Abstract

The purpose of this review is to collect and summarize all the scientific literature regarding the use of intracorneal ring segments (ICRS) in corneal ectatic disease. These implants, initially designed to correct myopia in normal eyes, are implanted in the deep corneal stroma with the aim of achieving modifications to the corneal curvature and subsequently refractive adjustments. Colin *et al.* in 2000 were the first to report the efficacy of these implants in reducing the refractive error and corneal steepening in keratoconus eyes. Two main types of ICRS have been developed and used for the treatment of ectatic corneal disease, different in profile and diameter of implantation: Intacs and Ferrara rings. Successful outcomes have been reported by several authors with these implants in keratoconic eyes using different nomograms. Besides keratoconus, ICRS have been also used successfully for the management of pellucid marginal degeneration and post-laser *in situ* keratomileusis corneal ectasia. The implantation procedure may be performed today by two surgical techniques to create the corneal channels where implants are inserted: mechanical dissection using a manual semicircular dissector (mechanical-assisted) and photodisruption of lamellar tissue using the femtosecond laser technology (femtosecond-assisted). With both techniques, visual, refractive and topographic improvements have been observed, although higher incidence of intraoperative and postoperative complications have been reported with the mechanical procedure according to the evidence found in the peer-reviewed literature. ICRS technology is a promising therapeutic option in corneal ectatic disease, avoiding corneal graft and allowing a visual and refractive rehabilitation.

Key words: cornea, corneoplastic, ectatic disorder, intracorneal ring segment, keratoconus.

Introduction

Intracorneal rings are small pieces made of synthetic material that are implanted in the deep corneal stroma with the aim of generating modifications of corneal curvature and refractive changes. The intrastromal corneal ring concept was proposed by Reynolds in 1978.[1] The initial implants were full rings inserted through a peripheral single corneal incision into a circumferential corneal channel.[2,3] The implantation of these 360-degree rings was an additive refractive technique aimed at correcting myopia.[1] In order to make its implantation easier and to avoid potential incision-related complications, these implants were refashioned into incomplete rings and ultimately to the C-shape rings.[1] They were renamed and the term 'intracorneal ring segments' (ICRS) was then coined.[1]

Keravision Intacs intrastromal ring segments were extensively investigated as an alternative for myopia correction. Several authors reported good outcomes with this kind of rings in low–moderate myopic patients.[4–8] Intacs technology for myopia received European CE certification in 1996 and Food and Drug Administration (FDA) approval in 1999.[9] This preliminary success of Intacs was overshadowed and overtaken by the rapid rise in popularity of laser *in situ* keratomileusis (LASIK) and they never achieved commercial success as a refractive surgical device.[9] However, ICRS technology was found to be a therapeutic indication for the correction of ectatic corneal

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Received 16 February 2009; accepted 14 July 2009.

disorders such as keratoconus because of the potential of this technology to remodel the corneal profile. Besides Intacs technology, Ferrara also reported successful outcomes for myopia correction with another ring segment design (Ferrara rings), even in high myopia.[10] This author also began to implant these segments in corneas with keratoconus and after keratoplasty.

In 2000, Colin *et al.* reported the first results of ICRS technology in keratoconus.[11] They found that Intacs technology could reduce the corneal steepening and astigmatism associated with keratoconus, being proposed as an additive surgical procedure for keratoconus management. This surgical option provided an interesting alternative aiming to delay if not to avoid corneal grafting in ectatic corneal disease. Since then, multiple reports about ICRS for ectatic corneal disorders, showing the visual and refractive outcomes of these implants, have been published.

Types of intracorneal ring segments

Two main types of ICRS, different in geometrical profile and diameter, have been developed and used for ectatic corneal management: Intacs and Ferrara rings (Figs 1,2). Intacs segments (now distributed and marketed by Addition technologies (Sunnyvale, CA, USA)) consist of a pair of semicircular pieces of polymethyl methacrylate (PMMA), each one having a circumference arc length of 150° and a hexagonal transverse shape (Fig. 1). Each segment has an external diameter of 8.10 mm, an internal diameter of 6.77 mm and a variable thickness (0.25–0.45 mm, with 0.05-mm increments) that allows modulation of refractive effect. There is an additional Intacs segment design (Intacs SK), with inner diameter of 6 mm, an oval cross-section shape and two different thicknesses (400 μm for steep *K*-value of 57–62 D and cylinder <5 D; 450 μm for steep *K* > 62 D and cylinder >5 D).[12] The Ferrara ring segments, manufactured initially by Mediphacos (Belo Horizonte, Brazil), are made as computer-lathed PMMA and camphorquinone (CQ)-acrylic segments. Initially they were available in two diameters (6.0 mm for myopia up to 7.00 D, 5.0 mm for higher degrees of myopia) and in thicknesses from 150 to 350 μm. The cross-section of this ICRS type is triangular with the aim of inducing a prismatic effect leading to a reduction of photic phenomena (Fig. 1).[13] KeraRings were developed years later but specifically for keratoconus management. These ring segments are mainly identical in design, composition and thicknesses to Ferrara rings, but different options of arc length are available in order to achieve a better astigmatic control (90°, 120°, 160° and 210°). Each segment has an internal diameter of 4.40 mm and an external diameter of 5.60 mm.

Besides Intacs and Ferrara rings, other kind of ring segments has been developed, but there are no published studies reporting the outcomes with these new segments in ectatic corneal disease: Bisantis (segmented perioptic implants) segments and Myoring (complete rings). The segment perioptic implants (Bisantis segments) are four segments of 80° of arc, with an oval cross-section, a vertical diameter of 250 μm and a horizontal diameter of 200 μm. The only variable parameter is the amount of curvature of the inserts to obtain optical zone parameters of 3.5, 4.0 and 4.5 mm.[12] The Myoring (DIOPTEX) is a flexible, continuous, PMMA ring designed to correct moderate and high myopia.[14] The diameter

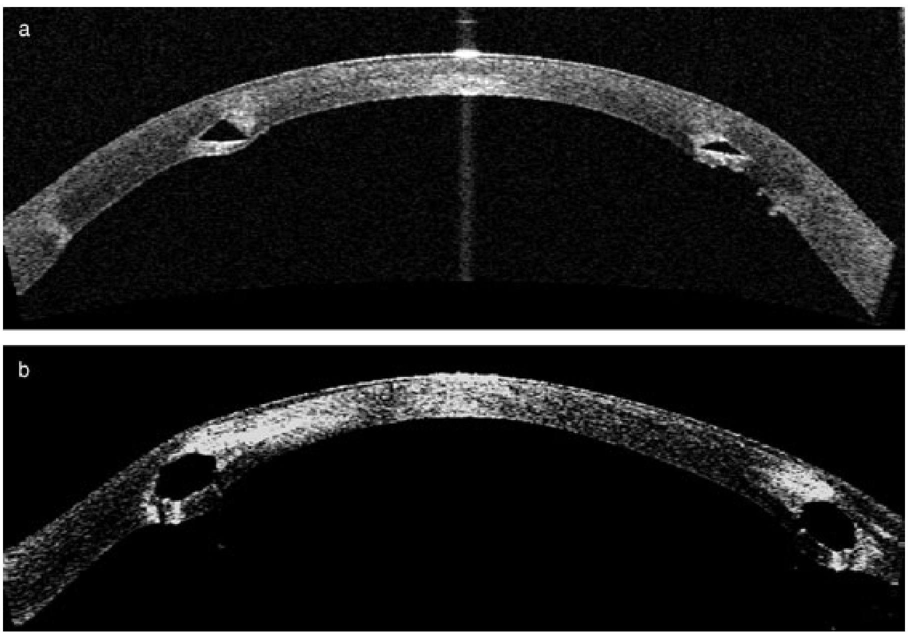


Figure 1. High resolution corneal image obtained by means of the Visante optical coherence tomography system (Zeiss) of two keratoconus eyes: (a) eye implanted with Kerarings, and (b) eye implanted with Intacs. The cross-section of both kind of intracorneal ring segments type can be distinguished in these images: triangular for Kerarings and hexagonal for Intacs.

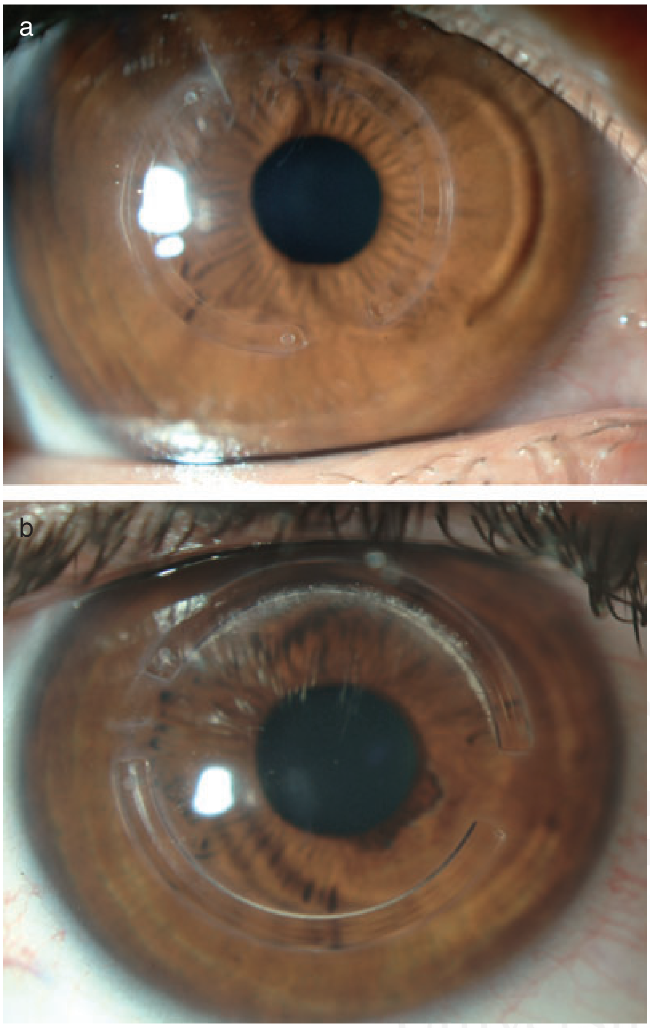


Figure 2. Frontal image obtained with a slit-lamp biomicroscope of two keratoconus eyes implanted with intracorneal ring segments: (a) eye implanted with KeraRing, and (b) eye implanted with Intacs. Intrastromal deposits accumulated in the inner side of the superior lamellar channel can be observed in the eye implanted with Intacs.

ranges from 5.0 to 8.0 mm, the thicknesses from 150 to 350 μm and the width of the ring is 0.5 mm. The anterior surface is convex and the posterior surface concave, with a radius of curvature of 8.0 mm. The particular shape and dimensions permit folding that makes implantation in a pocket via a small incision tunnel possible.[14]

HOW DO INTRACORNEAL RING SEGMENTS WORK?

Intracorneal ring segment acts as spacer elements between the bundles of corneal lamellae producing a shortening of the central arc length (arc shortening effect) that is proportional to the thickness of the device.[15] As a consequence of this effect, the central portion of the anterior corneal surface tends to flatten and the peripheral area adjacent to ring insertion is displaced forward (Figs 3,4).[3,16] There is a nearly linear relationship between the degree of central corneal flattening and ring thickness[17,18] when segments are implanted in normal eyes. Finite element modelling was used to define the change in corneal shape induced by ring segments and it correlated well with eye-bank and clinical data.[19]

Burris *et al.*[20] found in eye-bank eyes implanted with ICRS that the pericentral cornea was flattened more than the central cornea, thereby maintaining the prolate shape of the corneal optical zone (cornea flattens toward the periphery) (Fig. 4). This tendency was confirmed in human eyes implanted with Intacs for myopic correction from −1 to −6 D.[21] Patel *et al.* predicted changes in corneal asphericity with ICRS using an optical model that did not consider the occurrence of changes in the posterior corneal surface.[16] They concluded that ICRS cannot correct more than 4 D of myopia without significant changes in corneal asphericity and then without inducing spherical aberration. This model also predicted that the degree of myopic correction was a function of both ring thickness and diameter, with minimal changes in corneal asphericity when using large diameters and thin segments.[16] However, this model had two important limitations; the depth of the implant and the corneal biomechanical response were not considered.

Corneal changes induced by the ICRS must be in relation to the structural properties of the collagen framework in the corneal stroma. The stroma accounts for 90% of corneal thickness, and evidently its mechanical properties define for the most part the mechanical properties of the whole corneal structure. Specifically, the orientation of the successive fibril layers (lamellae) throughout the entire cornea is a very important factor determining the mechanical properties of the cornea.[22] In the central region of the normal cornea the lamellae are preferentially oriented in two directions: nasal-temporal and inferior-superior.[23] This structure involves about 66% of the lamellae, and the remaining 34% are randomly oriented.[24] Therefore, there is a preferred orientation of collagen lamellae along the horizontal and the vertical directions, but this trend is maintained to within about 1 mm from the limbus, where a circular or tangential disposition of fibrils occurs.[25] However, this well-organized lamellar structure is lost when the corneal tissue degenerates, as it happens in keratoconus.[24] The regular orthogonal arrangement of the collagen fibrils is destroyed within the apical scar of the keratoconus.[24] Therefore, ICRS effect in these ectatic corneas may be different from the effect achieved in normal corneas when myopia is corrected. The development of an adequate mathematical modelling of ICRS effect considering the

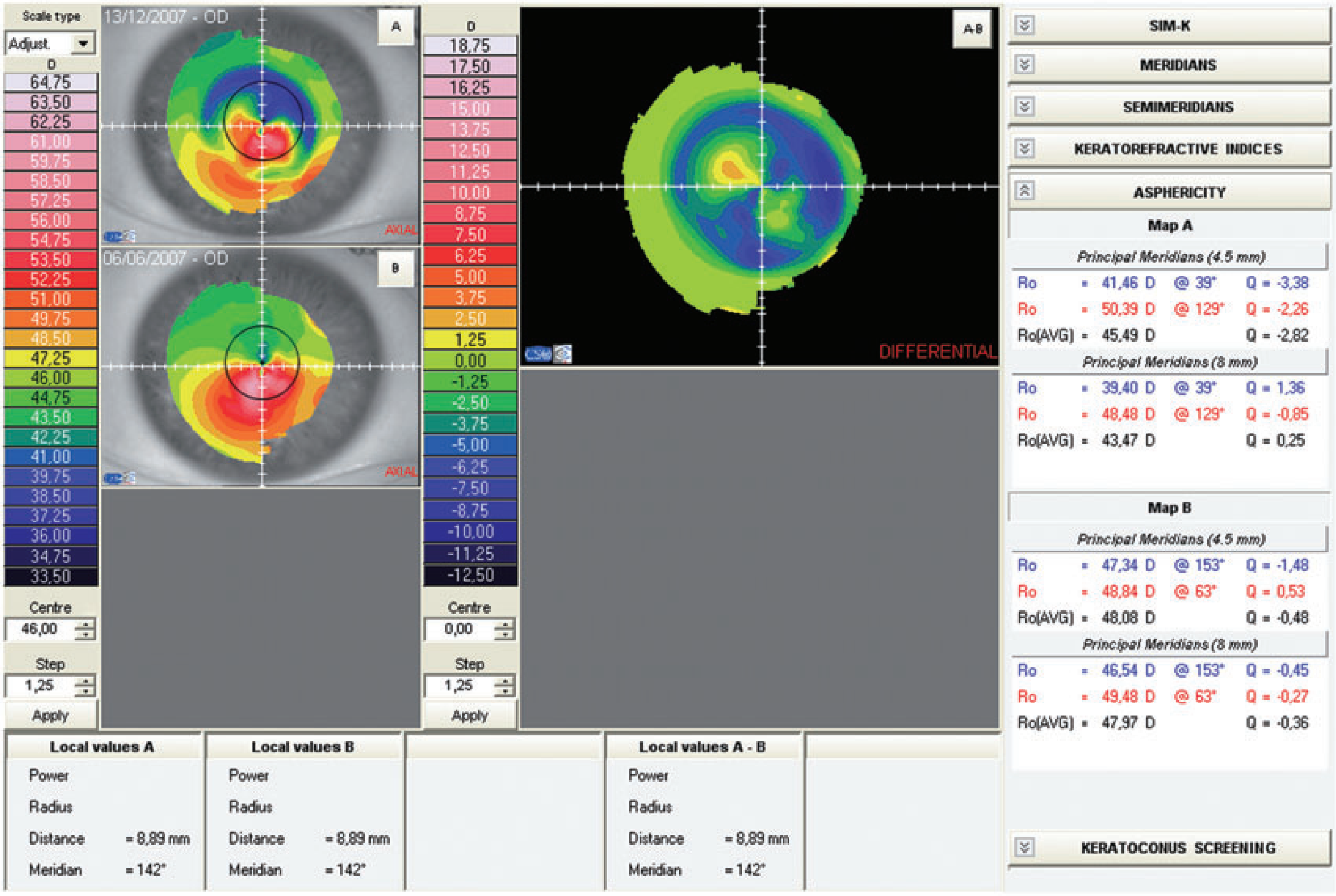
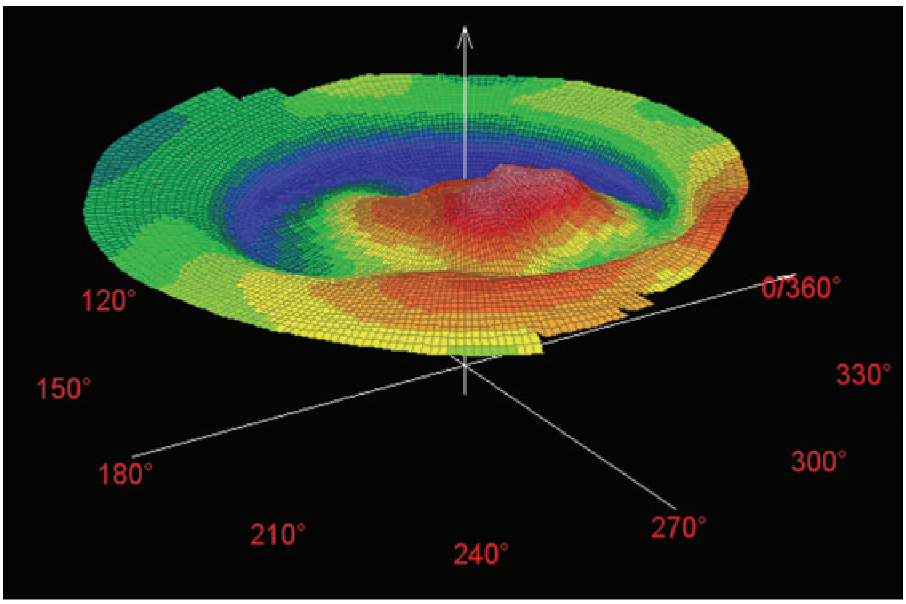


Figure 3. Differential corneal topographic map (right) showing the difference between the preoperative corneal topographic pattern (lower left) in a keratoconus eye and its postoperative pattern (upper left) after Intacs implantation.

Figure 4. Corneal topographic map showing the effect of a pair of Intacs implanted in a keratoconus cornea: central corneal flattening and displacement forward of the peripheral area adjacent to ring insertion.



ectatic corneal architecture is necessary to optimize nomograms of implantation.

Application of intracorneal ring segments in the correction of corneal ectatic disease

Indications

Initially, ICRS was found to be indicated for the correction of keratoconus.[11,13,26–44] Afterwards, several authors also reported the effectiveness of these implants for reducing corneal steepening and refractive errors in pellucid marginal degeneration[45–51] and post-LASIK ectasia.[52–60] All these corneal ectatic disorders are characterized by a progressive corneal thinning that results in corneal protrusion, irregular astigmatism and visual loss.[61,62] Visual rehabilitation is crucial in the management of these patients because the visual function is devastated because of the significant increase in lower and higher order aberrations (especially coma).[63–66] ICRS are a corneoplastic corrective alternative option for visual rehabilitation in these cases, aiming at delaying and preventing corneal graft.[32,33] Patients with contact lens intolerance are excellent candidates for this surgery because spectacle correction cannot provide in all cases an optimized visual quality (especially in moderate and advanced ectatic cases).

Keratoconus

Our research group reported better visual acuity, corneal topography quality and more significant reduction in spherical equivalent after Intacs implantation in less advanced keratoconus (relatively low mean $K \leq 53$ D and relatively low spherical equivalent) than in advanced cases (mean $K \geq 55$ D).[34] Zare *et al.* also found less predictable results in cases of advanced keratoconus implanted with Intacs.[31] Ertan and Kamburoglu also concluded that changes in uncorrected visual acuity (UCVA) and refractive error were not statistically significant in severe keratoconus.[29] However, Shetty *et al.* found a significant reduction in sphere and cylinder as well as in mean keratometry in keratoconus grade III, but most of the implanted cases were central cones (78.57%).[27] In addition, good visual and aberrometric outcomes were reported in keratoconus cases grades III and IV with KeraRings and Ferrara rings.[30,39,40] Boxer Wachler *et al.* reported improvement in visual acuity and astigmatism in corneas implanted with ICRS with and without scarring.[42]

Pellucid marginal degeneration

Intacs, Ferrara rings and KeraRings can reduce the corneal steepening and astigmatism associated with pellucid marginal degeneration (PMD)[46,49] in patients who are intolerant to contact lenses. They have been used in early to moderate PMD with successful outcomes.[45–51] It is advisable to use a thinner segment in the inferior part of the cornea in order to avoid corneal perforation.[50] A single Intacs can be used to treat superior PMD as in one reported case in which a significant visual improvement was obtained.[45]

Post-LASIK ectasia

Intracorneal ring segments have been also demonstrated to be an effective option in secondary or iatrogenic corneal ectasia,[52–60] especially in early stages of the disease when fewer topographic irregularities are present.[57] Corneal keratectasia after LASIK surgery is a serious complication, especially observed in corneas with a very significant ablation in the central area (high myopes).[62,67–74] It consists of a progressive corneal steepening, usually inferiorly, with an increase in myopia and astigmatism, loss of uncorrected (UCVA) and frequently best spectacle-corrected visual acuity (BSCVA),[67] and significant increase in corneal aberrations. Improvement in visual acuity and reduction in spherocylindrical error and keratometry have been found after ICRS implantation in post-LASIK ectasia,[52–60] even in severe cases.[52] Lovisolo and Fleming stated that Ferrara rings were preferable in advanced cases because of the enhanced effect of a reduced optical zone.[59]

Other options

Ring segments were also been demonstrated to be effective in reducing sphere and cylinder in post-penetrating keratoplasty corneas with recurrent keratoconus.[75]

Nomograms

Several surgical nomograms have been proposed for ICRS implantation in the ectatic cornea, all of them intuitive and based on anecdotic clinical data. A nomogram defined according to an accurate mathematical model characterizing the ICRS effect has still not been developed. Table 1 summarizes the implantation criteria used for Intacs in different published studies.[11,27,29,31–38,41,42,44,76] As can be seen, different approaches have been proposed for Intacs implantation in keratoconus, some of them based on spherical equivalent refraction and others on topographic profile. Good visual and refractive outcomes have been reported with all of them.[11,27,29,31–38,41,42,44,76] Regarding the number of segments, Sharma and Boxer Wachler[54] established that single-segment Intacs induced more physiological corneal shape

Table 1. Nomograms for Intacs implantation in keratoconus used in different studies

Author	Year	ICRS number	Surgical procedure	Incision location	Implantation criteria
Colin *et al.*[11]	2000	2	Mechanical	Temporal	0.35/0.45
Colin *et al.*[44]	2001	2	Mechanical	Temporal	0.25/0.45
Hellstedt *et al.*[38]	2005		Mechanical	Temporal	
Ertan *et al.*[29,35]	2008, 2006		Femtosecond	Temporal	
Kanellopoulos *et al.*[37]	2006		Mechanical	Temporal and superior to the horizontal meridian	
Boxer Wachler *et al.*[42]	2003	2	Mechanical	Axis of positive cylinder if it was not 90° away from topographic axis	SE < –3.00 D: 0.25/0.30 SE > –3.00 D: 0.25/0.35
Siganos *et al.*[41]	2003	2	Mechanical	–	Inferior ectasia: 0.45/0.45
Kymionis *et al.*[32]	2007				Central ectasia: 0.45 temporal/0.45 nasal
Alió *et al.*[34,76]	2005	1 or 2	Mechanical	Temporal	Inferior corneal steepening not involving the 180° meridian: 1 inferior segment 0.45
Alió *et al.*[33]	2006			Perpendicular to main axis of keratoconus (positive meridian)	Corneal steepening extending at least 1 mm above and beyond 180° meridian: 0.25/0.45
Colin[36]	2006	1 or 2	Mechanical	Temporal	SE < –3.00 D: low 0.25/0.30, moderate 0.35/0.40 and high topographic asymmetry 0.25/0.40; central cone 0.40/0.40 SE > –3.00 D: low 0.25/0.35, moderate 0.40/0.45 and high topographic asymmetry 0.25/0.45; central cone 0.45/0.45
Zare *et al.*[31]	2007	2	Mechanical	Temporal	SE 0–2 D: 0.25/0.35; SE 2–3 D: 0.25/0.40; SE 3–5 D: 0.25/
Shetty *et al.*[27]	2008			Steep topographic meridian	0.45; SE 5–8 D: 0.35/0.45; SE > 8 D: 0.40/0.45

The following notation was followed for showing the implantation criteria: thickness of superior ring in mm/thickness of inferior ring in mm. D, dioptre; ICRS, intracorneal ring segments; SE, spherical equivalent.

changes and better postoperative results in keratoconus and post-LASIK ectasia than double-segment Intacs. Furthermore, our research group found that one or two Intacs implanted according to corneal topographic profile provided good keratometric and refractive results: one inferior segment in inferior cones and two segments in central cones.[76]

Regarding Ferrara rings and KeraRings, different nomograms have been also proposed. Miranda *et al.*[40] used in eyes with severe keratoconus two Ferrara ring segments of 160° arc length and a specific thickness selected according to the following criteria: 0.20 μm for a correction of –2.00 D (cone stage I), 0.25 μm for a correction of –4.00 D (cone stage II), 0.30 μm for a correction of –6.00 D (cone stage III) and 0.35 μm for a correction of –8.00 D (cone stage IV). Kwitko and Severo used the same nomogram for segment thickness selection in keratoconus eyes,[39] although modifying also the arc length of the segment (between 120° and 160°). Siganos *et al.*[13] also proposed the use of two Ferrara ring segments (160° arc length) for keratoconus correction but selecting the thickness as a function of refractive error: 0.15 μm for less than –4 D of myopia, 0.20 μm for –4.25 to –6 D, 0.25 μm for –6.25 to –8 D, 0.30 μm for –8.25 to –10 D and 0.35 μm for more than –10 D of myopia. In 2007, a nomogram for KeraRings proposed by manufacturer was successfully used in a series of keratoconus eyes (Table 2).[30] This nomogram was created only for 160° arc length segments and it allowed a selection of segment distribution and thickness based on spherical equivalent and corneal topographic pattern (Table 2). A new nomogram for KeraRings was recently developed by the manufacturer that specifies segment thickness and arc length (4 options are now available: 90°, 120°, 160° and 210°) based on sphere, cylinder and corneal topographic pattern. There are no published studies reporting the outcomes with this new nomogram.

Surgical procedures

Two surgical procedures have been described for ICRS implantation: mechanical and femtosecond

Table 2. Nomograms for KeraRings implantation proposed by the manufacturer (2007)[30]

Spherical equivalent (D)	All ectasia is limited to one half of the cornea	75% of the ectasia in one half of the cornea and 25% situated in the other half	Two-thirds of the ectatic area in one half of the cornea and one-third in the other half	The ectasia is distributed evenly in both corneal halves
>–10 D	25/35	25/35	30/35	35/35
–8 to –10 D	20/30	20/30	25/30	30/30
–6 to –8 D	15/25	15/25	20/25	25/25
–2 to –6 D	0/20	0/20	15/20	20/20

This nomogram was created for 160° arc length segments only and it provided a selection of segment distribution and thickness based on spherical equivalent and corneal topographic pattern (distribution of ectasia). For defining the distribution of the ectasia the cornea is divided into two halves using the steepest meridian as axis of separation. Example: 25/35 = upper segment thickness/lower segment thickness (0.25 mm/0.35 mm). D, dioptre.

laser-assisted.[12] The difference between methods is in the mode of creating the corneal channels or tunnels where ring segments are going to be located. The mechanical procedure was the first method described for ICRS implantation. The geometric centre of the cornea or the pupil centre, depending on surgeon criteria, is located and then marked with a Sinskey hook. This point is used as a reference throughout the procedure to locate the incision and the centre of intrastromal dissection and also to position the segments properly. Intraoperative ultrasonic pachymetry is performed at the planned incision site. A calibrated diamond knife is then used to create the incision (1-mm radial incision) at approximately 70% or 80% of the measured corneal thickness. From the base of the incision, pocketing hooks are used to create corneal pockets on each side of the incision, taking care to maintain a uniform depth. After this, a device containing a semiautomated suction ring is placed around the limbus, guided by the previously marked reference point on the cornea. The vacuum system (KV 2000, Addition Technologies) is started on the low setting of 450 mbar and increased to 630 mbar after confirming the suction ring placement. Two semicircular dissectors are placed then sequentially into the lamellar pocket to be steadily advanced by a rotational movement (counterclockwise and clockwise dissectors). As a result, two semicircular dissections (tunnels) with a specific diameter are created. After removing the suction device, the ring segments are inserted into each of the semicircular channels.[27,31–34,36–43,45,47–51,53,55–57,59,76] Tunnelization can be also performed without vacuum, using an appropriate curved spatula, but this procedure was only described for Ferrara rings implantation.[39,40] Good visual results were reported using this surgical technique, with acceptable percentage of complications depending on the severity of the ectatic condition.[27,31–34,36–43,45,47–51,53,55–57,59,76]

The use of femtosecond laser for channel creation became widely accepted after the approval of its use by the FDA in the USA.[77] With this type of lasers (photodisruptive laser), an infrared Nd:Glass laser beam (wavelength 1053 nm) is focused at a desired corneal depth in order to induce an optical breakdown without thermal or shockwave damage to the surrounding tissue.[78] This beam forms cavitations, microbubbles of carbon dioxide and water vapour as a consequence of the photodisruption, and the interconnecting series of these bubbles forms a dissection plane. Therefore, this laser allows the surgeon to programme channel creation at a predetermined depth with a high degree of precision. The surgical procedure with this laser, as in the mechanical procedure, is typically performed under topical anaesthesia. After marking a reference point (pupil centre or first Purkinje reflex) on the cornea and measuring the corneal thickness by ultrasonic pachymetry at the area of implantation (5-mm diameter), the disposable suction ring of the femtoseond laser system is placed and centred. The disposable glass lens is applanated to the cornea to fixate the eye and help maintain the precise distance from the laser head to the focal point. If pupillary centre is used as centration reference, its nasal movement after applanation should be considered in order to avoid decentration.[79] First, an entry cut with the femtosecond laser was created with the aim of allowing access ring placement in the tunnel. The tunnel is then created at approximately 70–80% of the corneal thickness within 15 s with no manipulation of the cornea. After this, ring segments are inserted in the created tunnels.[26,28–30,35,46] Excellent visual, refractive and aberrometric outcomes were also reported with this kind of surgical procedure.[26,28–30,35,46]

Theoretically, the femtosecond laser-assisted procedure would generate a more accurate stromal dissection leading to better visual and refractive results. Mechanical tunnelization is more dependent on surgeon skills, being more difficult to create manually a stromal dissection exactly at the same plane. However, similar visual and refractive outcomes using both procedures were reported in a short-term follow up in keratoconus and post-LASIK ectasia eyes.[80,81]

Regarding the corneal incision, there is no general agreement about which location is the better option. Different reference points have been described in the literature, such as the temporal position,[11,29,31,34,36,38,44–49,76] the 12 o'clock position (superior),[53,56] on the axis of positive cylinder if it was not 90° away from topographic axis,[42] temporal location and at the 1 o'clock position superior to the horizontal middle meridian of the cornea[37] and on the steepest topographic meridian.[13,26,27,33,40] To this date, there are no published studies comparing the visual, refractive and keratometric outcomes after implanting ICRS using some of these incision locations. Theoretically, the ideal position would be on the steepest corneal meridian, as most of surgeons do currently, because this kind of incision would reduce the corneal power of the steepest meridian and it would increase the flattest keratometric reading. Therefore, this type of incision would minimize the corneal and manifest astigmatism. However, a significant reduction in manifest cylinder was also observed in eyes with the incision located on other locations.[29,34,35,37] Future studies clarifying the role of corneal incision in the outcomes obtained after ICRS implantation and its better location are required for optimizing this kind of surgical option.

In addition, there is no uniform agreement on what channel size is more effective for ICRS insertion. There is an apparent trend about using Intacs with narrow channels to provide better outcomes.[12] However, Ertan *et al.* did not find differences in refractive outcomes between keratoconus eyes implanted with Intacs using wide (6.7 × 8.2 mm) and narrow (6.6 × 7.6 mm) channels.[82] These authors only found a higher rate of mild to moderate complications in the narrow-channel group.

Outcomes of ICRS in corneal ectatic disease

Revising carefully all the peer-reviewed scientific literature regarding ICRS, we have found several articles showing the outcomes of these implants in different types of ectatic corneal disease. No prospective randomized controlled studies have ever been performed. The following three different types of publications were found in the scientific literature about ICRS in ectatic corneas: retrospective nonrandomized studies, retrospective studies and case reports. Similar number of prospective nonrandomized and retrospective studies published about the outcomes of ICRS implantation in keratoconus was found (Table 3). However, most of the published articles about the use of ICRS in PMD and post-LASIK ectasia were case reports probably because of the difficulty of finding such cases in the clinical practice.

Keratoconus

Several studies have reported the visual, refractive and keratometric changes occurring after the implantation of ICRS in keratoconic eyes (Table 3). In all of these studies, a central flattening was found after ICRS implantation that agrees with the expected change in curvature considering the mechanism of action of ring segments.[11,13,26,27,29–40,42,44,76] This flattening achieved with ICRS was reported as statistically significant by several authors.[13,26,27,29–32,35,39,76] Mean keratometric change with ICRS varies depending on the author and the ICRS type, with values from 2.14 to 9.60 D. Regarding the refractive outcomes after ICRS implantation, it has been demonstrated that ring segments are efficacious for reducing sphere,[11,27,29–31,33–35] cylinder,[11,26,27,29–31,33–37,39,44,76] and then spherical equivalent[11,13,26,27,29–40,42,44,76] in keratoconus (Table 3). However, differences in the changes achieved in manifest refraction with the implants are present in the different studies about this issue. Mean change in sphere ranged depending on the study between 0.43 and 5.00 D and mean change in cylinder between 0.75 and 2.88 D. In the long-term studies, a regression of the achieved spherical correction was observed in the medium–long term[13,32,33,36] that implied that the segments were useful for corneal remodelling, but not for stopping cone progression.

Besides refractive improvement, corneal irregularity also is reduced with these implants. Theoretically, this reduction in corneal irregularity would have a significant impact on BSCVA. In most of the studies, more than 50% of cases experienced an improvement in BSCVA (Table 3). Our research group[30] found that 70% of cases implanted with KeraRings gained lines of BSCVA. This visual improvement was consistent with an important reduction of corneal higher order aberrations, especially in those eyes with coma aberration higher than 3.0 μm. However, Chalita and Krueger reported an increased incidence of higher order ocular aberrations after implantation of a Ferrara ring in one keratoconic eye.[83] More studies about aberrometric changes with ICRS are necessary for a better understanding of visual changes with this kind of implants.

The ICRS implantation in keratoconus has been also demonstrated to be useful for improving the contact lens tolerance. It should be considered that after ICRS surgery there are cases with residual refraction that needs to be corrected. Our research group found that 13 keratoconic eyes with contact lens intolerance were able to use a contact lens after

Table 3. Visual and refractive outcomes reported in different studies after ICRS implantation in keratoconus eyes

Author	Type of study	Year	ICRS type	Surgical procedure	Follow up (months)	Mean change in SE (D)	Mean change in sphere (D)	Mean change in cylinder (D)	Gains of lines of BSCVA	Mean change in keratometry (D)
Colin *et al.*[11] (10 eyes)	Prospective nonrandomized	2000	Intacs	Mechanical	6	2.12	1.75	1.5	–	4.85
Colin *et al.*[44] (10 eyes)	Prospective nonrandomized	2001	Intacs	Mechanical	12	–	–	2.7	–	4.60 (max K)
Boxer Wachler *et al.*[42] (74 eyes)	Retrospective	2003	Intacs	Mechanical	20	2.43	–	–	45.0%	–
Siganos *et al.*[13] (33 eyes)	Prospective nonrandomized	2002	Intacs	Mechanical	24	1.39	–	–	75.75%	3.23
Miranda *et al.*[40] (36 eyes)	Prospective nonrandomized	2003	Ferrara	Mechanical	12	2.49	–	–	87.1%	9.60 (max K)
Kwitko and Severo[39] (51 eyes)	Retrospective	2004	Ferrara	Mechanical	39	2.27	–	1.57	86.4%	5.59
Hellstedt *et al.*[38] (50 eyes)	Prospective nonrandomized	2005	Intacs	Mechanical	12	2.67	–	–	76.70% (6 months)	4.20 (max K, 6 months)
Alió *et al.*[76] (26 eyes)	Prospective nonrandomized	2005	Intacs	Mechanical	12	1-segment group 3.27	–	1-segment group 2.47	1-segment group 81.81%	1-segment group 4.69 (max K)
						2-segment group 1.92		2-segment group 2.39	2-segment group 86.67%	2-segment group 5.27
Kanellopoulos *et al.*[37] (20 eyes)	Prospective nonrandomized	2006	Intacs	Mechanical	12	3.46	1.92	2.50	–	2.95
Colin[36] (57 eyes)	Prospective nonrandomized	2006	Intacs	Mechanical	12	1.53 (6 months)	–	2.88 (6 months)	62.0%	3.70 (6 months)
Alió *et al.*[34] (25 eyes)	Retrospective	2006	Intacs	Mechanical	6	Eyes gaining BSCVA 2.81	Eyes gaining BSCVA 2.11	Eyes gaining BSCVA 1.50	–	Eyes gaining BSCVA 2.14 (max K)
						Eyes losing BSCVA 2.25	Eyes losing BSCVA 1.40	Eyes losing BSCVA 1.71		Eyes losing BSCVA 4.23 (max K)
Ertan *et al.*[35] (118 eyes)	Retrospective	2006	Intacs	Femtosecond	12	3.85	2.97	1.7	73.7%	3.90
Alió *et al.*[33] (13 eyes)	Retrospective	2006	Intacs	Mechanical	48	1.45	0.43	2.07	–	2.56
Zare *et al.*[31] (30 eyes)	Prospective nonrandomized	2007	Intacs	Mechanical	6	3.64 ± 3.16	3.02	0.75	73.3%	2.13 ± 2.35
Kymionis *et al.*[32] (36 eyes)	Retrospective	2007	Intacs	Mechanical	60	2.52	–	–	59.0%	1.57 ± 2.18
Shabayek and Alió[30] (21 eyes)	Prospective nonrandomized	2007	KeraRings	Femtosecond	6	0.96	2.23	2.67	70.0%	2.24
Shetty *et al.*[27] (14 eyes)	Prospective nonrandomized	2008	Intacs	Mechanical	12	5.00	4.06	1.87	69.23%	3.98
Ertan and Kamburoglu[29] (306 ojos)	Retrospective	2008	Intacs	Femtosecond	4	3.09	2.95	0.29	–	2.79
Coskunseven *et al.*[26] (50 eyes)	Retrospective	2008	KeraRings	Femtosecond	24	3.12	–	1.95	68%	3.07

Mean changes achieved in spherical equivalent, sphere, cylinder and keratometry are shown. In addition, the percentage of eyes gaining lines of BSCVA is also reported. Caution must be taken when comparing these outcomes because different samples of keratoconus eyes were evaluated and additionally different nomograms have been used for ICRS implantation (see Tables 1,2). BSCVA, best spectacle-corrected visual acuity; D, dioptre; ICRS, intracorneal ring segments; max K, maximum keratometry; SE, spherical equivalent.

Intacs implantation.[33] Carrasquillo *et al.* found an 81% of increase in contact lens tolerance after Intacs implantation in keratoconus and post-LASIK ectasia.[80] Furthermore, Shetty *et al.* demonstrated that contact lens tolerance improved significantly in advanced keratoconus eyes after Intacs implantation.[27]

Pellucid marginal degeneration

Few case reports or studies including cases of PMD implanted with ICRS have been published because of the complexity of finding such cases in clinical practice.[45–51] A reduction of spherocylindrical error was observed in this kind of corneas after ICRS implantation.[45–50] Ertan and Bahadir found in nine eyes with PMD a mean reduction in sphere and cylinder of 1.59 and 1.47 D, respectively.[46] A more significant change in cylinder (4.59 D) was reported by Mularoni *et al.*[47] in eight eyes with PMD and implanted with Intacs. As could be expected, a central flattening is also induced by ICRS in this kind of corneas.[45–51] In the largest published series, around 1.5 D of central flattening was achieved on average with these implants.[46,47] Furthermore, Rodriguez-Prats *et al.* found that a significant visual improvement could be achieved with hybrid contact lenses after Intacs implantation in eyes with this type of corneas.[51]

Post-LASIK ectasia

The same visual, refractive and curvature changes as in keratoconus have been observed in post-LASIK ectatic corneas after ICRS implantation. A reduction in sphere and cylinder as well as a central corneal flattening was found with these implants.[52–60] A mean central flattening around 3 D and a mean reduction in spherical equivalent higher than 2 D has been reported.[53,54,57] According to previous studies, a great percentage of cases experienced an improvement in BSCVA[53,54] (70% or more) after ICRS implantation. This fact could be in relation with a probable partial correction of higher order aberrations in these corneas.

Complications

Intraoperative complications during ICRS implantation in ectatic corneas are rare. In any case, some intraoperative adverse events have been described with the mechanical procedure for corneal tunnelization, but always as isolated and rare events: segment decentration,[40] asymmetry of the implants,[40] inadequate depth of channel,[40] superficial channel dissection with anterior Bowman's layer perforation[42] and anterior chamber perforation.[37] Regarding postoperative complications, several events have been described: ring segment extrusion (Fig. 5),[29,31,37,39,40,42] corneal neovascularization (Fig. 6),[27,32,33,41,53,57,76,84] infectious keratitis,[30,39,40,80] mild channel deposits around Intacs (Fig. 2),[27,32,33,36,41,44,57] ring segment migration,[26,40,76] epithelial plug at the incision site,[35] corneal haze around segments[29] or at the incision site,[30] corneal melting,[31,37] night halos,[42] chronic pain (only 1 case described)[85] and focal oedema around segments (only 1 case described).[86] Most cases of extrusion have been observed in eyes implanted using mechanical dissection,[31,37,39,40,42] although three cases of ring extrusion in advanced keratoconus and one case of segment migration to the incision site have been reported using the femtosecond laser-assisted

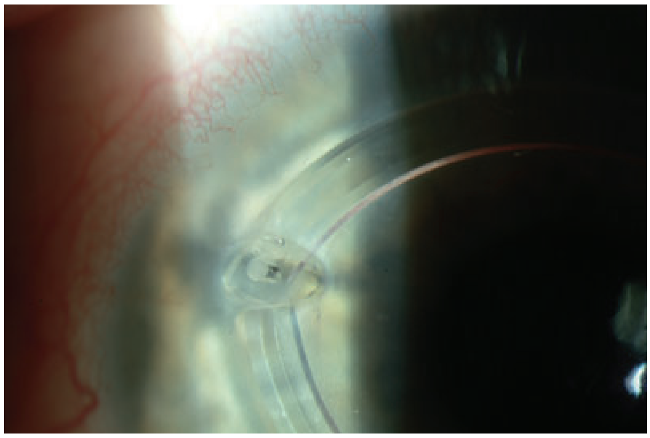


Figure 5. Ring segment extrusion at the incision site in one keratoconus eye implanted with Intacs using the mechanical spreader for corneal tunnelization.

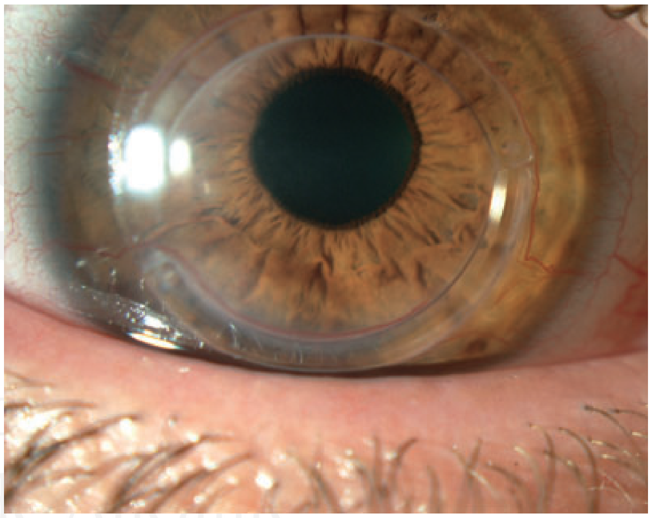


Figure 6. Neovascularization of inferior and superior corneal channels in a keratoconus eye implanted with Intacs using the mechanical spreader for corneal tunnelization.

procedure for channel creation.[26,29] Ring segment extrusion is one of the most common causes for explantation,[29,31,37,42,76] although dissatisfaction with outcomes is another important reason.[36] Explantation rate varies significantly depending on the study (surgeon, keratoconus severity, mechanical or femtosecond) and values from 0.98% to 30% have been obtained.[27,32,33,36,41,44,57] ICRS can be safely and easily explanted, with most of visual, refractive and topographic features returning to near the preimplantation levels.[87] In the specific case of pellucid marginal degeneration one case of ring segment explantation has been reported as a consequence of a Descemet's membrane detachment.[88]

Pokroy and Levinger[89] stated that approximately 10% of keratoconic eyes managed with Intacs may require adjustment surgery, which often has a good outcome. This adjustment normally consists on rotation of one segment or explantation of the superior segment.[26,41,71,89] The aim of this adjustment is to improve visual acuity and corneal regularity,[71,89] but sometimes also avoiding ring segment migration to the incision site with final extrusion.[26]

An additional common finding after Intacs implantation is the presence of intrastromal deposits that accumulate in the lamellar channel after implantation (Fig. 2). Its incidence could be as high as more than 60%.[90] The incidence and density of these deposits increased with segment thickness and duration of implantation and it consists of intracellular lipids as cholesterol ester or triglyceride.[91] The presence of this material did not result in alteration of the optical performance of Intacs or anatomical or physiological corneal deterioration.[90] Regarding histopathological studies, Samimi *et al.* found that Intacs induced keratocyte apoptosis,[92] probably through a switch to a collagenous synthetic phenotype. These histological changes seemed to be entirely reversible after implant removal, but long-term studies are necessary in order to corroborate this hypothesis.

Conclusion

The introduction of corneal reshaping techniques for the correction of refractive errors, such as the implantation of ICRS, is considered as a significant advance in ophthalmology. ICRS were developed originally for the correction of myopia but curiously a successful use was found in the corneal ectatic disease for reducing the spherocylindrical error and corneal irregularity. There is sufficient evidence of the efficacy of this kind of implants for the management of corneal ectasia and they are nowadays considered as a useful therapeutic tool for these corneas. There are two main advantages in implanting these segments: no elimination of corneal tissue is required and the changes induced in the corneal shape with this technique are reversible (if segments are explanted the cornea returns near to its original state). Several published studies have demonstrated the adequate biocompatibility and also the efficacy of ICRS in reducing the corneal curvature and refractive error. However, these implants should be investigated further, because their mechanism of action in the ectatic cornea is still not well understood.

Several nomograms for ICRS implantation have been developed, all of them based on empirical data. Good outcomes have been reported using all of them. However, there are anecdotal cases with minimal keratometric reductions or with no keratometric effect in spite of following the indications provided by these nomograms. Therefore, there is a need for readjusting them in order to obtain more predictable results. We believe that more preoperative data should be considered in the selection of the ring segment to implant, not only manifest refraction and topographic data. Biomechanical and aberrometric parameters should be considered in the future when developing new nomograms.

According to the published reports, ICRS can be implanted successfully in keratoconus, PMD and post-LASIK ectatic eyes, but poor results can be anticipated in the more advanced cases (mean keratometry higher than 55 D), especially if infero-superior asymmetry is significant. The surgical technique used for implantation also seems an important factor to be considered. Although it has been demonstrated that ICRS implanted with both mechanical and femtosecond laser-assisted surgical techniques provide good visual and refractive outcomes in ectatic corneas, the mechanical procedure seem to be more frequently associated to complications. Some of them are clearly related with the learning curve of the surgeon, because this surgical procedure is highly dependent on surgeon manual skills. In any case, in the last reported series the incidence of complications is low and they can be considered as rare events, which confirm the safety of ICRS surgery.

Future research is mandatory in this field in order to obtain models for predicting the corneal response in healthy and also in ectatic corneas. Mathematical models should be developed in order to achieve more appropriate and accurate nomograms for ICRS implantation. Well-designed prospective studies using these new adjusted nomograms based on accurate mathematical models and data analyses should be developed. ICRS today are to be considered a good option for the corrective treatment of keratoconus and other ectatic disorders, but in the future this treatment modality may experience an outstanding evolution with a more scientific knowledge applied to its use.

Acknowledgement

This study has been supported in part by a grant from the Spanish Ministry of Health, Instituto Carlos III, Red Temática de Investigación Cooperativa en Salud 'Patología ocular del envejecimiento, calidad visual y calidad de vida', Subproyecto de Calidad Visual (RD07/0062).

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Refractive and Aberrometric Outcomes of Intracorneal Ring Segments for Keratoconus: Mechanical versus Femtosecond-assisted Procedures

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Objective: To compare visual, refractive, and corneal aberrometric outcomes in keratoconic eyes implanted with intracorneal ring segments (ICRS) implantation using either a mechanical or a femtosecond laser-assisted procedure.

Design: Retrospective, consecutive case series.

Participants: A total of 146 consecutive eyes of 106 patients with the diagnosis of keratoconus (68 unilateral and 39 bilateral) were included. Two groups were created according to the surgical technique used for corneal tunnelization: Mechanical group (mechanical tunnelization, 63 eyes) and Femtosecond group (femtosecond laser-assisted tunnelization, 83 eyes). Intracorneal ring segments implantation was indicated because of the existence of reduced best spectacle-corrected visual acuity (BSCVA) or contact lens intolerance.

Methods: Intracorneal ring segments implantations were performed by 6 surgeons following the same protocol except for the incision location. A total of 55 eyes were implanted with Intacs (Addition Technology, Inc, Fremont, CA) and 8 eyes were implanted with KeraRings (Mediphacos, Belo Horizonte, Brazil) in the Mechanical group, and 25 eyes were implanted with Intacs and 58 eyes were implanted with KeraRings in the Femtosecond group. Mean follow-up was 10.66±8.20 months, ranging from 1 month to 24 months.

Main Outcome Measures: Uncorrected visual acuity (UCVA), BSCVA, refraction, keratometry, and root mean square (RMS) for different kinds of corneal aberrations.

Results: By reporting only for statistically significant changes, UCVA improved in both groups at 6 months ($P \leq 0.02$) and BSCVA improved in the Femtosecond group ($P < 0.01$). The refraction improved in both groups at 6 months ($P \leq 0.02$). The cornea on average was flatter in both groups at 6 months ($P < 0.01$). Root mean square astigmatism was reduced in the Femtosecond group ($P = 0.03$), but there was an increase in some higher-order aberrations ($P = 0.03$). Significant differences were found between the 2 groups for eyes implanted with Intacs for primary spherical aberration, coma, and other higher-order aberrations, favoring the Femtosecond group ($P \leq 0.01$). A significant negative correlation was found between the preoperative corneal aberrations and the postoperative BSCVA in the Mechanical group ($r > 0.63$, $P \leq 0.04$).

Conclusions: Intracorneal ring segments implantation using both mechanical and femtosecond laser-assisted procedures provide similar visual and refractive outcomes. A more limited aberrometric correction is observed for eyes with mechanical implantation.

Financial Disclosure(s): The author(s) have no proprietary or commercial interest in any materials discussed in this article. *Ophthalmology 2009;116:1675–1687 © 2009 by the American Academy of Ophthalmology.*

Keratoconus is an ectatic corneal disorder characterized by a progressive corneal thinning that results in corneal protrusion, irregular astigmatism, and decreased vision.[1] The management of patients with keratoconus must include visual rehabilitation because the visual function is devastated as a result of the significant increase in all ocular aberrations.[2–5] Spectacle correction is only adequate for early cases, whereas in advanced or moderate cases, contact lenses or surgical solutions are necessary to achieve a satisfactory visual outcome. Rigid gas-permeable and hybrid contact lenses provide good visual quality.[6] However, some patients can become intolerant to contact lenses[7] or achieve an unacceptable visual performance.[8]

Intrastromal corneal ring segments (ICRS) have been proposed and investigated as an additive surgical procedure for keratoconus correction,[9–28] providing an interesting alternative aiming at delaying and preventing corneal graft in patients with keratoconus.[15,16] This type of surgical treatment has proved to be effective in improving visual acuity, reducing the refractive error and mean keratometry. The addition of extra material at the corneal mid-periphery induces a displacement of the local anterior surface forward at

Published by Elsevier Inc.

ISSN 0161-6420/09/$–see front matter
doi:10.1016/j.ophtha.2009.05.016

this area and a flattening of the central portion of the anterior cornea because of the morphologic structure of corneal lamellae (arc-shortening effect).[29] The use of short arc-length ring ICRS has proved to be effective for the correction of astigmatism,[9,13,25] because this kind of procedure induces less corneal flattening and a significant change in corneal toricity as a result of the corneal architecture (predicted by finite element modeling).[30]

Mechanical dissection was the first method described for facilitating the insertion of ring segments (mechanical procedure).[26–28] Good visual results and reduced complications rates have been reported using the mechanical procedure in early to moderate keratoconus.[10,11,14–17,19–28] However, the use of femtosecond laser for corneal tunnelization became widely accepted after the approval of its use by the Food and Drug Administration in the United States.[31] This laser allows the surgeon to program the tunnelization at a predetermined depth with a high degree of precision. Theoretically, this femtosecond laser-assisted procedure would generate a more accurate stromal dissection, reducing surgical error and leading to better visual and refractive results. However, in 2 studies[32,33] comparing both femtosecond and mechanical tunnelization procedures in ectatic eyes, no differences in visual and refractive outcomes were detected. However, the follow-up period was no greater than 12 months.

The aim of the present study was to compare visual, refractive, and corneal aberrometric outcomes in keratoconic eyes in which ICRS implantation was facilitated using either the mechanical or the femtosecond-laser assisted procedure with a follow-up period up to 24 months.

Patients and Methods

Patients

In the current study, a multicenter retrospective analysis of a nonrandomized consecutive series of cases was performed. Data of all patients who underwent ICRS implantation for keratoconus treatment from September 2000 to June 2007 in 6 different ophthalmologic centers, 5 Spanish (Vissum Alicante, Vissum Sevilla, Vissum Albacete, Vissum Almería, University Clinic of University of Navarra) and 1 Turkish (Refractive Surgery Department of Dunya Eye Hospital, Istanbul), were reviewed and analyzed comprehensively. Table 1 summarizes the contribution of each participating center to the current study. A total of 146 consecutive eyes of 106 patients diagnosed with keratoconus (68 unilateral and 39 bilateral cases) were included. Two different groups were created according to the surgical technique used for creation of corneal channels: eyes operated using mechanical tunnelization (Mechanical group: 63 eyes, 43.15%) and eyes operated using femtosecond laser-assisted tunnelization (Femtosecond group: 83 eyes, 56.85%). In all cases, ICRS implantation was indicated because of the existence of reduced best spectacle-corrected visual acuity (BSCVA) or contact lens intolerance.

A comprehensive examination was performed in all cases before ICRS implantation to ensure the viability of the surgery. This examination included Snellen uncorrected visual acuity (UCVA) and BSCVA (decimal notation), manifest refraction, slit-lamp biomicroscopy, Goldman tonometry, fundus evaluation, ultrasonic pachymetry, and corneal topography. Keratoconus diagnosis was

Table 1. Contribution of Each Participating Ophthalmologic Center to this Retrospective Study

Investigator	Surgeon	Ophthalmologic Center	Eyes Implanted with ICRS
1	Dr Alió	Vissum Alicante (Spain)	116
2	Dr Coşkunseven	Refractive Surgery Department of Dunya Eye Hospital, Istanbul (Turkey)	14
3	Dr Morbelli	Vissum Albacete (Spain)	6
3	Dr Uceda	Vissum Sevilla (Spain)	4
4	Dr Maldonado	University Clinic, University of Navarra	3
5	Dr Cuevas	Vissum Almería (Spain)	3

ICRS = intracorneal ring segments.

based on corneal topography and slit-lamp observation: asymmetric bowtie pattern with or without skewed axes and presence of stromal thinning, corneal conical protrusion at the apex, Fleischer ring, Vogt striae, or anterior stromal scar.[1]

Because topographic data were collected from different periods and different centers, 3 different corneal topographic systems were used for corneal examination: CMS 100 Topometer (G. Rodenstock Instrument GmbH, Ottobrunn, Germany), CSO (CSO, Firenze, Italy), and Orbscan IIz system (Bausch & Lomb, Rochester, NY). The first 2 devices are Placido-based systems, and the Orbscan IIz is a combined scanning-slit and Placido-disc topographic system. Although agreement between these specific devices has not been reported, Orbscan and Placido-based devices have been proved to provide similar accuracy and precision on calibrated spherical test surfaces.[34] In the study, the following topographic data were evaluated and recorded with all corneal topographic devices: the corneal dioptric power in the flattest meridian for the 3 mm central zone (K1), corneal dioptric power in the steepest meridian for the 3 mm central zone (K2), mean corneal power in the 3 mm zone (KM), and inferosuperior asymmetry index, calculated as the difference between the dioptric power at 3 mm below and above the corneal geometric center.

Corneal aberrometry was also recorded and analyzed only in those patients examined at all visits with the CSO topography system (85 eyes), because this device was the only one with the capability to calculate directly this specific information. The CSO topography system analyzes a total of 6144 corneal points of a corneal area enclosed in a circular annulus defined by an inner radius of 0.33 and an outer radius of 10 mm in respect to corneal vertex. The software of this system, the EyeTop2005 (CSO), automatically performs the conversion of corneal elevation profile into corneal wavefront data using the Zernike polynomials with an expansion up to the seventh order. In this study, aberration coefficients and root mean square (RMS) values were always calculated for a 6-mm pupil. The following aberrometric parameters were recorded and analyzed: higher-order RMS (computed for third to seventh Zernike terms), primary coma RMS (computed for the Zernike terms $Z_3^{\pm 1}$), coma-like RMS (computed for third, fifth, and seventh-order Zernike terms), spherical-like RMS (computed for fourth and sixth-order Zernike terms), and residual RMS (computed considering all Zernike terms except those corresponding with primary coma and spherical aberration). The corresponding Zernike coefficient for primary spherical aberration (Z_4^0) was also reported with its sign.

Table 2. Nomogram for Intacs (Addition Technology, Inc, Fremont, CA) Implantation Based on Corneal Topographic Pattern and Defined by our Research Group[36]

Corneal Topography Pattern	Indication
Steepening area not involving the 180-degree meridian of the cornea (inferior cone)	1 segment of 0.45-mm thickness
Steepening extending at least 1 mm above and beyond the 180-degree meridian (central cone)	2 segments: 0.45-mm thickness segment inferiorly and 0.25-mm thickness segment superiorly

This nomogram was used in the current study.

Ethical board committee approval of our institution (Vissum Instituto Oftalmologico de Alicante) was obtained for this investigation. In addition, during the process of consent for this surgery, consent was taken to later include clinical information in scientific studies.

Surgery

Surgical procedures were performed by 6 surgeons, 1 from each participating center in the study (JLA, Vissum Alicante; EC, Dunya Eye Hospital; HM, Vissum Albacete; AUM, Vissum Sevilla; MML, University of Navarra; and DC, Vissum Almería). In all cases an antibiotic prophylaxis was prescribed before surgery, consisting of topical ciprofloxacin (Oftacilox; Alcon Cusí, Barcelona, Spain) every 8 hours for 2 days. All procedures were performed under topical anesthesia.

The mechanical surgical procedure was initiated marking a reference point for centration (pupil center) and performing a radial incision of approximately 1.8 mm in length. After this, a calibrated diamond knife was set at approximately 70% of the mean corneal thickness determined by ultrasonic pachymetry. From the base of the incision, pocketing hooks were used to create corneal pockets on each side of the incision, taking care to maintain a uniform depth. A device containing a semiautomated suction ring was placed around the limbus, guided by the previously marked reference point on the cornea. Two semicircular dissectors were placed sequentially into the lamellar pocket to be steadily advanced by a rotational movement (counterclockwise and clockwise dissectors).[35] In the femtosecond laser-assisted surgical procedure, the disposable glass lens of the laser system was first applanated to the cornea to fixate the eye and help maintain a precise distance from the laser head to the focal point.[13] Then, a continuous circular stromal tunnel was created at approximately 80% of corneal depth (if this depth was $<400\ \mu m$; if not, a channel was dissected exactly at $400\ \mu m$) within 15 seconds with no corneal manipulation.[13] The 30-kHz IntraLase femtosecond system was always used (IntraLase Corp, Irvine, CA), which could not dissect more than $400\ \mu m$. Incision location was dependent on the surgeon criteria: on the steepest meridian in 122 eyes (83.56%) and on the flattest meridian in 24 eyes (16.44%).

In regard to the ICRS type, Intacs (Addition Technology, Inc, Fremont, CA) were implanted in 80 eyes (54.79%) and KeraRings (Mediphacos, Belo Horizonte, Brazil) were implanted in 66 eyes (45.21%). In the Mechanical group, 55 eyes were implanted with Intacs (37.67%) and only 8 eyes were implanted with KeraRings (5.48%). In the Femtosecond group, 25 eyes (17.12%) were implanted with Intacs and 58 eyes were implanted with KeraRings (39.73%). A tunnel with an inner diameter of 6.6 mm and an outer diameter of 7.8 mm was planned for Intacs implantation, and a tunnel with an inner diameter of 4.8 mm and an outer diameter of 5.7 mm was planned for KeraRings implantation.

The selection of the number (1 or 2) and thickness of Intacs segments was performed following the criteria defined and reported by our research group[35] (Table 2). In regard to KeraRings, arc-length, thickness, and number of segments were selected considering the nomogram defined by the manufacturer[13] (Table 3). Only 1 ring segment was implanted in 26 eyes (17.81%), whereas 2 segments were necessary in the other 120 eyes (82.19%).

Only 2 intraoperative complications were reported in our series: a microperforation in 1 eye (0.68%) using the mechanical spreader and decentered channels with segments over the pupillary area using the IntraLase technology in another eye (0.68%). In addition, in another eye operated using the mechanical tunnelization, a superficial channel was created and finally had to be explanted (extrusion at 1 month).

Topical tobramycin and dexamethasone eye drops (TobraDex; Alcon Laboratories, Inc., Fort Worth, TX) were used postoperatively every 6 hours for 1 week and stopped. Topical lubricants were also prescribed every 6 hours for 1 month (Systane, Alcon Laboratories, Inc.).

Follow-up Evaluation

Postoperative visits were scheduled for the first postoperative day and for months 1, 3, 6, 12, and 24 postoperatively. On the first postoperative day, UCVA measurement and slit-lamp examination (intracorneal rings position and corneal integrity) were performed. Snellen UCVA and BSCVA measurement, manifest refraction, slit-lamp examination, and corneal topography were performed in the rest of postoperative examinations. The mean follow-up was

Table 3. Nomogram for KeraRings (Mediphacos, Belo Horizonte, Brazil) Implantation Proposed by the Manufacturer (2007)[13]

Spherical Equivalent (D)	All Ectasia Is Limited to One Half of the Cornea	75% of the Ectasia in One Half of the Cornea and 25% Situated in the Other Half	Two Thirds of the Ectatic Area in One Half of the Cornea and One Third in the Other Half	Ectasia is Distributed Evenly in Both Corneal Halves
>-10 D	25/35	25/35	30/35	35/35
-8 to -10 D	20/30	20/30	25/30	30/30
-6 to -8 D	15/25	15/25	20/25	25/25
-2 to -6 D	0/20	0/20	15/20	20/20

D = diopters.
This nomogram was created for 160-degree arc-length segments only, and it provided a selection of segment distribution and thickness based on spherical equivalent and corneal topographic pattern (distribution of ectasia). For defining the distribution of the ectasia, the cornea is divided into 2 halves using the steepest meridian as axis of separation. Nomogram notation: 25/35 = upper segment thickness/lower segment thickness (0.25 mm/0.35 mm).

Table 4. Distribution of Keratoconus Cases According to the Amsler-Krumeich and Alió-Shabayek Classifications in the Mechanical and Femtosecond Groups

	Grade I	Grade II	Grade III	Grade IV
Mechanical				
Amsler-Krumeich	30 (47.62%)	16 (25.40%)	5 (7.94%)	12 (19.05%)
Alió-Shabayek	6 (28.6%)	9 (14.3%)	1 (1.6%)	5 (7.9%)
Femtosecond				
Amsler-Krumeich	38 (45.78%)	21 (25.30%)	10 (12.05%)	14 (16.87%)
Alió-Shabayek	22 (36.1%)	18 (29.5%)	8 (13.1%)	13 (21.3%)

10.66±8.20 months, ranging from 1 month to 24 months. A total of 39 eyes completed the 24-month follow-up. In a total of 38 eyes, ring segments were explanted or repositioned, and the 24-month follow-up could not be completed. The postoperative visits after ring reposition or explantation were not included in the analysis to avoid bias. In addition, corneal crosslinking was performed in 6 eyes during the follow-up; data were not included from visits after corneal crosslinking.

Main Outcome Measures

Uncorrected visual acuity, BSCVA, spherocylindrical refraction, keratometry, and corneal aberrometry were the main outcome measures.

Statistical Analysis

The Statistical Package for the Social Sciences version 15.0 for Windows (SPSS, Chicago, IL) was used for statistical analysis. Normality of all data samples was first checked by means of the Kolmogorov–Smirnov test. When parametric analysis was possible, the Student *t* test for paired data was performed for all parameter comparisons between preoperative and postoperative examinations or consecutive postoperative visits, whereas the Student *t* test for unpaired data was performed to compare outcomes obtained with mechanical and femtosecond-assisted techniques.

When parametric analysis was not possible, the Wilcoxon rank-sum test was applied to assess the significance of differences between preoperative and postoperative data, and the Mann–Whitney test was performed for the comparison of outcomes with both techniques, using the same level of significance ($P<0.05$) in all cases. Statistical analysis of differences in each complication rate between the Mechanical and Femtosecond groups was performed by the chi-square test.

Correlation coefficients (Pearson or Spearman depending if normality condition could be assumed) were used to assess the correlation between different variables. Finally, the efficacy index was calculated as the ratio of the postoperative UCVA to the preoperative BSCVA, and the safety index was calculated as the ratio of the postoperative BSCVA to the preoperative BSCVA.

Results

A total of 146 eyes of 106 patients with a mean age of 31.44±10.29 years (range, 15–64 years) were included. Sixty-three patients were male (59.43%), and 43 patients were female (40.57%). There was a balanced distribution of right and left eyes (74 vs. 72 eyes). Opacity of the cone area was observed in only 12 eyes (8.22%). According to the Amsler–Krumeich grading system,[3] 68 eyes had cone grade I (46.58%), 37 eyes had cone grade II (25.34%), 15 eyes had cone grade III (10.27%), and 26 eyes had cone grade IV (17.81%) (Table 4). By considering the corneal aberrations and according to the Alió-Shabayek grading system,[3] 28 eyes had cone grade I (32.94%), 27 eyes had cone grade II (31.76%), 10 eyes had cone grade III (11.77%), and 20 eyes had cone grade IV (23.53%) (Table 4).

Mechanical Group

Table 5 summarizes the visual, refractive, and keratometric outcomes in eyes implanted with ICRS using the mechanical tunnelization (Mechanical group). At 6 months postoperatively, a statistically significant reduction was found in sphere, cylinder, and spherical equivalent (all $P\leq0.02$, Wilcoxon test). No statistically significant changes were observed in these refractive parameters during the rest of follow-up ($P\geq0.34$, Student *t* and Wilcoxon tests), although a small but insignificant regression of the achieved spherical correction was observed at 12 months ($P = 0.34$, Wilcoxon test).

Table 5. Summary of Visual, Refractive, and

Parameter (Range)	Preoperative	3 Mos
UCVA	0.18±0.18 (0.01–0.60)	0.30±0.19 (0.05–0.70)
Sphere (D)	−3.41±3.70 (−14.00 to +2.50)	−1.91±4.06 (−12.00 to +3.50)
Cylinder (D)	−4.33±2.33 (−11.00 to 0.00)	−2.48±1.74 (−6.00 to 0.00)
SE (D)	−5.58±3.85 (−15.00 to +0.50)	−3.15±4.36 (−13.75 to +1.75)
BSCVA	0.52±0.29 (0.05–1.15)	0.55±0.25 (0.05–1.00)
K1 (D)	47.91±4.80 (40.60–59.11)	45.63±3.82 (39.70–54.84)
K2 (D)	53.16±6.00 (42.88–67.90)	50.01±4.49 (43.00–58.56)
KM (D)	50.08±5.20 (39.90–60.65)	46.92±4.26 (40.70–56.70)
ISAI (D)	9.38±6.27 (0.74–24.00)	7.48±5.18 (−2.38 to 19.88)
No. of eyes	63	33

BSCVA = best spectacle-corrected visual acuity; D = diopters; ISAI = inferosuperior asymmetry index; K1 = corneal dioptric power in the flattest 3-mm zone; SE = spherical equivalent; UCVA = uncorrected visual acuity.
Ranges are shown in brackets below each mean value.

A statistically significant improvement was found in UCVA at 6 months ($P<0.01$, Wilcoxon test), with no significant changes during the rest of follow-up ($P \geq 0.66$, Wilcoxon test). In contrast, BSCVA did not change significantly after surgery ($P \geq 0.33$, Student *t* test); 41.18% of eyes at 6 months and 42.11% of eyes at 24 months gained ≥2 lines of BSCVA (Fig 1), and 35.29% of eyes at 6 months and a similar percentage of eyes (36.84%) at 24 months lost lines of BSCVA (Fig 1). Two eyes losing lines of BSCVA had a significant cone opacity, and 2 eyes presented a corneal melting at the incision area with a posterior ring segment extrusion (in both cases, segments were explanted). Mean efficacy and safety indices at 6 months were 0.59±0.31 (range, 0.14–1.40) and 1.14±0.63 (range, 0.17–2.67), respectively. These indices increased to 0.80±0.67 and 1.35±0.80, respectively, at 24 months.

Mean keratometry decreased significantly from 50.08 diopters preoperatively to 45.55 diopters at 6 months after surgery ($P<0.01$, Student *t* test). There was a regression of this flattening effect at 12 months, but it was not statistically significant ($P = 0.37$, Student *t* test). In addition, no significant changes were found in inferosuperior asymmetry index after surgery ($P \geq 0.71$, Student *t* test).

Table 6 summarizes corneal aberrometric outcomes in the Mechanical group. At 6 months, no statistically significant changes were found in any corneal aberrometric parameter, although a slight but insignificant reduction was observed in the RMS for higher-order, astigmatism, primary coma, and coma-like aberrations ($P \geq 0.31$, paired Student *t* and Wilcoxon tests). There was an insignificant increase in higher-order, primary coma, spherical-like, and coma-like RMS between months 6 and 12 ($P \geq 0.35$, paired Student *t* test). In addition, no significant changes were detected between months 12 and 24, although there was a tendency toward a reduction in higher-order, primary coma, spherical-like, and coma-like RMS ($P \geq 0.11$, paired Student *t* and Wilcoxon tests).

Negative significant correlations were found between postoperative BSCVA at 6 months and several preoperative corneal aberrometric parameters: higher-order ($r = -0.67$, $P = 0.02$), primary coma ($r = -0.66$, $P = 0.02$), spherical-like ($r = -0.81$, $P<0.01$), and coma-like ($r = -0.63$, $P = 0.03$) RMS. Significant correlations were also observed between postoperative BSCVA at 12 months and the same aberrometric parameters: higher-order ($r = -0.75$, $P<0.01$), primary coma ($r = -0.63$, $P = 0.04$), spherical-like ($r = -0.85$, $P<0.01$), and coma-like ($r = -0.72$, $P = 0.01$) RMS.

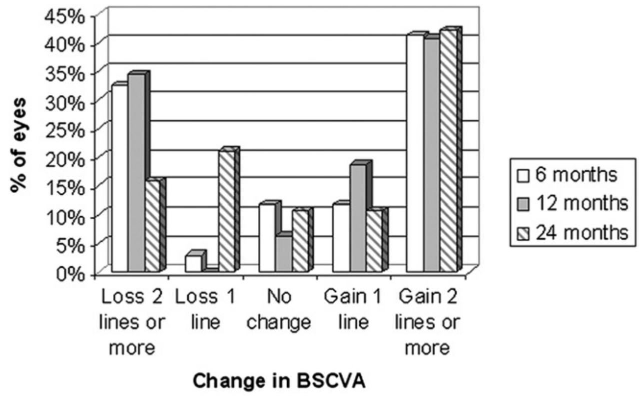

Figure 1. Changes in lines of BSCVA postoperatively in eyes operated with the mechanical procedure. Gains of ≥2 lines of BSCVA were found in 41.18% of eyes at 6 months, 40.63% of eyes at 12 months, and 42.11% of eyes at 24 months. BSCVA = best spectacle-corrected visual acuity.

Femtosecond Group

Table 7 summarizes the visual, refractive, and keratometric outcomes in eyes implanted with ICRS using the femtosecond laser-assisted tunnelization (Femtosecond group). A statistically significant reduction was found in sphere, cylinder, and spherical equivalent at 6 months ($P<0.01$, Wilcoxon test). During the remainder of the follow-up, no significant changes in these parameters were found, although a slight but insignificant additional reduction was observed between months 12 and 24 ($P \geq 0.13$, Wilcoxon test).

Statistically significant improvements in UCVA and BSCVA were found at 6 months ($P \leq 0.02$, Wilcoxon test), remaining stable during the rest of the follow-up ($P \geq 0.33$, Wilcoxon test); 46.55% of eyes gained ≥2 lines of BSCVA at 6 months, whereas 5 eyes lost lines of BSCVA (Fig 2). Ring segment extrusion occurred in 2 of those eyes with BSCVA loss, and an irregular position of the ring with no manifest extrusion was observed in 1 eye (tilted ring, not positioned in the correct plane). Mean efficacy and safety indices at 6 months were 0.77±0.72 (range, 0.07–3.73) and 1.61±1.66 (range, 0.50–12.00), respectively. These indices increased to 0.99±1.94 and 1.96±2.51, respectively, at 24 months.

A statistically significant central flattening was found 6 months postoperatively ($P<0.01$, Wilcoxon test). No significant changes

Keratometric Outcomes in the Mechanical Group

6 Mos	12 Mos	24 Mos
0.36±0.23 (0.05–0.85)	0.33±0.25 (0.02–0.90)	0.35±0.25 (0.02–0.90)
−1.26±2.71 (−11.00 to +3.00)	−2.09±4.19 (−16.00 to +3.00)	−2.15±4.35 (−12.00 to +2.50)
−2.56±1.76 (−6.00 to 0.00)	−2.86±1.75 (−6.00 to 0.00)	−2.03±1.99 (−7.00 to 0.00)
−2.48±2.74 (−11.00 to +1.00)	−3.52±4.17 (−16.00 to +1.00)	−3.16±4.52 (−14.25 to +0.75)
0.60±0.28 (0.05–1.00)	0.53±0.27 (0.05–1.00)	0.59±0.27 (0.20–1.00)
43.97±2.82 (40.05–50.52)	46.37±5.28 (36.82–60.88)	46.75±4.71 (40.84–55.49)
48.07±4.01 (41.50–56.49)	49.97±5.47 (41.89–62.07)	50.01±4.92 (43.05–59.09)
45.55±3.31 (39.60–52.03)	47.90±5.22 (39.36–61.80)	47.89±4.66 (42.20–56.07)
8.77±1.47 (7.44–11.47)	8.84±4.48 (2.15–16.82)	5.22±4.13 (−1.00 to 12.18)
32	30	18

meridian for the 3-mm central zone; K2 = corneal dioptric power in the steepest meridian for the 3-mm central zone; KM = mean corneal power in the

Table 6. Summary of the Corneal Aberrometric

Parameter	Preoperative	3 Mos
Higher-order RMS (μm)	3.62±1.65 (0.91–5.99)	3.74±1.64 (1.19–7.32)
RMS astigmatism (μm)	3.30±1.92 (1.42–7.35)	2.48±1.11 (0.79–4.61)
Primary coma RMS (μm)	3.18±1.61 (0.57–5.65)	3.13±1.64 (1.05–7.08)
Z_4^0 (μm)	−0.25±0.65 (−1.90 to 0.78)	−0.88±0.72 (−2.04 to 0.36)
Residual RMS (μm)	1.44±0.73 (0.38–3.06)	1.60±0.69 (0.42–2.60)
Spherical-like RMS (μm)	1.06±0.47 (0.42–2.00)	1.41±0.63 (0.43–2.48)
Coma-like RMS (μm)	3.45±1.62 (0.62–5.86)	3.43±1.61 (1.11–7.10)
No. of eyes	22	13

RMS = root mean square.
Ranges are given in brackets below each mean value. Aberrometric definitions: primary coma, terms $Z_3^{\pm 1}$; primary spherical aberration, term Z_4^0; residual fifth, and seventh order.

were detected in keratometry during the rest of the follow-up ($P \geq 0.08$, Student *t* and Wilcoxon tests). In addition, no significant changes were found in inferosuperior asymmetry index after surgery ($P = 0.82$, Student *t* test). In regard to corneal aberrometry (Table 8), a statistically significant reduction in the RMS for astigmatism was observed ($P = 0.03$, Wilcoxon test) at 6 months. A significant increase in residual higher-order RMS was observed ($P = 0.03$, Wilcoxon test) at 6 months. A progressive reduction in higher-order, primary coma, and coma-like aberrations RMS was also observed during the follow-up, but these changes did not reach statistical significance ($P \geq 0.34$, Student *t* and Wilcoxon tests). No significant correlations were found between postoperative BSCVA and preoperative corneal aberrometric parameters.

Mechanical versus Femtosecond

Comparison of outcomes obtained with the mechanical and femtosecond-guided procedures for each segment type (Intacs and KeraRings) and for each keratoconus grade was planned initially to avoid the possible variability introduced by these 2 factors. However, only this comparison was feasible for cases of early to moderate keratoconus (grade I and II) implanted with Intacs (mechanical subgroup 24 eyes vs. femtosecond subgroup 19 eyes) because the samples in the remaining groups were not large enough for plausible statistical testing. Only 8 eyes were implanted with KeraRings using the mechanical procedure, 6 eyes with keratoconus grade I and 2 eyes with keratoconus grade II (only 2 of these 8 eyes with available aberrometric data). In addition, only 2 cases of advanced keratoconus were implanted with Intacs using the IntraLase system. Therefore, only comparison of outcomes achieved with Intacs in early to moderate keratoconus (grades I and II) using the mechanical and femtosecond-guided procedures was performed because of these sample limitations.

Preoperatively, statistically significant differences between the mechanical and the femtosecond Intacs subgroups for early to moderate keratoconus were found only in sphere, K2, and KM ($P \leq 0.03$, unpaired Student *t* and Mann–Whitney tests). Because significant differences were present preoperatively, these parameters were not compared postoperatively. In regard to UCVA, cylinder, BSCVA, and K1, no statistically significant differences were found postoperatively between the mechanical and the femtosecond Intacs subgroups ($P \geq 0.06$, unpaired Student *t* and Mann–Whitney tests). The postoperative spherical equivalent only differed significantly at 12 and 24 months, with a mean higher value in the Femtosecond group ($P \leq 0.04$, unpaired Student *t* and Mann–Whitney tests). Significant differences in corneal asymmetry were found at 6 months postoperatively ($P = 0.02$, unpaired Student *t* test, mechanical 8.28±1.08 vs. femtosecond 4.41±4.76 diopters), with a higher asymmetry in those eyes operated using the mechanical dissection. The trend of higher asymmetry in eyes from the mechanical subgroup was maintained at 12 and 24 months postoperatively, but differences between the mechanical and the femtosecond subgroups did not reach statistical significance ($P \geq 0.20$, Mann–Whitney test).

In regard to the aberrometric analysis, no significant postoperative differences were found in RMS corneal astigmatism ($P \geq 0.13$, unpaired Student *t* and Mann–Whitney tests), although mean postoperative values were higher in all visits for the me-

Table 7. Summary of Visual, Refractive, and Keratometric

Parameter (Range)	Preoperative	3 Mos
UCVA	0.26±0.25 (0.01–0.90)	0.29±0.21 (0.01–0.75)
Sphere (D)	−3.60±4.88 (−20.00–+3.00)	−2.54±5.09 (−20.00–+4.00)
Cylinder (D)	−3.67±2.50 (−9.00–0.00)	−2.72±1.60 (−7.00–0.00)
SE (D)	−5.42±5.17 (−22.00–+1.25)	−3.88±5.24 (−22.00–+3.13)
BSCVA	0.51±0.28 (0.03–1.00)	0.62±0.27 (0.10–1.20)
K1 (D)	46.53±4.61 (39.78–60.20)	44.98±5.20 (37.00–59.18)
K2 (D)	51.39±5.85 (42.14–68.53)	48.62±5.54 (38.70–63.25)
KM (D)	49.02±5.10 (41.30–63.25)	46.79±5.19 (37.85–60.71)
ISAI (D)	10.28±7.12 (−1.65–37.67)	10.30±9.25 (−3.02–46.50)
No. of eyes	83	46

BSCVA = best spectacle-corrected visual acuity; D = diopters; ISAI = inferosuperior asymmetry index; K1 = corneal dioptric power in the flattest 3 mm zone; SE = spherical equivalent; UCVA = uncorrected visual acuity.
Ranges are shown in brackets below each mean value.

Outcomes in the Mechanical Group

6 Mos	12 Mos	24 Mos
2.99±0.86 (1.66–4.50)	4.10±2.10 (2.30–9.49)	3.51±1.38 (1.83–5.17)
3.00±1.95 (1.65–7.09)	2.85±1.43 (0.87–6.32)	2.40±1.35 (0.83–3.93)
2.62±0.77 (1.47–4.01)	3.20±1.51 (1.28–6.53)	2.50±1.08 (1.26–3.89)
−0.47±0.70 (−1.34 to 0.45)	−1.09±1.11 (−3.13 to −0.10)	−0.95±0.47 (−1.50 to −0.43)
1.21±0.29 (0.68–1.55)	1.98±1.52 (1.03–6.33)	2.10±1.23 (0.84–4.12)
0.95±0.41 (0.56–1.52)	1.83±1.41 (0.57–5.25)	1.46±0.75 (0.69–2.69)
2.83±0.79 (1.56–4.24)	3.59±1.73 (1.92–7.91)	3.18±1.21 (1.70–4.41)
10	18	10

aberrations, all Zernike terms except $Z_3^{\pm 1}$ and Z_4^0; spherical-like aberrations, terms from fourth and sixth order; coma-like aberrations, terms from third,

chanical subgroup. Higher-order RMS was significantly higher for the mechanical subgroup at 6 months postoperatively ($P = 0.03$, Mann–Whitney test, mechanical 3.24±1.95 vs. femtosecond 1.74±1.06 μm). Primary spherical aberration was significantly more negative in the mechanical subgroup at 1, 3, 6, and 24 months postoperatively ($P \leq 0.03$, unpaired Student *t* and Mann–Whitney tests). Figure 3A shows the postoperative changes in primary spherical aberration and spherical-like RMS in the mechanical and femtosecond Intacs subgroups. As can be observed in this graph, a significant negativization of primary spherical aberration occurred after Intacs implantation using the mechanical procedure ($P = 0.03$, Wilcoxon test). Spherical-like aberration RMS also increased postoperatively, especially in the mechanical subgroup, but differences between the mechanical and femtosecond subgroups did not reach statistical significance ($P \geq 0.07$, unpaired Student *t* test). Mean postoperative values of coma, residual, and coma-like RMS were higher at all postoperative visits for the eyes operated using the mechanical procedure (Fig 3B), and the differences reached statistical significance only for primary coma and coma-like aberration RMS at 3 and 6 months postoperatively ($P \leq 0.02$, unpaired Student *t* and Mann–Whitney tests). In addition, differences between the mechanical and femtosecond subgroups were significant at 12 months for primary coma at 12 months ($P = 0.05$, unpaired Student *t* test).

Complications

Complications in the Mechanical and Femtosecond groups are summarized in Table 9. Segment ring explantation was performed in 12 eyes (18.46%) of the Mechanical group and 11 eyes (13.25%) of the Femtosecond group (Table 9). The reasons for ring segment explantation were extrusion (8 eyes), corneal melting (3 eyes), corneal neovascularization (2 eyes), and very poor visual outcomes. All extrusion and melting cases (Table 9) showed a significant increase in corneal irregularity with large amounts of corneal higher-order aberrations (Figs 4 and 5). Extrusion occurred at 6 months or later in 5 eyes that underwent mechanical tunnelization and in 3 eyes operated using the femtosecond laser. Ring reposition was performed in a total of 11 eyes with the aim of improving the ring effect and the visual and refractive outcomes. Seven of these repositioned segments were finally explanted because of extrusion or poor visual outcomes. Infectious keratitis occurred in 1 eye at 6 months postoperatively, which was appropriately treated with an intensive fortified antibiotic and corticosteroid combination. In this eye, an extrusion of superior ring segment occurred and it was finally explanted.

When comparing the level of complications in the mechanical and femtosecond procedures for eyes with early to moderate keratoconus implanted with Intacs, we found similar rates for extrusion (mechanical 8.33% vs. femtosecond 10.52%), corneal melting (mechanical 4.17% vs. femtosecond 0.00%), neovascularization (mechanical 4.17% vs. femtosecond 0.00%), infection (0.00% in both groups), and ring reposition (mechanical 4.17% vs. femtosecond 0.00%) ($P \geq 0.37$, chi-square test). The explantation rate was higher in the mechanical subgroup (mechanical 20.83% vs. femtosecond 10.53%), but differences did not reach statistical significance ($P = 0.36$, chi-square test).

Outcomes in the Femtosecond Group

6 Mos	12 Mos	24 Mos
0.36±0.26 (0.03–1.00)	0.35±0.25 (0.02–1.00)	0.29±0.22 (0.05–0.90)
−2.45±4.57 (−20.00–+3.50)	−2.24±2.48 (−7.50–+1.50)	−1.17±2.12 (−6.00–+2.75)
−2.81±1.68 (−6.75–0.00)	−3.08±1.86 (0.00–−8.00)	−2.67±1.40 (−7.00 to −1.00)
−3.88±4.71 (−22.00–+2.00)	−3.79±3.56 (−16.00–+0.88)	−2.51±2.11 (−7.00–+2.25)
0.65±0.28 (0.05–1.20)	0.66±0.25 (0.10–1.00)	0.70±0.25 (0.30–1.00)
44.76±3.89 (36.88–54.20)	45.09±4.70 (38.05–59.17)	45.41±4.93 (39.33–58.54)
48.39±4.75 (40.43–61.93)	48.34±5.04 (40.65–62.32)	48.67±5.18 (42.29–61.41)
46.57±4.23 (39.89–57.34)	46.68±4.71 (40.29–60.59)	47.04±4.99 (41.37–59.97)
9.93±6.79 (−3.28–28.96)	8.02±6.93 (−15.98–26.71)	7.20±5.30 (−3.00–14.03)
58	36	19

meridian for the 3 mm central zone; K2 = corneal dioptric power in the steepest meridian for the 3 mm central zone; KM = mean corneal power in the

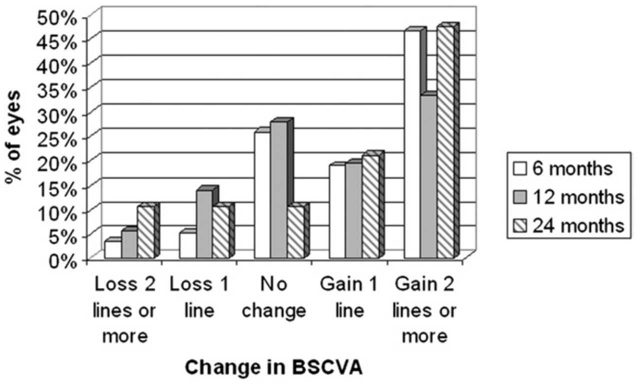

Figure 2. Changes in lines of BSCVA postoperatively in eyes operated with the femtosecond-assisted procedure. Gains of ≥2 lines of BSCVA were found in 46.55% of eyes at 6 months. BSCVA = best spectacle-corrected visual acuity.

Discussion

The current study analyzed the refractive and corneal aberrometric effect of ICRS in keratoconic eyes. We have also studied how this effect can be influenced by the surgical technique used for corneal tunnelization: mechanical (Mechanical group) or femtosecond laser-assisted (Femtosecond group). A significant reduction in manifest sphere, cylinder, and spherical equivalent was found after surgery using both surgical procedures for creation of corneal channels. These refractive changes are in concordance with those reported by previous authors.[9–13,16–20,35] In the Mechanical group, a slight but insignificant regression of spherical correction occurred at 12 months. A similar variability in sphere in a medium to long-term follow-up was also observed previously after Intacs implantation using the mechanical procedure.[15,16,19,23] Part of this variability in spherical correction could be due to the loss of effect of ring segments leading to postoperative complications, such as extrusion or corneal melting (most complications occur at ≥6 months).

Uncorrected visual acuity significantly improved after surgery in both the Mechanical and Femtosecond groups, which is consistent with the significant reduction achieved in refraction. This visual improvement was also reported in other studies on ICRS in corneal ectasia.[9–14,18–20,23,24,26,27,33,35] BSCVA improved significantly only in the Femtosecond group, which supports the findings of other authors.[9,11–13,18] However, there are published reports citing an improvement in BSCVA with ICRS using the mechanical procedure, which is contradictory to the findings of the present study.[10,14,16,17,19,20,23,24,26,33,35] Several factors could explain the difference between our findings and the previous findings. For example, we may have included more moderate and severe cases and observed more complications in the Mechanical group compared with previous studies. Nevertheless, the safety indices of both surgical techniques proved to be excellent with 41.18% (Mechanical group) and 46.55% (Femtosecond group) of eyes gaining ≥2 lines of BSCVA at 6 months.

In regard to corneal curvature, a significant central flattening was achieved in both surgical techniques, in keeping with previous studies on ICRS for keratoconus management.[9–20,23,35] This flattening is responsible for the reduction of refraction and increase in UCVA. However, a regression of the achieved corneal central flattening was observed at 12 months in those eyes implanted with ICRS using the mechanical surgical procedure. This change did not reach statistical significance, but it was consistent with the regression in myopic spherical correction also observed at 12 months. This regression of the central flattening achieved with ICRS implanted using the mechanical procedure in a medium to long-term follow-up has been reported.[15,16,23] Inferosuperior asymmetry also decreased in both groups, but changes did not reach statistical significance because of the high variability of this parameter (not all cones were decentered inferiorly).

In addition to visual and refractive outcomes, changes in anterior corneal aberrations were also evaluated in this study. To the best of our knowledge, this is the first study comparing the corneal aberrometric performance of ICRS implanted using 2 different surgical procedures: mechanical and femtosecond laser-assisted techniques. It should be remembered that anterior corneal aberrometric analysis is an important tool in clinical practice for evaluating the ocular optical quality because the first refractive interface (air–cornea) is the most important contributor to the total power of the eye because of the large difference in refractive index existing at this point. In highly aberrated corneas,

Table 8. Summary of the Corneal Aberrometric

Parameter	Preoperative	3 Mos
Higher-order RMS (μm)	3.35±2.02 (0.33–10.66)	3.19±1.87 (0.72–8.60)
RMS astigmatism (μm)	2.93±2.09 (0.20–10.86)	2.65±1.72 (0.33–8.59)
Primary coma RMS (μm)	2.83±1.94 (0.04–10.07)	2.62±1.88 (0.28–8.46)
Z_4^0 (μm)	−0.14±0.84 (−1.86–2.69)	−0.17±0.71 (−1.75–0.98)
Residual RMS (μm)	1.35±1.01 (0.17–8.10)	1.39±0.95 (0.40–5.72)
Spherical-like RMS (μm)	1.10±0.82 (0.28–6.38)	1.13±0.79 (0.36–4.41)
Coma-like RMS (μm)	3.11±1.93 (0.17–10.46)	2.90±1.83 (0.53–8.50)
No. of eyes	64	34

RMS = root mean square.
Aberrometric definitions: primary coma, terms $Z_3^{\pm1}$; primary spherical aberration, term Z_4^0; residual aberrations, all Zernike terms except $Z_3^{\pm1}$ and Z_4^0; Ranges are shown in brackets below each mean value.

such as in keratoconus, the corneal aberrations of the anterior corneal surface are the most important source of optical errors in the eye. In the current study, we found the effect on the corneal aberrations was dependent on the mechanism used to create the tunnel. After ICRS implantation using the mechanical surgical procedure, no significant changes were achieved in any corneal aberrometric parameter, although reduction was achieved in astigmatism, primary coma, and coma-like aberrations. At 12 months, a significant increase was found in higher-order, primary coma, spherical-like, and coma-like aberrations in the Mechanical group. Furthermore, an increase in primary spherical aberration, higher-order residual, and spherical-like aberrations was induced with ICRS in this group, although changes did not reach statistical significance. Therefore, there was a significant variability in corneal aberrations after ICRS implantation using the mechanical procedure, which implies that corneal irregularity is not well controlled with this kind of surgical intervention. This supports the marginal improvement in BSCVA observed in the Mechanical group.

In corneas implanted with ICRS using the femtosecond-assisted surgical procedure, a significant reduction was observed in the RMS for astigmatism after surgery. In addition, a significant increase in higher-order residual aberrations was found postoperatively. Total higher-order, primary coma, and coma-like aberrations were also reduced postoperatively, but changes did not reach statistical significance. During all follow-up sessions, no significant regressions in the achieved aberrometric correction were observed, confirming the stability of ICRS effect on corneal irregularity in the Femtosecond group. These findings support the conclusions reached by Shabayek and Alió,[13] who found a statistically significant reduction in higher-order RMS for those eyes with a relatively high preoperative RMS ($\geq$3.0 μm) and implanted with KeraRings using the femtosecond laser for corneal tunnelization.

Part of these differences in the aberration profile between the Mechanical and Femtosecond groups, as well as in the refractive and keratometric parameters, could be due to the different ring segment profile implanted in each group (e.g., Intacs were implanted in 87.30% of eyes in the Mechanical group and in 31.25% of eyes in the Femtosecond group). It should be remembered that 2 different kinds of ring segments were used, Intacs and KeraRings, each with a different cross-sectional profile and diameter of implantation. Another factor to consider is the severity of the ectatic disease because higher rates of complications and poorer outcomes have been reported for eyes with advanced keratoconus implanted with ICRS.[17,20] For all these reasons, a comparative analysis of the outcomes achieved with the mechanical and femtosecond-based techniques for each segment type and for early to moderate and advanced keratoconus cases was initially planned to avoid the possible variability introduced by these 2 factors. With this detailed analysis, the aberrometric and refractive variability induced by the technique of corneal tunnelization could be evaluated. However, this comparative analysis was only feasible for eyes with early to moderate keratoconus (grades I and II) implanted with Intacs (mechanical subgroup 24 eyes vs. femtosecond subgroup 19 eyes) because the remaining samples were not large enough to perform a plausible statistical analysis. Examples of the limitations are as follows: Only 8 eyes were implanted with KeraRings using the mechanical procedure (only 2 of these 8 eyes with aberrometric data), and only 2 eyes with advanced keratoconus were implanted with Intacs using the IntraLase system. This study is a retrospective analysis of a consecutive case series and as such has its own limitations. For example, there were an unequal number of Intacs and KeraRings cases implanted with the mechanical and femtosecond-guided procedures.

When comparing the mechanical and femtosecond subgroups in early to moderate keratoconus eyes implanted with Intacs, no significant differences were found in the visual outcomes and magnitude of astigmatic correction. Significant differences were found at 6 months postoperatively in the magnitude of corneal asymmetry. Furthermore, after surgery there was a tendency toward a greater extent of asymmetry in those eyes operated with the mechanical technique. This trend was maintained at 12 and 24 months, but the differences did not reach statistical significance. This greater asymmetry in the mechanical subgroup was consistent with the significantly greater magnitude of primary coma found in this subgroup at 3, 6, and 12 months. In addition, significant differences between the mechanical and the femtosecond subgroups were found in other aberrometric parameters, such as higher-order RMS, coma-like RMS, and primary spherical aberration. Primary spherical aberration changed significantly in the initial postoperative

Outcomes in the Femtosecond Group

6 Mos	12 Mos	24 Mos
3.17±2.21 (0.75–10.39)	3.07±1.54 (0.81–6.78)	2.65±1.19 (0.63–5.44)
2.72±1.87 (0.81–8.83)	2.71±1.58 (0.34–6.95)	2.22±0.90 (0.82–4.05)
2.50±2.04 (0.31–9.08)	2.45±1.56 (0.16–6.38)	2.12±1.36 (0.22–4.87)
0.04±0.85 (−3.28–1.67)	−0.09±0.71 (−2.30–1.61)	−0.16±0.68 (−2.03–0.70)
1.58±1.16 (0.51–6.25)	1.49±0.83 (0.50–4.77)	1.18±0.53 (0.35–2.13)
1.28±0.99 (0.45–5.28)	1.15±0.55 (0.49–2.78)	1.02±0.49 (0.28–2.30)
2.83±2.08 (0.58–9.35)	2.79±1.56 (0.62–6.51)	2.39±1.20 (0.56–4.93)
41	39	18

spherical-like aberrations, terms from fourth and sixth order; coma-like aberrations, terms from third, fifth, and seventh order.

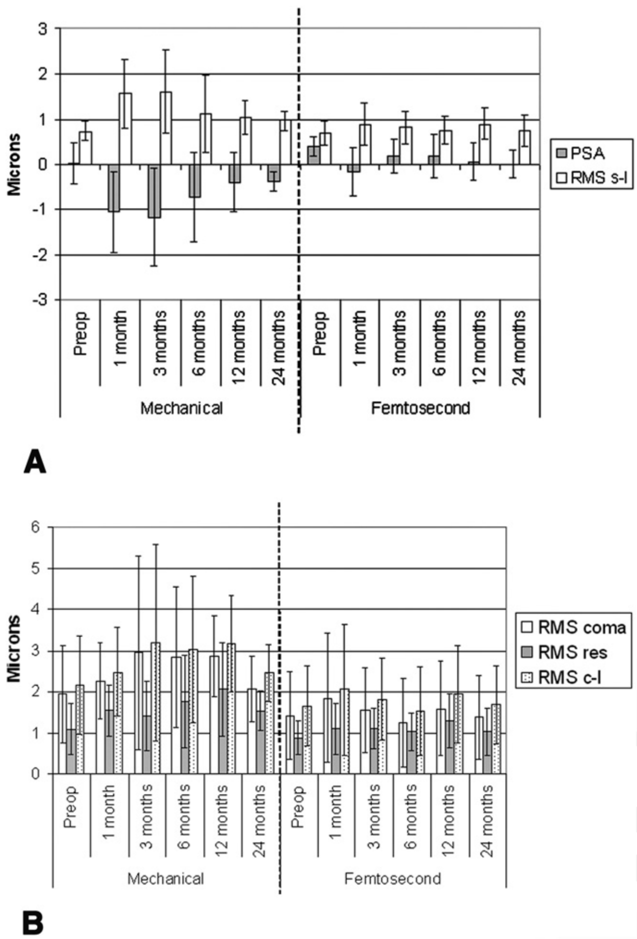

Figure 3. Comparison of corneal aberrometric outcomes after Intacs (Addition Technology, Inc, Fremont, CA) implantation in eyes with early to moderate keratoconus (grades I and II) using the mechanical (*left*) and femtosecond-guided procedures (*right*). **A,** Changes in primary spherical aberration (*grey bars*) and spherical-like (*white bars*) RMS. **B,** Changes in primary coma (*white bars*), residual (*grey bars*), and coma-like (*dotted bars*) RMS. RMS = root mean square; PSA = primary spherical aberration; s-l = spherical-like; res, residual; c-l = coma-like.

period (3 and 6 months) in those eyes operated using the mechanical procedure, with an insignificant regression between 12 and 24 months. The spherical-like and higher-order residual aberrations also were higher for the mechanical subgroup, but differences did not reach statistical significance.

The mechanical tunnelization procedure may lack sufficient precision, and this may affect corneal aberrations, leading to reduced optical performance in the Intacs subgroup. In addition, the impact on corneal biomechanics may lead to instability of the implantation, and this would affect visual quality with more limited visual outcomes. It should be remembered that primary spherical aberration and coma have been proved to have a negative impact on visual acuity because of the optical blur that they induce.[36] Therefore, the limited improvement in BSCVA for eyes implanted with ICRS using the mechanical procedure could be related to the induction of aberrations. Several factors could explain the better aberrometric performance of ring segments implanted using the femtosecond laser, for example, less surgical trauma, better corneal biomechanical control, or more accurate positioning of implants. All of these issues should be considered when performing the surgery. In addition to these conclusions concerning the aberrometric performance, a slight improvement in the aberrometric outcomes was observed at 12 to 24 months in the mechanical Intacs subgroup. This slight improvement observed in the medium term could have several explanations. There was better stability of the implants inside the created tunnels. All cases with complications as extrusions or corneal melting were already explanted at this time or even the smaller sample achieved in the study for these late visits (several cases were excluded as explants, repositions, or crosslinking-treated eyes, and there were some dropouts).

Higher-order, primary coma, spherical-like, and coma-like aberrations were found to be inversely correlated with postoperative BSCVA (6 and 12 months) only in the Mechanical group. This means that visual outcomes are very sensitive to the preoperative level of corneal aberrations in eyes implanted with ICRS using the mechanical procedure. Because a poorer corneal aberrometric performance was achieved in the Mechanical group, less improvement in BSCVA was expected in the most aberrated eyes of this group.

Extrusion, corneal neovascularization, and corneal melting were more frequent complications in eyes implanted with ICRS using the mechanical technique. These complications were associated with a more significant corneal irregularity and higher levels of corneal aberrations. One potential limitation of these outcomes and of

Table 9. Complications in Mechanical and Femtosecond Groups

Event	Mechanical Intacs/KeraRings 55 Eyes/8 Eyes		Femtosecond-assisted Intacs/KeraRings 25 Eyes/58 Eyes	
Extrusion	5 eyes (7.94%)	1 eye (1.52%)	2 eyes (2.41%)	2 eyes (2.41%)
Corneal melting	4 eyes (6.35%)	0 eyes (0.00%)	0 eyes (0.00%)	0 eyes (0.00%)
Reposition	6 eyes (9.23%)	0 eyes (0.00%)	1 eye (1.20%)	4 eyes (4.82%)
Explantation	11 eyes (17.46%)	1 eye (1.52%)	5 eyes (6.02%)	6 eyes (7.23%)
Corneal neovascularization	2 eyes (3.17%)	0 eyes (0.00%)	0 eyes (0.00%)	0 eyes (0.00%)
Infectious keratitis	0 eyes (0.00%)	0 eyes (0.00%)	0 eyes (0.00%)	1 eye (1.20%)

Ring extrusion, corneal melting, and neovascularization incidence, as well as the percentage of repositions and explantations, are shown. Each complication rate is given for each segment type: Intacs and KeraRings.

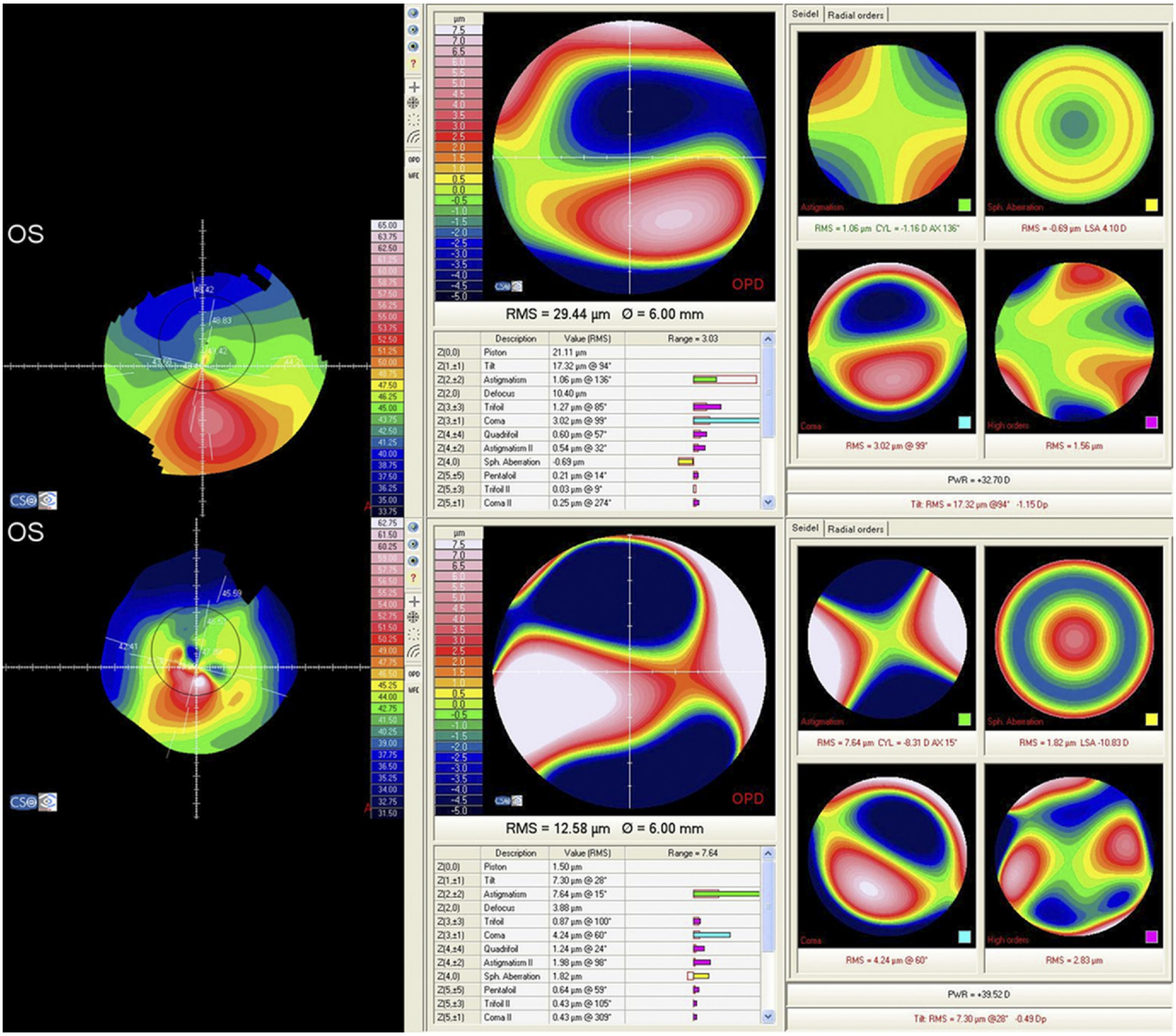

Figure 4. Corneal topography and aberrometric analysis of a keratoconus implanted with Intacs (mechanical procedure) and with both ring segments extruded (superior and inferior) 12 months after surgery. Corneal topographic (*left*) and aberrometric (*right*) maps 4 months before ring segments extrusion (*up*) and when extrusion was detected are shown (*down*). Each corneal aberrometry includes different maps simulating the wavefront considering, from left to right and from up to down, the following optical errors: all aberrations, astigmatism, primary spherical aberration (Z_4^0), primary coma ($Z_3^{\pm 1}$) and the residual aberrations without considering the astigmatism, primary coma, and primary spherical aberration. In addition, the RMS associated with the described optical error is provided below each map. As can be observed, there is a large increase in primary spherical aberration (it becomes more negative, increase of 2.51 μm) and coma (increase of 1.22 μm). RMS = root mean square.

the current study is the learning curve of the surgeon. We have compared the outcomes from different surgeons, and their learning curve could be a potential source of variability, especially for corneal tunnelization with the mechanical device, because it is highly dependent on surgeon manual dexterity. A higher magnitude of variability with 1 specific surgical procedure would imply that this surgical procedure is less reproducible and highly dependent on surgeon skills, leading to less predictable outcomes. Part of the variability in refractive and aberrometric outcomes observed during the follow-up in the Mechanical group could be attributed to this limiting factor: the learning curve of the surgeon. In addition, we have observed that no significant differences were present in the explantation, reposition, corneal neovascularization, corneal melting, extrusion, and infection rates between the mechanical and the femtosecond Intacs subgroups, although the explantation rate was slightly higher for the mechanical subgroup. This could be associated with other patient-related factors.

In conclusion, intracorneal ring segments implantation with Intacs or KeraRings is an effective option for the treatment of spherocylindrical error and corneal irregularity in keratoconus. As other authors have found,[32,33] there were

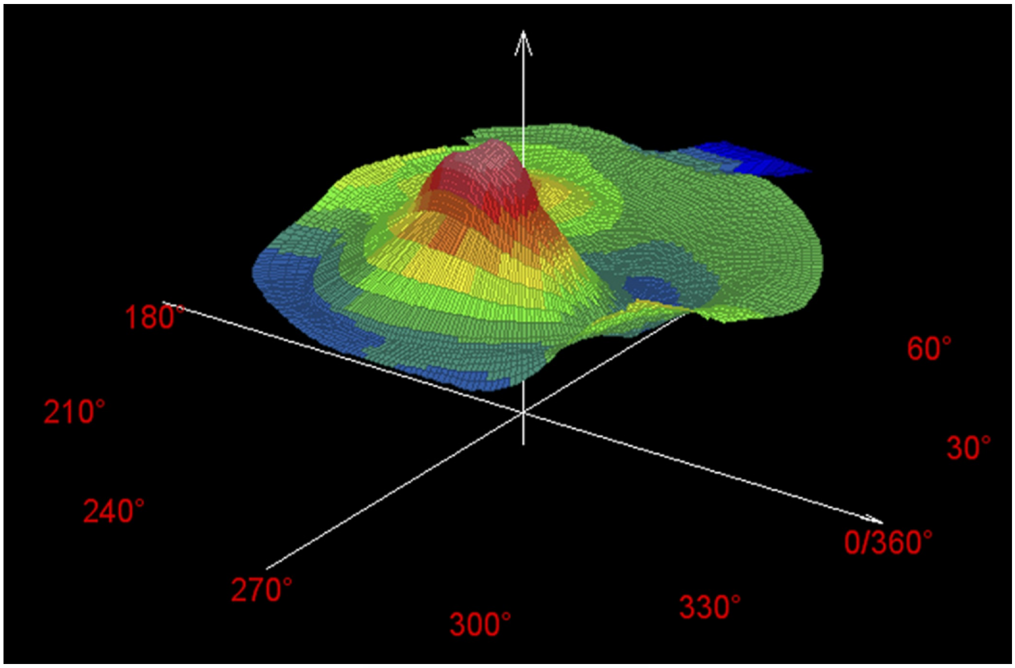

Figure 5. Three-dimensional postoperative corneal profile of a cornea implanted with KeraRings (Mediphacos, Belo Horizonte, Brazil). In this corneal examination, extrusion of the inferior ring segment was present.

no significant differences in refractive and visual outcomes between the mechanical and the femtosecond-assisted surgical techniques for ICRS implantation. Furthermore, it has been demonstrated that final visual outcomes with ICRS (mostly Intacs) implanted using mechanical tunnelization were dependent on the preoperative magnitude of corneal irregularity, exerting a more limited visual improvement in highly aberrated eyes. The use of mechanical tunnelization specifically for Intacs implantation in eyes with early to moderate keratoconus has been demonstrated to limit the potential aberrometric correction of these implants because the procedure itself generates new aberrations, especially negative primary spherical aberration and primary coma. This trend could not be specifically confirmed for KeraRings segments because of the limitations of this retrospective study in the sample size for this segment type. In addition, the impact of the surgical technique specifically in advanced keratoconus should be addressed in future studies with a more complete series of advanced keratoconus cases (homogeneous samples of eyes implanted with Intacs and KeraRings). Longer follow-up is needed to corroborate the stability of visual, refractive, and aberrometric outcomes achieved by these implants using both surgical techniques, mechanical and femtosecond-assisted implantation.

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Footnotes and Financial Disclosures

Originally received: December 19, 2008.
Final revision: May 11, 2009.
Accepted: May 12, 2009.
Available online: July 29, 2009. Manuscript no. 2008-1525.

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Financial Disclosure(s):
The author(s) have no proprietary or commercial interest in any materials discussed in this article.

Supported in part by a grant of the Spanish Ministry of Health, Instituto Carlos III, Red Temática de Investigación Cooperativa en Salud "Patología ocular del envejecimiento, calidad visual y calidad de vida," Subproyecto de Calidad Visual (RD07/0062).

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Refractive and Corneal Aberrometric Changes after Intracorneal Ring Implantation in Corneas with Pellucid Marginal Degeneration

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Purpose: To evaluate refractive, visual, and aberrometric changes in corneas with pellucid marginal degeneration (PMD) implanted with intracorneal ring segments (ICRS) during a 6-month follow-up.

Design: Retrospective, consecutive case series.

Participants: We included 21 consecutive eyes of 15 patients ranging in age from 21 to 73 years old and with a diagnosis of PMD. This diagnosis was made on the basis of slit-lamp (inferior corneal thinning), corneal topography ("butterfly" pattern), and refractive findings (significant against-the-rule astigmatism with best spectacle-corrected visual acuity loss).

Methods: A multicenter, retrospective analysis of patients undergoing ICRS implantation for the management of PMD in 4 ophthalmologic centers was performed. Surgery was indicated in all cases because of reduced best spectacle-corrected visual acuity (BSCVA) and/or contact lens intolerance or dissatisfaction. Mechanical corneal tunnelization was performed in 7 eyes and femtosecond laser-assisted tunnelization in 14 eyes. Intacs were implanted in only 3 eyes whereas KeraRings in 18 eyes. Refractive and corneal aberrometric changes were analyzed during a 6-month follow-up.

Main Outcomes Measures: Uncorrected corrected visual acuity (UCVA) and BSCVA, refraction, keratometry, and root mean square (RMS) for different kinds of corneal aberrations.

Results: The UCVA did not improve at 6 months after surgery ($P = 0.11$). The BSCVA increased from a mean preoperative value of 0.54 to a mean postoperative value of 0.75 ($P = 0.06$). At 6 months, 44.44% of eyes gained ≥2 lines of BSCVA. Sphere ($P = 0.02$), cylinder ($P<0.01$), and spherical equivalent ($P<0.01$) were reduced significantly after surgery ($P\leq0.02$). Mean keratometry decreased significantly from 44.95 diopters (D) preoperatively to 43.19 D at 6 months postoperatively ($P<0.01$). The RMS values for astigmatism, higher order residual, and coma-like aberrations were significantly reduced with surgery ($P = 0.03$). In addition, significant negative correlations of preoperative RMS astigmatism ($r = -0.90$) and primary spherical aberration ($r = -0.86$) with postoperative BSCVA were also found. Segment ring explantation was performed in a total of 4 eyes owing to poor visual outcome.

Conclusions: Implantation of an ICRS is an effective option for the treatment of 2nd-order and higher aberrations in corneas with PMD. Preoperative corneal astigmatism and spherical aberration seem to be limiting factors for a good visual outcome.

Financial Disclosure(s): The authors have no proprietary or commercial interest in any materials discussed in this manuscript. *Ophthalmology 2009;116:1656–1664 © 2009 by the American Academy of Ophthalmology.*

Pellucid marginal degeneration (PMD) is an idiopathic, progressive, noninflammatory, ectatic disorder characterized by a peripheral band of corneal inferior thinning in a crescent-shaped pattern.[1] The area of thinning is typically found in the inferior cornea, extending from the 4 o'clock to 8 o'clock positions,[1] although PMD cases with areas of superior thinning can also be found.[2] This disease is usually asymptomatic, although a progressive deterioration in uncorrected visual acuity (UCVA) and best-corrected visual acuity can occur owing to the irregular astigmatism induced by the corneal ectasia in the most advanced cases.

Corneal topographic analysis reveals a flattening in the vertical meridian, inducing a significant against-the-rule astigmatism and a significant steepening around the area of maximum thinning.[3] This corneal configuration corresponds with a topographic map that shows the classical "butterfly" pattern. Although corneal topography is an important tool for the diagnosis of this corneal pathology, it should not be used as the only diagnostic criterion. Indeed, it has been demonstrated that a characteristic, claw-like pattern of peripheral steepening on corneal topography is not always associated with the diagnosis of PMD.[4] Pachymetric and biomicroscopic findings must also be considered for a reliable diagnosis.

ISSN 0161-6420/09/$–see front matter
doi:10.1016/j.ophtha.2009.06.002

Several possible alternatives to manage PMD have been described, such as rigid, gas-permeable contact lenses,[5–7] intracorneal ring segment (ICRS) implantation,[8–14] crescentic lamellar keratoplasty,[15] penetrating keratoplasty,[16] and corneal wedge excision.[17] Regarding the ICRS, it was demonstrated that the addition of extra material at the normal corneal midperiphery induces a displacement of the local anterior surface forward at this area. This modification generates a peripheral steepening and a flattening of the central portion of the anterior cornea owing to the morphologic structure of the corneal lamellae.[18] If it is assumed that changes induced by ICRS in the normal cornea are similar to those generated in the PMD cornea, these ring segments would be able to minimize and center the peripheral corneal protrusion, inducing a significant change in corneal asymmetry and refraction (especially astigmatism). As a consequence, visual acuity would be also expected to improve. Our research group described and reported the first case of PMD implanted successfully with ICRS.[14] Since then, several authors have reported astigmatic reductions[8–10,12] and improvements in best-spectacle corrected visual acuity (BSCVA)[8–14] after ICRS implantation in corneas with PMD. The improvement in BSCVA induced by ICRS in this kind of corneas could be explained by the reduction of corneal aberrations and asymmetry. However, this issue has not still been analyzed and reported.

The aim of the present study was to analyze refractive, visual, and corneal aberrometric changes in a large sample of PMD corneas implanted with ICRS during a 6-month follow-up. To the best of our knowledge, in this study we present the largest series of cases of corneas with PMD treated with ICRS. Furthermore, this study is the first that attempts to analyze the corneal aberrometric changes that occur in these corneas with these kinds of implants.

Patients and Methods

Patients

A retrospective analysis of outcomes of all patients who underwent ICRS implantation for the management of PMD from September 2005 to February 2008 in 4 different ophthalmologic centers (Spanish centers: Vissum Alicante, Vissum Sevilla and Vissum Albacete; Turkish center: Dunya Eye Hospital from Istanbul) was performed. Table 1 summarizes the contribution of each center to the present study. Twenty-one consecutive eyes from 15 patients with a diagnosis of PMD (9 unilateral and 6 bilateral) were included. This diagnosis was made on the basis of slit-lamp (inferior corneal thinning and ectasia above the area of maximum thinning), corneal topography ("butterfly" pattern, very steep contour in the peripheral inferior cornea with high keratometric powers radiating toward the center from the inferior oblique meridians), and refractive findings (significant against-the-rule astigmatism with BSCVA loss).[9] In all cases, ICRS implantation was indicated because of reduced BSCVA (>2 lines BSCVA) and/or contact lens intolerance or dissatisfaction.

A comprehensive examination was performed in all cases before the ICRS implantation, which included Snellen UCVA (decimal notation), Snellen BSCVA (decimal notation), manifest refraction, slit-lamp biomicroscopy, Goldman tonometry, fundus evaluation, ultrasonic pachymetry, and corneal topographic analysis. Because topographic data were collected from different periods and from 2 different centers, a total of 3 different corneal topography systems were used for corneal examination: CMS 100 Topometer (G. Rodenstock Instrument GmbH, Ottobrunn, Germany), CSO (CSO, Firenze, Italy), and Orbscan IIz system (Bausch & Lomb, Rochester, NY). The first 2 devices are Placido-based systems and the Orbscan II is a combined scanning-slit and Placido-disc topography system. Although agreement between these specific devices has not been reported, Orbscan and Placido-based devices have been demonstrated to provide similar accuracy and precision on calibrated spherical test surfaces.[19] In this study, the following topographic data were evaluated and recorded with all corneal topographic devices: corneal dioptric power in the flattest meridian for the 3-mm central zone (K1), corneal dioptric power in the steepest meridian for the 3-mm central zone (K2), mean corneal power in the 3-mm central zone (KM) and the inferosuperior asymmetry index, calculated as the difference between the dioptric power at 3 mm below and above the corneal geometric center. Additional topographic parameters were analyzed and recorded in patients examined with the CSO topographic system (15 eyes): corneal astigmatism in the 3-mm central zone (AST3), corneal astigmatism in the 6-mm central zone (AST6), mean asphericity for a corneal area of 4.5-mm diameter (Q45), and mean asphericity for a corneal area of 8-mm diameter (Q8).

During the process of consent for this surgery, consent was taken to later include clinical information in scientific studies. Ethical board committee approval of our institution was obtained for this investigation. For all cases, a 6-month follow-up was completed.

Corneal Aberrations of the Anterior Surface

Corneal aberrometry was also recorded and analyzed only in those patients examined at all visits with the CSO topography system (10 eyes), because this device was the only one with the capability to calculate directly this specific information. This topographic system analyses a total of 6144 corneal points of a corneal area enclosed in a circular annulus defined by an inner radius of 0.33

Table 1. Contribution of Each Participating Ophthalmologic Center

Investigator	Surgeon	Ophthalmologic Center	Eyes Implanted with ICRS
1	Dr Alió	Vissum Alicante (Spain)	10
2	Dr Morbelli	Vissum Albacete (Spain)	7
3	Dr Uceda	Vissum Sevilla (Spain)	3
4	Dr Çoşkunseven	Refractive Surgery Department of Dunya Eye Hospital, Istanbul (Turkey)	1

ICRS = intracorneal ring segments.

Table 2. KeraRings Nomogram Used for the Present Study: Segment Distribution and Thickness According to Area of Ectasia and Spherical Equivalent

Spherical Equivalent (D)	All Ectasia Is Limited to One Half of the Cornea	75% of the Ectasia in One Half of the Cornea and 25% Situated in the Other Half	Two thirds of the Ectatic Area in One Half of the Cornea and One Third in the Other Half	The Ectasia is Distributed Evenly in Both Corneal Halves
> −10	25/35	25/35	30/35	35/35
−8 to −10 D	20/30	20/30	25/30	30/30
−6 to −8 D	15/25	15/25	20/25	25/25
−2 to −6 D	0/20	0/20	15/20	20/20

D = diopters.
For defining the distribution of the ectasia the cornea was divided into 2 halves using the steepest meridian as axis of separation. Example: 25/35 = upper segment thickness/lower segment thickness (0.25 mm/0.35 mm).

and an outer radius of 10 mm with respect to the corneal vertex. The software of the CSO, the EyeTop2005, automatically performs the conversion of corneal elevation profile into corneal wavefront data using the Zernike polynomials with an expansion up to the 7th order. In this study, aberration coefficients and root mean square (RMS) values were calculated for a 6-mm pupil in all cases. The following parameters were analyzed and recorded: total RMS, RMS for corneal astigmatism primary coma RMS (computed for the Zernike terms $Z_3^{\pm 1}$), coma-like RMS (computed for third-, fifth-, and seventh-order Zernike terms), spherical-like RMS (computed for 4th- and 6th-order Zernike terms) and higher order residual RMS (computed considering all Zernike terms except those corresponding with primary coma and spherical aberration). The corresponding Zernike coefficient for primary spherical aberration (Z_4^0) was also reported with its sign.

Surgery

Operative procedures were performed by a total of 4 different surgeons, one from each participating center (JLA, HM, AUM, EC). In all cases, an antibiotic prophylaxis before surgery consisting of topical ciprofloxacin (Oftacilox; Alcon Cusí, Barcelona, Spain) to be applied every 8 hours for 2 days was prescribed. All procedures were performed under topical anesthesia.

Corneal tunnelization for facilitating the ring segment insertion was performed using the mechanical procedure in a total of 7 eyes (33.3%) and by means of femtosecond technology in 14 eyes (66.6%). Incision was located on the steepest meridian of the anterior corneal surface in all patients. A tunnel with inner and outer diameters of 6.6 and 7.8 mm, respectively, was always planned for Intacs implantation, whereas inner and outer diameters of 4.8 mm and 5.7 mm, respectively, were planned for KeraRings implantation. No complications occurred intraoperatively.

The mechanical operative procedure was initiated marking a reference point for centration (pupil center) and performing a radial incision of approximately 1.8 mm long. After this, a calibrated diamond knife was set at approximately 70% of the mean corneal thickness determined by ultrasonic pachymetry. From the base of the incision, pocketing hooks were used to create corneal pockets on each side of the incision, taking care to maintain a uniform depth. A device containing a semiautomated suction ring was placed around the limbus, guided by the previously marked reference point on the cornea. Two semicircular dissectors then were placed sequentially into the lamellar pocket to be steadily advanced by a rotational movement (counterclockwise and clockwise dissectors).[20] In the femtosecond laser-assisted operative procedure, the disposable glass lens of the laser system was first applanated to the cornea to fixate the eye and help to maintain a precise distance from the laser head to the focal point.[21] Then, a continuous circular stromal tunnel was created at approximately 80% of corneal depth within 15 seconds with no corneal manipulation.[21] The 30-kHz IntraLase femtosecond system was always used (IntraLase Corp, Irvine, CA).

Two different kinds of ICRS were used: Intacs (Addition Technology, Inc, Fremont, CA) in only 3 eyes (14.29%) and KeraRings (Mediphacos, Belo Horizonte, Brazil) in 18 eyes (85.71%). All Intacs cases were implanted using the femtosecond technology, whereas KeraRings were implanted using this same technology only in 11 eyes (52.38%). The remaining KeraRings cases were implanted using the mechanical procedure (cases from Vissum Albacete, where this technology was not yet available). Intacs were always implanted following the protocol described and used by several authors[9,10,20]: a 0.25-mm implant placed superiorly and a 0.45-mm implant placed inferiorly. Regarding KeraRings, the nomogram defined by the manufacturer[21] was used for defining the modality of implant (Table 2). In the analyzed sample, only 2 cases were implanted with a single ring segment (9.52%).

Topical tobramycin and dexamethasone eye drops (TobraDex; Alcon Laboratories, Inc, Fort Worth, TX) were used postoperatively every 6 hours for 1 week and stopped. Topical lubricants were also prescribed to be applied every 6 hours for 1 month (Systane, Alcon Laboratories, Inc, Fort Worth, TX).

Follow-up Evaluation

Postoperative visits were scheduled for the first postoperative day and for months 1, 3, and 6 postoperatively. On the first postoperative day, UCVA measurement and slit-lamp examination (ICRS position and corneal integrity) were performed. We performed UCVA and BSCVA measurement, manifest refraction, slit-lamp biomicroscopy, and corneal topographic analysis at the rest of postoperative visits.

Main Outcome Measures

We collected UCVA, BSCVA, spherocylindrical refraction, keratometry, and corneal aberrometry measurements.

Statistical Analysis

The SPSS statistics software package version 10.1 for Windows (SPSS, Chicago, IL) was used for statistical analysis. Normality of all data samples was first checked by means of the Shapiro-Wilk test. When parametric analysis was possible, the Student *t* test for paired data was used for comparison between preoperative and postoperative data and the Student *t* test for unpaired data was performed to compare the outcomes of specific groups (mechanical vs femtosecond; explanted vs nonexplanted). When parametric

Table 3. Summary of Refractive Outcomes during Follow-up*

Parameter (range)	Preoperatively	1 Month	3 Months	6 Months	*P* (preoperatively to 6 mos)
UCVA	0.12±0.19 (0.02 to 0.70)	0.23±0.29 (0.02 to 1.20)	0.20±0.13 (0.05 to 0.40)	0.29±0.19 (0.05 to 0.60)	0.11 (Wilcoxon)
Sphere (D)	−0.74±3.41 (−9.00 to +5.00)	0.63±4.07 (−6.00 to +9.00)	0.78±3.93 (−6.00 to +8.00)	0.75±3.90 (−5.50 to +7.50)	0.02 (Paired Student *t* test)
Cylinder (D)	−5.36±1.59 (−8.25 to −2.50)	−3.53±2.06 (−8.00 to −0.75)	−3.52±2.01 (−6.50 to −1.00)	−3.21±1.80 (−6.00 to −1.00)	<0.01 (Paired Student *t* test)
SE (D)	−3.42±3.25 (−11.00 to +2.25)	−1.14±4.02 (−7.25 to +7.25)	−0.97±3.73 (−6.50 to +7.25)	−0.87±3.55 (−6.00 to +6.25)	<0.01 (Wilcoxon)
BSCVA	0.54±0.32 (0.02 to 0.95)	0.63±0.33 (0.10 to 1.20)	0.68±0.28 (0.40 to 1.20)	0.75±0.31 (0.30 to 1.20)	0.06 (Wilcoxon)
Efficacy	—	0.53±0.52 (0.02 to 1.67)	0.76±0.82 (0.08 to 3.00)	0.84±1.33 (0.11 to 5.00)	—
Safety	—	1.29±0.91 (0.23 to 3.33)	1.46±0.88 (0.44 to 3.33)	1.87±2.27 (0.78 to 9.00)	—
No. of eyes†	21	17	15	18	

BSCVA = best spectacle-corrected visual acuity; D = diopters; SE = spherical equivalent; UCVA = uncorrected visual acuity.
*The UCVA, sphere, cylinder, spherical equivalent, BSCVA, efficacy, and safety outcomes are shown. Ranges are shown in brackets below each mean value. Below each p-value the statistical test used is indicated.
†No data from explanted eyes were included after explantation to avoid biasing the final outcomes.

analysis was not possible, the Wilcoxon rank sum test was used to assess the significance of the differences between preoperative and postoperative data and the Mann-Whitney test was used for the comparison between groups. Statistical significance was considered when $P<0.05$.

Correlation coefficients (Pearson or Spearman depending if normality condition could be assumed) were used to assess the correlation between different variables. The efficacy index was calculated as the ratio of the postoperative UCVA to the preoperative best-corrected visual acuity and safety index as the ratio of the postoperative best-corrected visual acuity to the preoperative best-corrected visual acuity.

Results

A total of 21 eyes of 15 patients with a mean age of 44.19±15.78 years (range, 21–73) were analyzed in this study. There were 13 male (86.68%) and 2 female (13.33%) patients. Nine implanted eyes were right eyes (42.9%) and 12 were left eyes (57.1%). No cone opacity was observed in any case.

Refractive Outcomes

Refractive outcomes are summarized in Table 3. A statistically significant reduction was observed in spherical equivalent at 6 months which changed from a mean value of −3.84 diopters (D) preoperatively to a mean value of −0.87 D postoperatively ($P<0.01$; Wilcoxon test). This change was consistent with the significant reduction also found in sphere ($P = 0.02$; paired Student *t* test) and cylinder ($P<0.01$; paired Student *t* test; Table 3). Mean cylinder decreased from a mean preoperative value of −5.36 D to a mean postoperative value of −3.21 D. Mean sphere changed from a mean preoperative value of −0.74 D to a mean postoperative value of +0.75 D (hyperopic shift). No significant correlations were found between postoperative BSCVA and preoperative sphere ($r = -0.32$; $P = 0.31$) or cylinder ($r = 0.49$; $P = 0.10$).

No statistically significant changes were observed in UCVA at 6 months ($P = 0.11$; Wilcoxon test). On the contrary, BSCVA improved progressively during the postoperative follow-up, with a change in the limit of statistical significance at 6 months ($P = 0.06$; Wilcoxon test). At 6 months after surgery, 44.44% of eyes gained ≥2 lines of BSCVA (Fig 1). Losses of lines of BSCVA were observed in 2 eyes at 3 months (14.28%) and in 3 eyes (16.67%) at 6 months (Fig 1). In one of these eyes, ring segments were explanted at 6 months owing to the poor visual outcome.

The mean efficacy and safety indices at 6 months were 0.84±1.33 (range, 0.11–5.00) and 1.87±2.27 (range, 0.78–9.00), respectively. There was an improvement of both parameters between months 1 and 3 after surgery, although with no statistical significance (efficacy, $P = 0.07$; safety, $P = 0.99$; Wilcoxon test; Table 3).

Corneal Changes

Mean keratometry decreased significantly from 44.95 D preoperatively to 43.19 D at 6 months postoperatively ($P<0.01$; paired Student *t* test; Fig 2). A significant reduction was also observed for the steepest central curvature (K2 $P<0.01$; paired Student *t* test), but not for the flattest (K1 $P = 0.70$; paired Student *t* test; Fig 2).

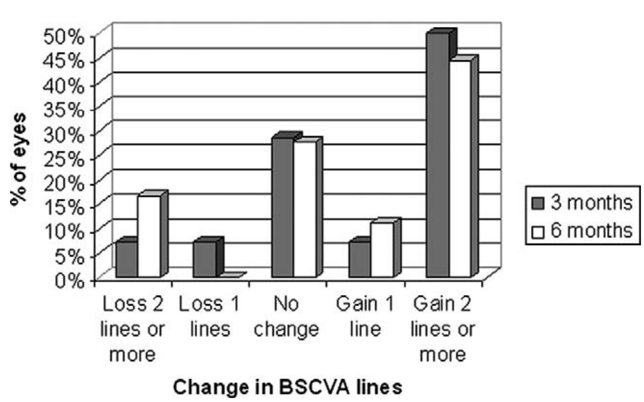

Figure 1. Changes in lines of best spectacle-corrected visual acuity (BSCVA) postoperatively. At 6 months after surgery, 44.44% of eyes gained ≥2 lines of best spectacle-corrected visual acuity.

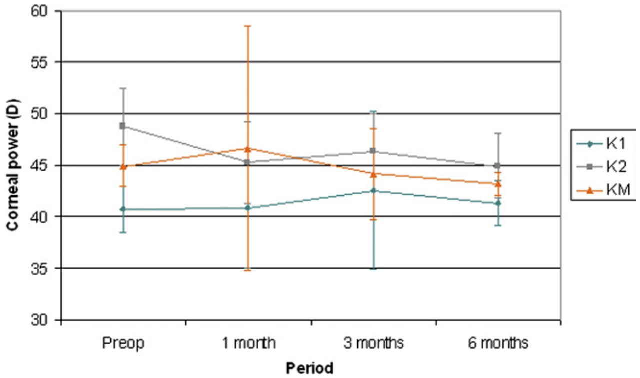

Figure 2. Changes in keratometric parameters during the follow-up: corneal dioptric power in the flattest meridian for the 3-mm central zone (K1; green line), corneal dioptric power in the steepest meridian for the 3-mm central zone (K2; gray line), and mean corneal power in the 3-mm zone (KM; orange line). A statistically significant reduction was observed in K2 and KM, but not in K1. D = diopters.

The inferosuperior asymmetry index decreased from a mean preoperative value of 10.37±11.34 D to a mean postoperative value of 7.60±10.03 D at 6 months. This change did not reach statistical significance ($P = 0.40$; Wilcoxon test). Regarding the topographic corneal parameters provided by the CSO system (Table 4), statistically significant changes were found in Q8 at 6 months (Q8 $P = 0.01$; paired Student t test) and in corneal astigmatism calculated in the central 3- and 6-mm zones (AST3, $P = 0.01$; AST6, $P = 0.01$; paired Student t test).

The K2 ($r = -0.86$; $P<0.01$) and KM ($r = -0.76$; $P<0.01$) were significantly correlated with postoperative BSCVA at 6 months, but not K1 ($r = 0.05$; $P = 0.91$). In addition, a correlation in the limit of statistical significance was found between inferosuperior asymmetry index and postoperative BSCVA ($r = -0.70$; $P = 0.05$).

Corneal Aberrations of the Anterior Surface

A detailed report of the corneal aberrometric outcomes is shown in Table 5. At 6 months after surgery, a statistically significant reduction was found in the RMS for corneal astigmatism ($P = 0.03$, Wilcoxon test) and also in the higher order residual ($P = 0.03$; paired Student t test) and coma-like RMS ($P = 0.03$; paired Student t test). However, no statistically significant changes were observed in the spherical-like RMS ($P = 0.50$; Wilcoxon test) and primary spherical aberration coefficient ($P = 0.74$; Wilcoxon test), which maintained the positive sign during all the follow-up (Table 5).

The preoperative RMS value for corneal astigmatism ($r = -0.90$; $P<0.01$) and primary spherical aberration Zernike term ($r = -0.86$; $P = 0.01$) were significantly correlated with postoperative BSCVA at 6 months. However, primary coma showed a very weak correlation with postoperative BSCVA ($r = -0.07$; $P = 0.88$).

Comparison between Mechanical and Femtosecond-Guided Procedures

Table 6 shows a comparative analysis of the preoperative and early postoperative refractive data for the 2 kind of operative procedures used in this study for corneal tunnelization, mechanical and femtosecond-assisted procedures. Sphere was increased (hyperopic shift) at 1 month postoperatively using the mechanical tunnelization, whereas it was reduced when the femtosecond technology was used (Table 6). It should be considered that statistically significant differences between mechanical and femtosecond groups were present preoperatively, with a higher percentage of cases with positive sphere in the group of eyes implanted using the mechanical dissection (Fig 3).

The cylinder was effectively reduced using both procedures. No significant differences in postoperative cylinder were found between operative techniques (Mann–Whitney test; $P>0.70$; Table 6). Comparison of aberrometric data was not feasible because all patients evaluated with the CSO topography system were operated on using the femtosecond-assisted tunnelization.

Complications

Segment ring explantation was performed in a total of 4 eyes (19.0%). In all these cases, ring segments were explanted owing to significant visual deterioration during the follow-up. In this series, all the explanted ring segments were KeraRings. Table 7 shows a comparative analysis of preoperative refractive and keratometric data of explanted and nonexplanted eyes. A difference between groups in the limit of statistical significance was only found for cylinder (Table 7). Ring extrusion or migrations were not observed in any case. No severe complications, such as infections, occurred.

Figure 4 shows the topographic changes occurred in 2 specific cases, a successful and an explanted case. As shown, ring segments induced no effect in corneal profile in the explanted case. In this specific unsuccessful case a significant against-the-rule astigmatism was present preoperatively (8 D).

Discussion

Pellucid marginal degeneration is a progressive ectatic corneal disease that can lead to a significant visual deteriora-

Table 4. Summary of Changes Found in the Costruzione Strumenti Oftalmici Topographic Corneal Parameters after Intracorneal Ring Segment Implantation

Parameter	Preoperatively	3 Months	6 Months	P (preoperatively to 6 mos)
AST3 (D)	8.68±4.95	5.38±5.10	4.77±4.42	0.01 (paired Student t test)
AST6 (D)	7.21±4.58	4.21±4.15	3.91±3.76	0.01 (paired Student t test)
Q45	0.20±0.76	−0.33±0.99	−0.56±0.87	0.11 (paired Student t test)
Q8	−0.04±0.63	0.28±0.65	0.24±0.65	0.01 (paired Student t test)
No. of eyes*	10	8	8	—

AST3 = corneal astigmatism in the 3-mm zone; AST6 = corneal astigmatism in the 6-mm zone; D = diopters; Q45 = mean asphericity for a corneal area of 4.5-mm diameter; Q8 = mean asphericity for a corneal area of 8-mm diameter.
*No data from explanted eyes were included after explantation to avoid biasing the final outcomes.

Table 5. Summary of Corneal Aberrometric Outcomes*

Parameter	Preoperatively	1 Month	3 Months	6 Months	*P* (preoperatively to 6 mos)
Total RMS (microns)	12.76±11.75 (4.36 to 42.04)	8.90±7.17 (2.41 to 24.30)	11.26±15.98 (3.23 to 47.35)	11.63±15.76 (3.35 to 47.19)	0.50 (Wilcoxon)
Astigmatism RMS (microns)	6.29±5.05 (1.66 to 17.50)	4.74±4.50 (0.83 to 15.13)	3.96±5.15 (0.39 to 14.89)	3.99±4.76 (0.28 to 14.13)	0.03 (Wilcoxon)
Primary coma RMS (microns)	1.40±0.87 (0.25 to 3.14)	1.68±1.75 (0.27 to 6.33)	1.19±0.51 (0.38 to 1.90)	1.34±0.37 (0.85 to 1.90)	0.37 (Paired Student t)
Z_4^0 (microns)	0.60±0.43 (0.11 to 1.41)	0.77±1.01 (−0.11 to 3.43)	0.50±0.55 (−0.21 to 1.31)	0.55±0.78 (−0.05 to 2.14)	0.74 (Wilcoxon)
Residual RMS (microns)	2.38±1.03 (0.83 to 4.41)	2.41±1.72 (0.40 to 6.43)	1.43±0.69 (0.75 to 2.64)	1.32±0.50 (0.62 to 1.98)	0.03 (Paired Student t)
Spherical-like RMS (microns)	1.22±0.59 (0.44 to 2.22)	1.36±1.49 (0.44 to 5.40)	0.95±0.44 (0.51 to 1.53)	0.96±0.80 (0.35 to 2.50)	0.50 (Wilcoxon)
Coma-like RMS (microns)	2.72±0.80 (1.48 to 4.14)	2.64±2.14 (0.45 to 8.00)	1.79±0.62 (0.90 to 2.59)	1.73±0.56 (0.95 to 2.45)	0.03 (Paired Student t)
No. of eyes†	10	8	8	—	

Coma-like = terms third and fifth order; primary coma = terms Z3 ± 1; primary spherical aberration = term Z_4^0; residual aberrations = all Zernike terms except $Z_3^{\pm 1}$ and Z_4^0; RMS = root mean square; spherical-like = terms 4th and 6th order.
*Changes in total RMS, astigmatism RMS, primary coma RMS, primary spherical aberration coefficient, spherical-like RMS and coma-like RMS are shown. Ranges are given in brackets below each mean value.
†No data from explanted eyes were included after explantation to avoid biasing the final outcomes.

tion. As topographic changes progress, large amounts of against-the-rule astigmatism and coma-like aberrations are induced.[22] As in other corneal ectatic disorders,[23–27] it was demonstrated that the use of ICRS is very effective for reducing astigmatism[8–10,12] and improving BSCVA.[8–14] The insertion of these ring segments (extra material) in the deep stroma induces a modification of the central corneal curvature and corneal shape. These changes are in direct proportion to the thickness of the implant and in inverse proportion to its diameter.[18] In a healthy cornea, these implants located on the midperipheral cornea generate a central flattening due to the configuration of the stromal collagen structure.[18] However, this stromal configuration is altered in the ectatic cornea, with a nonorthogonal lamellar architecture.[28,29] Relative centration and minimization of the peripheral corneal protrusion were observed after ICRS implantation in corneas with PMD.[12–14] The present study attempts to characterize the refractive and aberrometric effect of ICRS in this specific group of ectatic corneas, namely, corneas with PMD. These changes would be the result of the modification of corneal biomechanical behavior induced by the implants as a consequence of changes in the distribution of corneal peripheral lamellae.

Case reports or studies including a limited number of cases of PMD implanted with ICRS were only reported previously due to the complexity of finding such cases in clinical practice.[8–14] In this study, we collected data retrospectively from 4 ophthalmologic centers to obtain a significant number of cases. To the best of our knowledge, the current study includes the largest reported series of cases of PMD implanted with ICRS (21 eyes).

In our series, a statistically significant reduction was found in sphere and cylinder after ICRS implantation. On average, manifest astigmatism was reduced with the implants by 50%. This reduction in spherocylindrical error was consistent with changes reported in previous studies and case reports.[8–13] Furthermore, a trend toward postoperative increasing hyperopia after ICRS implantation was observed. This seems logical because it is supposed that ring segments induce a central corneal flattening and then a reduction of

Table 6. Summary of Refractive Outcomes Depending on the Operative Procedure Used for Intracorneal Ring Segment Implantation*

	Mechanical (7 eyes)		Femtosecond (14 eyes)		*P*	
Parameter	*Preoperatively*	*1 Month Postop*	*Preoperatively*	*1 Month Postop*	*Preoperatively*	*Postoperatively*
UCVA	0.07±0.07	0.14±0.16	0.17±0.27	0.29±0.34	0.73	0.17
Sphere (D)	+1.75±2.46	+5.00±3.16	−2.08±3.14	−1.19±2.85	0.01	<0.01
Cylinder (D)	−5.39±0.76	−3.25±1.70	−5.35±1.92	−3.65±2.25	0.70	0.88
SE (D)	−0.95±2.55	+3.35±3.38	−4.75±2.83	−3.01±2.52	0.01	<0.01
BSCVA	0.35±0.31	0.49±0.20	0.64±0.29	0.69±0.36	0.08	0.26

BSCVA = best spectacle-corrected visual acuity; D = diopters; SE = spherical equivalent; UCVA = uncorrected visual acuity.
*A comparative analysis of the preoperative and early postoperative data obtained using the mechanical and femtosecond-guided procedures is shown. Statistical significance of differences between groups preoperatively and postoperatively is provided in this table for each refractive parameter (all Mann–Whitney tests).

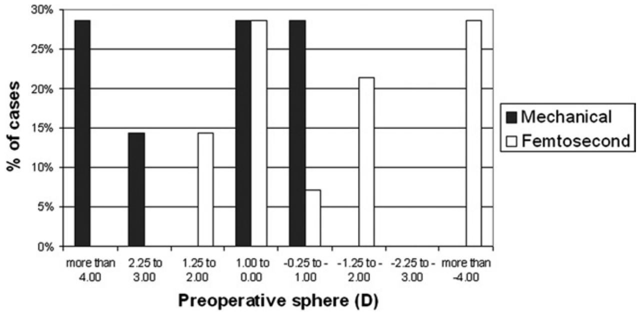

Figure 3. Distribution of preoperative sphere in the group of eyes operated using the mechanical dissection and in the group of eyes operated using the femtosecond laser technology. As shown, a higher percentage of cases with positive sphere was present in the group of eyes implanted using the mechanical dissection.

the corneal and ocular refractive power, leading theoretically to a postoperative hyperopia. However, this fact was not confirmed in our series. There were cases with myopic astigmatism and very important postoperative hyperopic shift. In addition, no significant correlation was found between preoperative sphere and postoperative visual outcome.

Mean corneal curvature was reduced significantly with the ICRS, as in previous experiences.[8–14] This flattening effect was due to the significant reduction of curvature that occurred in the steepest meridian. This fact could be explained by the combination of 2 flattening factors, the insertion of the midperipheral implants, and the weakening effect induced by corneal incision. This significant flattening was consistent with the significant reduction observed in sphere.

A reduction, although not significant, was found in inferosuperior asymmetry, which implies that ring segments were inducing a relative centration of the peripheral corneal protrusion. In addition, all corneal astigmatic coefficients (only obtained with the CSO topography system) were significantly reduced after ICRS implantation. A significant change was also found in corneal asphericity, with a trend toward oblateness (in concordance with central flattening and spherical reduction).

To the best of our knowledge, this is the first report on anterior corneal aberrometric outcomes after ICRS implantation in corneas with PMD. It should be remembered that anterior corneal aberrometric analysis is a very important tool in the clinical practice for evaluating the ocular optical quality because the first refractive interface (air–cornea) is the most important contributor to the total power of the eye because of the large difference in refractive index existing at this point. In highly aberrated corneas, such as in PMD, the corneal aberrations of the anterior corneal surface are the most important sources of optical errors in the eye. In the current study, we found that astigmatism, higher order residual, and coma-like aberrations were significantly reduced with surgery. In addition, a reduction in spherical-like aberrations was also observed, but this change did not reach significance. All these changes in corneal aberrations were consistent with the improvement in BSCVA (55.55% of eyes gaining lines of BSCVA) and also with the reduction in inferosuperior asymmetry. These findings supports the conclusions reached by Shabayek and Alió,[21] who found a significant reduction in higher order RMS for those eyes with a relatively high preoperative RMS (≥3.0 microns) and implanted with KeraRings using the femtosecond laser for corneal tunnelization. Furthermore, it should be remarked that primary spherical aberration was not modified significantly with the implants, maintaining the positive sign during all follow-up.

When comparing operative techniques for corneal tunnelization, no significant differences in cylindrical correction were found between techniques. On the contrary, the eyes implanted with the mechanical procedure experienced an increase in sphere in the early postoperative period, whereas a reduction of this parameter was observed in those eyes implanted using the femtosecond technology. A statistically significant difference between techniques was found in sphere postoperatively, but this difference was also present preoperatively. A significantly higher percentage of cases with positive sphere was present in the group of eyes implanted using the mechanical dissection. It is logical to think that an increase in sphere could have happened in these cases with hyperopic astigmatism as a consequence of the central flattening induced by the segments. However, we found several hyperopic shifts in eyes with myopic astigmatism. Therefore, we cannot extract general conclusions regarding sphere in this comparative analysis. Carrasquillo et al[30] did not find previously statistically significant differences in refractive and visual acuity outcomes between mechanical and femtosecond-guided procedures when implanting ICRS in corneas with keratoconus and post-LASIK ectasia. Differences in corneal aberrometric changes induced by each operative procedure could not be analyzed

Table 7. Comparative Analysis of Preoperative Refractive and Keratometric Data of Explanted and Nonexplanted Eyes*

Parameter	Explanted (4 eyes)	Nonexplanted (17 eyes)	P
UCVA	0.08±0.09 (0.02 to 0.15)	0.12±0.20 (0.02 to 0.70)	0.99
Sphere (D)	+1.56±2.13 (0.00 to +4.50)	−1.31±3.48 (−9.00 to +5.00)	0.10
Cylinder (D)	−6.81±1.72 (−8.25 to −4.50)	−5.00±1.38 (−8.00 to −2.50)	0.05
SE (D)	−1.84±2.81 (−4.00 to +2.25)	−3.81±3.31 (−11.00 to +2.00)	0.34
BSCVA	0.59±0.35 (0.10 to 0.95)	0.53±0.32 (0.02 to 0.95)	0.68
K1 (D)	39.64±2.09 (37.26 to 41.16)	41.01±2.24 (37.17 to 44.90)	0.66
K2 (D)	50.60±2.29 (49.15 to 53.24)	48.24±3.94 (42.00 to 55.60)	0.23
KM (D)	44.96±0.25 (44.72 to 45.21)	44.74±2.29 (40.85 to 48.40)	0.64

D = diopters; BSCVA = best-spectacle corrected visual acuity; K1 = corneal dioptric power in the flattest meridian for the 3 mm central zone; K2 = corneal dioptric power in the steepest meridian for the 3 mm central zone; KM = mean corneal power in the 3-mm zone; SE = spherical equivalent; UCVA = uncorrected visual acuity.

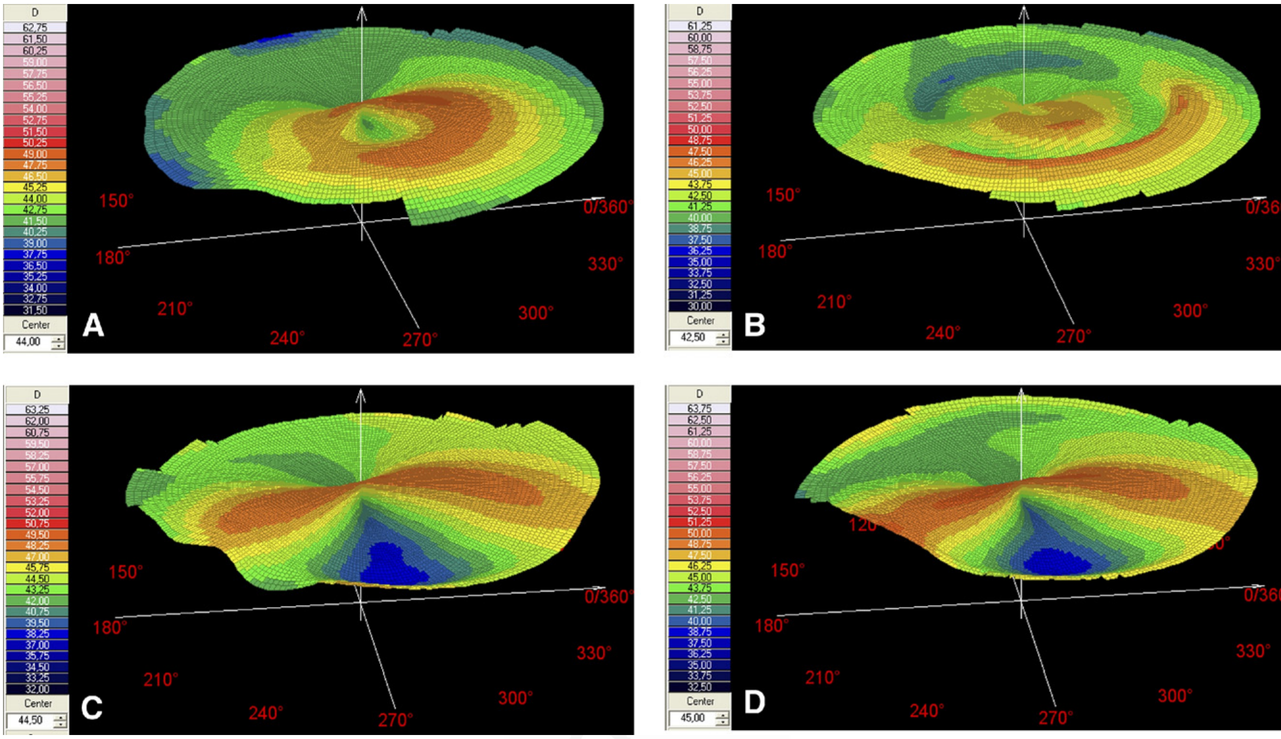

Figure 4. Topographic changes occurring after intracorneal ring segments (ICRS) implantation in a successful (**A** and **B**) and in an explanted case (**C** and **D**). The upper figures show the preoperative (**A**) and 1-month postoperative (**B**) corneal topographies in a case with a successful outcome (reduction of 3.25 diopters in cylinder and postoperative best spectacle-corrected visual acuity [BSCVA] of 0.9). The lower figures show the preoperative (**C**) and 1-month postoperative (**D**) corneal topographies in a case with an unsuccessful outcome (loss of 2 lines of BSCVA and increase in astigmatism). In this last case, ring segments were finally explanted.

because all corneas examined with the CSO system were operated on using the femtosecond technology.

No severe complications were observed during the 6-month follow-up of this study. Explantation of the ICRS was performed in 4 eyes owing to the poor visual quality outcome. A significantly higher level of astigmatism was found in this group of explanted eyes. Therefore, the magnitude of manifest astigmatism seems to have an important role in the success of this treatment option. Corneas with PMD and a significant astigmatic configuration could be associated to a specific corneal structure limiting the effect of ring segments and providing poorer outcomes. It was demonstrated that lamellar structure of ectatic corneas is different compared with normal corneas with regions of more highly aligned collagen intermixed with regions in which there was little aligned collagen (distortion of the orthogonal lamellar matrix).[28,29] Probably in these cases with PMD and a significant astigmatic configuration the distribution of corneal lamellae is highly irregular with poor or unpredictable response to a peripheral addition of tissue. In any case, future studies are required to understand how the configuration of ectatic corneal structure is modified or altered with the ICRS.

Furthermore, we found some factors correlated with the postoperative BSCVA outcome. The RMS for corneal astigmatism and primary spherical aberration were found to be in linear relation with postoperative BSCVA. Specifically, the larger the preoperative RMS for astigmatism or spherical aberration term, the poorer the postoperative visual outcomes was. Therefore, corneal and manifest astigmatism seem to be limiting factors for a good visual prognosis after ICRS implantation. All these limiting factors should be considered before any ICRS implantation in corneas with PMD to establish the convenience of the operative procedure.

In conclusion, ICRS implantation—Intacs or KeraRings—is an effective option for the treatment of 2nd-order and higher aberrations in corneas with PMD. Anterior corneal higher order aberrations (higher order residual and coma-like) are reduced significantly after ICRS implantation in concordance with an improvement in BSCVA. The magnitude of corneal astigmatism and primary spherical aberration seem to be important limiting factors for a good visual outcome with this operative therapeutic option. In this study, only a 6-month follow-up could be completed. Future studies of the outcomes with ICRS in corneas with PMD in the long term are required to corroborate the stability of these implants.

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Footnotes and Financial Disclosures

Originally received: October 2, 2008.
Final revision: May 26, 2009.
Accepted: June 2, 2009.
Available online: July 29, 2009. Manuscript no.: 2008-1177.

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Financial Disclosure(s):
The authors have no proprietary or commercial interest in any materials discussed in this manuscript.

Supported in part by a grant from the Spanish Ministry of Health, Instituto Carlos III, Red Temática de Investigación Cooperativa en Salud "Patología ocular del envejecimiento, calidad visual y calidad de vida", Subproyecto de Calidad Visual (RD07/0062).

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Intracorneal Ring Segment Implantation in Corneas with Post-Laser In Situ Keratomileusis Keratectasia

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Purpose: To evaluate the refractive and aberrometric changes in corneas with post-LASIK keratectasia implanted with intracorneal ring segments (ICRS) during a 2-year follow-up.

Design: Retrospective, consecutive case series.

Participants: Thirty-four eyes of 25 patients (age range, 20–59 years) with post-LASIK ectasia were included. Ectasia was diagnosed by slit-lamp appearance of corneal thinning, unstable topographic steepening, progressive corneal thinning on ultrasonic pachymetry, decreased visual acuity, and unstable refraction.

Methods: Intracorneal ring segment implantation was performed in all cases by 2 surgeons from 2 different ophthalmologic centers with the aim of correcting the spherocylindrical error and improving the visual quality. Corneal tunnels were created by means of mechanical dissection in 20 eyes and femtosecond laser technology in 14 eyes. Intacs (Addition Technology, Inc, Fremont, CA) were inserted in 24 eyes, and KeraRings (Mediphacos, Belo Horizonte, Brazil) in 10 eyes. In all cases a follow-up of 12 months was completed, with a total of 15 eyes examined 24 months after surgery.

Main Outcome Measures: Uncorrected visual acuity (UCVA), best spectacle-corrected visual acuity (BSCVA), refraction, keratometry, and corneal aberrations.

Results: Uncorrected visual acuity did not improve after surgery ($P = 0.17$). Best spectacle-corrected visual acuity increased significantly at 6 months ($P = 0.02$). Some 38.89% of eyes gained 2 or more lines of BSCVA at 6 months, and this percentage increased to 60% at 24 months. There was a nonsignificant reduction of sphere at 6 months ($P = 0.28$). Manifest cylinder was reduced significantly during the postoperative follow-up ($P = 0.05$, preoperative to 6 months; $P = 0.04$, 6–12 months). The cornea was on average flatter at 6 months ($P<0.01$), with a posterior nonsignificant regression of the achieved flattening ($P = 0.73$). In regard to corneal aberrations, a statistically significant reduction was found in coma-like root mean square (RMS) ($P = 0.03$) after surgery. Segment ring explantation was performed in 6 eyes, and ring reposition was performed in 2 eyes. The apical curvature gradient was significantly higher in the group of explanted eyes ($P = 0.03$).

Conclusions: Intracorneal ring segment implantation is a useful option for the treatment of coma-like aberrations and astigmatism in post-LASIK corneal ectasia.

Financial Disclosure(s): The author(s) have no proprietary or commercial interest in any materials discussed in this article. *Ophthalmology 2009;116:1665–1674 © 2009 by the American Academy of Ophthalmology.*

Corneal keratectasia is a serious complication of LASIK surgery[1–9] and is especially observed in corneas significantly ablated centrally with the excimer laser (high myopes).[2–5] This was first described by Seiler et al[8,9] in 1998. It consists of a progressive corneal steepening, usually inferiorly, with an increase in all ocular aberrations, and loss of uncorrected visual acuity (UCVA) and frequently best spectacle-corrected visual acuity (BSCVA).[2] This ectatic disorder has an estimated incidence that ranges from 0.04% to 0.6%.[10] The specific mechanism resulting in these corneal alterations still remains unknown.[2,4,11] The corneal weakening induced by the excimer laser ablation seems to have a significant role in the development of this complication.[4,12,13] Several risk factors have been identified for the development of post-LASIK ectasia, such as the presence of a large preoperative myopic refractive error, a low residual stromal bed thickness,[2,4,10,11,14] a small modulus of elasticity,[15] or some corneal topographic abnormalities.[2,4,10,11,14]

A variety of therapeutic options have been described for the post-LASIK keratectasia, such as rigid gas permeable contact lenses,[2,16] intracorneal ring segment (ICRS) implantation,[13,17–24] or corneal transplantation.[2,16] The management of these patients must include visual rehabilitation because the visual function is devastated as the result of the significant increase in all ocular aberrations. The control of the keratectasia progression is another objective when treating these eyes. ICRS implantation has been proved effective in improving visual acuity,[1] reducing the refractive error and keratometry.[17–24] In addition, this kind of treatment has been demonstrated to be useful to prevent the need for keratoplasty and the progression of the iatrogenic cone.[18]

Published by Elsevier Inc.

ISSN 0161-6420/09/$–see front matter
doi:10.1016/j.ophtha.2009.05.030

The addition of extra material at the normal corneal mid-periphery induces a displacement of the local anterior surface. This displacement induces a steepening of the peripheral cornea and a flattening of the central portion of the anterior cornea because of the morphologic structure of corneal lamellae.[25] If changes induced by ICRS in the normal cornea are assumed to be similar in the post-LASIK ectatic cornea, these segments would minimize the corneal protrusion. As a consequence, significant changes in refraction and corneal regularity would be induced. This potential corneal regularization would induce a significant reduction of corneal aberrations and then an improvement of BSCVA. Although a best-corrected visual improvement was reported by previous authors in eyes with post-LASIK ectasia and ICRS, aberrometric changes have still not been analyzed and reported.

To the best of our knowledge, this study is the first to analyze the corneal aberrometric changes in post-LASIK ectatic corneas after ICRS implantation. In addition, we report in this study the largest series of cases with post-LASIK ectasia and treated with ICRS. The objective of the present study was to analyze the refractive and corneal aberrometric changes in a medium to long-term follow-up after the implantation of ICRS in eyes with post-LASIK corneal ectasia. Refractive and aberrometric stability, as well as late sequelae, were carefully analyzed. In addition, factors related to a good prognosis were identified.

Patients and Methods

Patients

A retrospective analysis of outcomes of all patients who underwent ICRS implantation for the management of post-LASIK ectasia from September 2000 to June 2007 in 2 different Spanish ophthalmologic centers (Vissum Alicante and Vissum Sevilla) was performed. A total of 37 eyes with post-LASIK ectasia were diagnosed and examined during this period, some of them from our clinic and others referred by other centers. In all cases the implantation of ICRS was indicated, but finally 3 patients did not undergo operation because they preferred to wait and see the evolution of the case. Thirty-four consecutive eyes of 25 patients who had undergone 1 or more previous LASIK procedures and with post-LASIK corneal ectasia (17 unilateral and 8 bilateral) were finally included. Ectasia was diagnosed by slit-lamp appearance of corneal thinning, unstable topographic steepening (>1 D for each 6-month follow-up), progressive corneal thinning on ultrasonic pachymetry, decreased visual acuity, and unstable refraction (>0.5 D for spherical equivalent [SE] for each 6-month follow-up).[18]

A comprehensive examination was performed in all cases before the ICRS implantation, which included Snellen UCVA (decimal notation), Snellen BSCVA (decimal notation), manifest refraction, slit-lamp biomicroscopy, Goldman tonometry, fundus evaluation, ultrasonic pachymetry, and corneal topographic analysis. Because topographic data were collected from different periods and 2 different centers, a total of 3 different corneal topography systems were used for corneal examination: CMS 100 Topometer (G. Rodenstock Instrument GmbH, Ottobrunn, Germany), Costruzione Strumenti Oftalmici (CSO, Firenze, Italy), and Orbscan IIz system (Bausch & Lomb, Rochester, NY). The first 2 devices are Placido-based systems, and the Orbscan II is a combined scanning-slit and Placido-disc topography system. Although the agreement between these specific devices has not been reported, Orbscan and Placido-based devices have been proved to provide similar accuracy and precision on calibrated spherical test surfaces.[26] In this study, the following topographic data were evaluated and recorded with all corneal topographic devices: the corneal dioptric power in the flattest meridian for the 3-mm central zone (K1), corneal dioptric power in the steepest meridian for the 3-mm central zone (K2); mean corneal power in the 3-mm zone (KM); and inferosuperior asymmetry index (ISAI), calculated as the difference between the dioptric power at 3 mm below and above the corneal geometric center. Additional topographic parameters were analyzed and recorded in patients examined with the CSO topographic system (15 eyes): the corneal astigmatism in the 3-mm zone (AST3), corneal astigmatism in the 6-mm zone (AST6), mean asphericity for a corneal area of 4.5-mm diameter (Q45), mean asphericity for a corneal area of 8-mm diameter (Q8), apical keratometry, and apical curvature gradient (ACG).

All patients had undergone LASIK surgery at least 12 months before ICRS implantation. During the process of consent for this surgery, consent was taken to later include clinical information in scientific studies. Ethical board committee approval of our institution (Vissum Instituto Oftalmológico de Alicante) was obtained for this investigation. In all cases, a follow-up of 12 months or more was completed, with a total of 15 eyes examined 24 months after surgery.

Corneal Aberrations of Anterior Surface

Corneal aberrometry was also recorded and analyzed only in those patients examined in all visits with the CSO topography system (15 eyes), because this device was the only one with the capability to calculate directly this specific information. This topography system analyzes a total of 6144 corneal points of a corneal area enclosed in a circular annulus defined by an inner radius of 0.33 and an outer radius of 10 mm with respect to corneal vertex. The software of the CSO, the EyeTop2005 (CSO), automatically performs the conversion of corneal elevation profile into corneal wavefront data using the Zernike polynomials with an expansion up to the seventh order. In this study, the aberration coefficients and root mean square (RMS) values were calculated for a 6-mm pupil in all cases. The following parameters were analyzed and recorded: total RMS, RMS for corneal astigmatism, primary coma RMS (computed for the Zernike terms $Z_3^{\pm 1}$), coma-like RMS (computed for third, fifth, and seventh-order Zernike terms), spherical-like RMS (computed for fourth and sixth-order Zernike terms), and higher-order residual RMS (computed considering all Zernike terms except those corresponding with primary coma and spherical aberration). The corresponding Zernike coefficient for primary spherical aberration (Z_4^0) was also reported with its sign.

Surgery

Surgical procedures were performed by 2 surgeons, one from Vissum Alicante (JLA) and the other from Vissum Sevilla (AUM). In all cases, an antibiotic prophylaxis before surgery consisting of topical ciprofloxacin (Oftacilox; Alcon Cusí, Barcelona, Spain) to be applied every 8 hours for 2 days was prescribed. All procedures were performed under topical anesthesia.

Corneal tunnelization for ring segment insertion was performed by mechanical dissection in 20 eyes (58.8%) and by femtosecond laser technology in 14 eyes (41.2%). Incision was located on the steepest meridian of the anterior corneal surface in all patients except 4 (11.8%). A tunnel with an inner and outer diameter of 6.6 and 7.8 mm, respectively, was always planned for Intacs (Addition Technology, Inc, Fremont, CA) implantation, and an inner and outer diameter of 4.8 mm and 5.7 mm, respectively, was planned

Table 1. Implantation Nomogram Used for Intacs in this Study: Number of Segments and Their Thicknesses Were Selected According to the Corneal Topographic Pattern

Corneal Topography Pattern	Indication
Steepening area not involving the 180-degree meridian of the cornea (inferior cone)	1 segment of 0.45-mm thickness
Steepening extending at least 1 mm above and beyond the 180-degree meridian (central cone)	2 segments: 0.45-mm thickness segment inferiorly and 0.25-mm thickness segment superiorly

Intacs; Addition Technology, Inc, Fremont, CA.

for KeraRings (Mediphacos, Belo Horizonte, Brazil) implantation. No complications occurred intraoperatively.

The mechanical surgical procedure was initiated by marking a reference point for centration (pupil center) and performing a radial incision of approximately 1.8 mm in length. After this, a calibrated diamond knife was set at approximately 70% of the mean corneal thickness determined by ultrasonic pachymetry. From the base of the incision, pocketing hooks were used to create corneal pockets on each side of the incision, taking care to maintain a uniform depth. A device containing a semiautomated suction ring was placed around the limbus, guided by the previously marked reference point on the cornea. Two semicircular dissectors were placed sequentially into the lamellar pocket to be steadily advanced by a rotational movement (counterclockwise and clockwise dissectors).[27] In the femtosecond laser-assisted surgical procedure, the disposable glass lens of the laser system was first applanated to the cornea to fixate the eye and help maintain a precise distance from the laser head to the focal point.[28] Then, a continuous circular stromal tunnel was created at approximately 80% of corneal depth (if this depth was <400 μm; if not, a channel was dissected exactly at 400 μm) within 15 seconds with no corneal manipulation.[28] The 30-kHz IntraLase femtosecond system was always used (IntraLase Corp, Irvine, CA).

Intacs were inserted in 24 eyes (70.6%), and KeraRings were inserted in 10 eyes (29.4%). Intacs were implanted using the femtosecond technology in only 4 eyes (20%), and KeraRings were implanted in all cases using this technology. Intacs were indicated if SE was less than −2 D to induce small modifications in refraction. Selection of the number of Intacs (1 or 2) to implant and thicknesses was performed following the criteria defined previously by our research group,[27] which is based on corneal topography pattern (Table 1). For KeraRings, the nomogram defined by the manufacturer[28] was followed for defining the modality of implant (Table 2). In this study, all KeraRings that were implanted had an arc length of 160 degrees. Only 1 ring segment was implanted in 16 eyes (47.1%), whereas 2 segments were necessary in 18 eyes (52.9%).

Topical tobramycin and dexamethasone eye drops (TobraDex; Alcon Laboratories, Inc, Fort Worth, TX) were used postoperatively every 6 hours for 1 week and stopped. Topical lubricants were also prescribed to be applied every 6 hours for 1 month (Systane, Alcon Laboratories, Inc).

Follow-up Evaluation

Postoperative visits were scheduled for the first postoperative day and for months 1, 3, 6, 12, and 24 postoperatively. On the first postoperative day, UCVA measurement and slit-lamp examination (ICRS position and corneal integrity) were performed. In the remaining postoperative visits the measurement of UCVA and BSCVA, manifest refraction, slit-lamp biomicroscopy, and corneal topographic analysis were performed. Follow-up ranged from 12 to 24 months.

Statistical Analysis

The Statistical Package for the Social Sciences version 10.1 for Windows (SPSS, Chicago, IL) was used for statistical analysis. Normality of all data samples was first checked by means of the Shapiro–Wilk test. When parametric analysis was possible, the Student *t* test for paired data was used for the comparison between preoperative and postoperative data, and the Student *t* test for unpaired data was performed to compare outcomes between specific groups (explanted vs. nonexplanted, mechanical vs. femtosecond).

When parametric analysis was not possible, the Wilcoxon rank-sum test was applied to assess the significance of differences between preoperative and postoperative data and the Mann–Whitney test was performed for the comparison between specific groups, using the same level of significance in all cases ($P<0.05$).

Correlation coefficients (Pearson or Spearman depending if normality condition could be assumed) were used to assess the correlation between different variables. Finally, efficacy index was calculated as the ratio of the postoperative UCVA to the preoperative best-corrected visual acuity, and safety index was calculated as the ratio of the postoperative best-corrected visual acuity to the preoperative best-corrected visual acuity.

Table 2. Implantation Nomogram Used for KeraRings in this Study: Segment Distribution and Thickness Were Selected According to the Area of Ectasia and Spherical Equivalent

Spherical Equivalent (D)	All Ectasia Is Limited to One Half of the Cornea	75% of the Ectasia in One Half of the Cornea and 25% Situated in the Other Half	Two Thirds of the Ectatic Area in One Half of the Cornea and One Third in the Other Half	Ectasia is Distributed Evenly in Both Corneal Halves
>−10 D	25/35	25/35	30/35	35/35
−8 to −10 D	20/30	20/30	25/30	30/30
−6 to −8 D	15/25	15/25	20/25	25/25
−2 to −6 D	0/20	0/20	15/20	20/20

D = diopters.
For defining the distribution of the ectasia, the cornea was divided into 2 halves using the steepest meridian as axis of separation, for example, 25/35 = upper segment thickness/lower segment thickness (0.25 mm/0.35 mm).
KeraRings; Mediphacos, Belo Horizonte, Brazil.

Table 3. Summary of the Refractive Outcomes during Follow-up

Parameter (Range)	Preoperative	3 Mos	6 Mos	12 Mos	24 Mos	*P* Value (Preoperative to 6 Mos)
UCVA	0.25±0.17 (0.05–0.60)	0.25±0.17 (0.05–0.60)	0.34±0.22 (0.05–0.80)	0.28±0.19 (0.05–0.70)	0.35±0.21 (0.05–0.80)	0.17
Sphere (D)	−2.10±3.37 (−13.00 to +3.50)	−1.17±3.72 (−12.50 to +5.00)	−1.58±4.51 (−14.00 to +5.00)	−2.55±5.11 (−13.00 to +9.00)	−2.64±5.46 (−15.00 to +3.00)	0.28
Cylinder (D)	−3.47±1.97 (−8.00 to 0.00)	−2.34±1.58 (−5.00 to 0.00)	−2.64±1.12 (−4.50 to −1.00)	−2.69±1.26 (−5.00 to −1.00)	−1.91±1.45 (−5.00 to 0.00)	0.05
SE (D)	−3.84±3.66 (−16.00 to +3.00)	−2.35±3.58 (−12.50 to +3.00)	−2.91±4.59 (−16.00 to +3.00)	−3.89±5.15 (−14.50 to +7.00)	−3.60±5.66 (−16.50 to +3.00)	0.17
BSCVA	0.48±0.24 (0.05–0.80)	0.52±0.23 (0.05–1.00)	0.61±0.30 (0.15–1.20)	0.55±0.21 (0.15–0.80)	0.54±0.27 (0.10–1.00)	0.02
Efficacy	—	0.67±0.66 (0.08–3.33)	0.75±0.60 (0.05–2.67)	0.86±0.86 (0.05–3.33)	1.09±0.87 (0.05–3.33)	—
Safety	—	1.40±1.26 (0.33–6.00)	1.80±1.44 (0.71–5.33)	2.01±1.92 (0.43–8.00)	1.71±1.03 (0.63–4.00)	—
No. of eyes	34	23	18	20	15	

BSCVA = best spectacle-corrected visual acuity; D = diopters; SE = spherical equivalent; UCVA = uncorrected visual acuity.
Ranges are shown in parentheses below each mean value. All patients completed a follow-up of at least 12 mos. During the first year of follow-up, no dropouts were found.

Results

A total of 34 eyes of 25 patients with a mean age of 37.27±9.27 years (range, 20–59 years) were included. Eleven patients were female (44%), and 14 patients were male (56%). There were an equal number of right and left eyes (17). Preoperatively, the location of the iatrogenic cone was central in 10 eyes (29.4%), inferior in 21 eyes (61.8%), and inferotemporal in 3 eyes (8.8%). Opacity of the cone area was observed in only 3 eyes (8.8%). According to the Amsler–Krumeich grading system,[29] 22 eyes had a cone grade I (64.7%), 6 eyes had grade II (17.6%), 4 eyes had grade III (11.8%), and 2 eyes had grade IV (5.9%). In regard to the corneal aberrations and according to the Alió–Shabayek grading system,[27] 9 eyes had a cone grade I (50%), 6 eyes had grade II (33.3%), 2 eyes had grade III (11.1%), and only 1 eye had grade IV (5.6%). In 5 eyes, corneal cross-linking treatment was applied after a 12-month follow-up. This kind of treatment was performed only if a significant regression of the corneal flattening and refractive correction achieved with the ICRS was observed. In these cases, data from the post-corneal cross-linking visits were not included to avoid biasing the final outcomes.

Refractive Outcomes

Refractive outcomes are summarized in Table 3. At 6 months postoperatively, a mean reduction of 0.93 diopters (D) in the SE was observed. This refractive change did not reach statistical significance ($P = 0.17$, Wilcoxon test). From 6 to 24 months, a nonstatistically significant increase was observed in this parameter ($P = 0.33$; Wilcoxon test). In regard to manifest cylinder, a decrease in the limit of statistical significance was found at 6 months (mean change = 0.83 D; $P = 0.05$; Student *t* test for paired data), with an additional significant reduction in the period from 6 to 24 months (mean change = 0.73 D; $P = 0.04$; Student *t* test for paired data). A nonsignificant reduction of 0.52 D in sphere was also found at 6 months ($P = 0.28$; Wilcoxon test), with a small but insignificant regression of the achieved correction during the rest of follow-up ($P = 1.00$; Wilcoxon test).

No statistically significant changes in UCVA were observed during the follow-up ($P = 0.17$, Wilcoxon test). Best spectacle-corrected visual acuity increased significantly at 6 months ($P = 0.02$, Wilcoxon test), with no significant changes during the rest of follow-up ($P = 0.50$, Wilcoxon test). At 6 months, 38.89% of eyes gained 2 or more lines of BSCVA, and this percentage increased to 60% at 24 months (Fig 1). Losses of lines of BSCVA were observed in 4 eyes (22.22%) at 6 months and in 3 eyes (20%) at 24 months (Fig 1). One eye with a loss of BSCVA developed a significant corticonuclear cataract during the follow-up (cataract surgery 12 months after the ring segment implantation). In 2 additional cases with a best-corrected visual loss, segment ring explantation was performed because of the poor postoperative visual outcome achieved.

Mean efficacy and safety indexes at 6 months were 0.75±0.60 (range, 0.05–2.67) and 1.80±1.44 (range, 0.71–5.33), respectively. There was an improvement of both parameters between months 6 and 12, although with no statistical significance (efficacy $P = 0.25$; safety $P = 0.74$; Wilcoxon test) (Table 1).

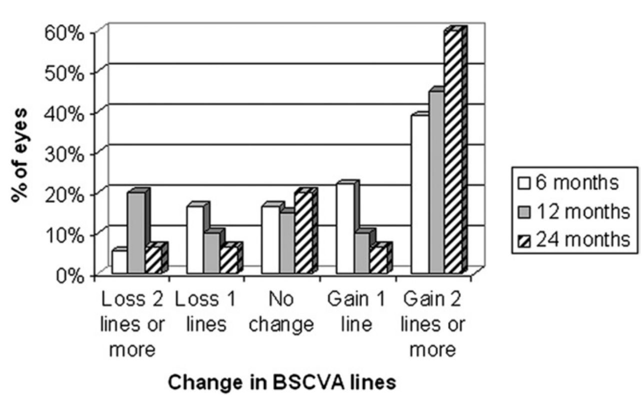

Figure 1. Changes in lines of BSCVA after ICRS implantation; 38.89% of eyes gained ≥2 lines of BSCVA at 6 months after surgery, and this percentage increased to 60% at 24 months. BSCVA = best spectacle-corrected visual acuity; ICRS = intracorneal ring segments.

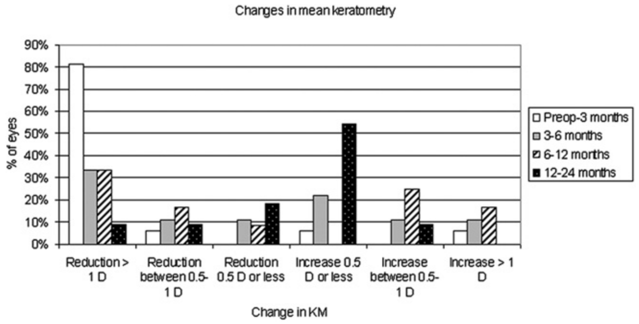

Figure 2. Analysis of changes in mean KM in different periods of the follow-up. At 3 months a reduction in KM was observed in 87.5% of eyes, whereas at 24 months this percentage decreased to 36.36%. D = diopters; KM = mean corneal power in the 3-mm zone.

Corneal Changes

A mean significant reduction of 1.54 D in mean keratometry was found at 6 months postoperatively ($P<0.01$; Student *t* test for paired data) (preoperative: 45.76±6.03 D vs. 6 months: 44.22±5.06 D). A regression of the achieved central flattening was observed during the rest of the follow-up, but changes were not statistically significant ($P = 0.73$; Student *t* test for paired data) (6 months 44.22±5.06 D vs. 24 months 45.96±7.78 D). This finding was consistent with the decrease observed in the percentage of patients with a reduction in mean keratometry during the follow-up (Fig 2). At 3 months an increase in KM was observed in only 12.5% of eyes, whereas at 24 months this percentage increased to 63.64%.

No statistically significant changes were observed in any CSO topographic parameter during the follow-up, except for asphericity over a 4.5-mm diameter at 6 months, which became more negative ($P = 0.01$, Student *t* test for paired data) (Table 4). It means that the anterior corneal surface became more prolate after the ICRS implantation. In addition, there was a reduction in the ISAI, AST3, AST6, apical keratometry, and ACG, but changes did not reach statistical significance probably because of the small sample size and the high variability of these parameters. Finally, a statistically significant correlation was found between postoperative BSCVA at 6 months and the ISAI index ($r = -0.83$, $P = 0.01$; Spearman correlation coefficient).

Corneal Aberrations of the Anterior Surface

A detailed report of the corneal aberrometric outcomes is shown in Table 5. At 6 months only a statistically significant reduction was found in coma-like RMS ($P = 0.03$, Wilcoxon test). RMS values for total, astigmatism, and primary coma aberrations were also reduced, but changes did not reach statistical significance (Table 5). A tendency to postoperative negative primary spherical aberration was also observed (Table 5), which was consistent with the significant negativization of corneal asphericity. In addition, a nonsignificant increase in higher-order residual and spherical-like RMS was found ($P = 0.48$ and $P = 0.26$, respectively, Wilcoxon test). Preoperative primary spherical aberration Zernike term ($r = 0.71$, $P = 0.04$), coma ($r = -0.92$, $P<0.01$) and coma-like RMS ($r = -0.92$, $P<0.01$) were significantly correlated with postoperative BSCVA at 6 months (Spearman correlation coefficient).

Table 6 shows a comparative analysis of the preoperative and early postoperative aberrometric outcomes in 2 groups of eyes: those implanted with ring segments using the mechanical dissection for corneal tunnelization (20 eyes) and those implanted using the femtosecond laser technology (14 eyes). As shown in Table 6, the initial postoperative higher-order residual, spherical-like, and coma-like RMS values were higher in the group of eyes receiving the mechanical procedure, but differences reached statistical significance for only spherical-like RMS ($P = 0.03$, Mann–Whitney test). In addition, there was a nonstatistically significant trend of primary spherical aberration to negative values in the group of eyes receiving the mechanical procedure.

Figure 3 shows a comparative analysis of the initial postoperative aberrometric data in eyes implanted with Intacs (24 eyes) and eyes implanted with KeraRings (10 eyes). No statistically significant differences were found between both groups of eyes preoperatively (all $P>0.20$, Mann–Whitney test) and at 1 month after surgery (all $P>0.24$, Mann–Whitney test).

Complications

Segment ring explantation was performed in 6 eyes (17.6%). Three eyes were explanted because of significant postoperative visual problems (loss of BSCVA and patient dissatisfaction with the visual quality achieved). In the remaining 3 eyes, explantation was performed because of ring segment extrusion or migration problems (all of them receiving the mechanical procedure, mean corneal depth of implantation 381.33±22.71 μm). Five of the 6 explanted ring segments were Intacs, and only 1 ring segment was KeraRing. In addition, in 2 cases (5.9%) ring segment reposition

Table 4. Summary of Changes in Topographic Corneal Parameters Provided by the Costruzione Strumenti Oftalmici System

Parameter	Preoperative	3 Mos	6 Mos	12 Mos	24 Mos	*P* Value (Preoperative to 6 Mos)
ISAI (D)	11.52±7.25	6.52±8.06	8.52±7.92	5.40±9.41	5.08±9.43	0.16
AST3 (D)	5.18±2.36	3.02±1.12	3.42±2.41	2.94±2.04	3.61±3.20	0.15
AST6 (D)	3.97±1.74	2.70±0.82	3.02±1.56	2.21±1.47	3.20±1.24	0.43
Q45	−1.78±2.28	−3.12±3.59	−3.33±3.40	−1.28±4.31	−3.68±3.13	0.02
Q8	−0.42±1.29	−0.33±1.05	−1.03±1.66	0.98±3.69	−1.35±1.44	0.25
AK (D)	65.98±14.04	69.90±13.10	63.36±13.29	62.73±9.87	65.52±12.52	0.58
ACG (mm/D)	10.37±7.93	9.37±3.78	10.35±7.60	9.87±5.10	9.02±6.87	0.78
No. of eyes	15	10	10	12	6	

ACG = apical curvature gradient; AK = apical keratometry; AST3 = corneal astigmatism in the 3-mm zone; AST6 = corneal astigmatism in the 6-mm zone; CSO = Costruzione Strumenti Oftalmici; D = diopters; ISAI = inferosuperior asymmetry index; Q45 = mean asphericity for a corneal area of 4.5-mm diameter; Q8 = mean asphericity for a corneal area of 8-mm diameter.
All patients completed a follow-up of at least 12 mos. During the first year of follow-up, no dropouts were found.

Table 5. Summary of the Corneal Aberrometric Outcomes

Parameter	Preoperative	3 Mos	6 Mos	12 Mos	24 Mos	*P* Value (Preoperative to 6 Mos)
Total RMS (μm)	17.20±17.59 (3.14–67.04)	12.12±9.80 (2.73–29.25)	14.23±8.92 (2.41–26.33)	10.87±7.73 (2.65–24.39)	10.10±4.83 (5.33–18.16)	1.00
RMS Astigmatism (μm)	2.89±2.06 (0.41–7.08)	2.39±0.91 (0.89–3.78)	2.30±0.73 (0.53–3.32)	2.00±0.83 (0.56–3.55)	2.51±1.13 (0.55–3.89)	0.89
Primary coma RMS (μm)	3.17±1.94 (0.69–7.84)	2.03±1.22 (0.59–4.03)	2.35±1.75 (0.46–6.30)	2.31±1.18 (1.06–4.84)	2.08±1.16 (0.77–3.73)	0.09
Z_4^0 (μm)	0.02±0.96 (−2.29 to 1.52)	0.02±0.70 (−1.14 to 1.30)	−0.01±0.70 (−1.09 to 1.32)	−0.85±1.36 (−4.59 to 0.62)	−0.90±0.97 (−2.71 to 0.00)	0.67
Residual RMS (μm)	1.60±0.67 (0.75–2.87)	1.80±0.67 (0.91–3.13)	1.96±0.70 (0.77–3.04)	1.98±0.65 (1.00–2.91)	1.98±0.61 (1.12–2.91)	0.48
Spherical-like RMS (μm)	1.28±0.60 (0.47–2.49)	1.07±0.51 (0.63–2.14)	1.36±0.51 (0.64–2.13)	1.59±1.16 (0.55–5.05)	1.61±0.91 (0.38–3.20)	0.26
Coma-like RMS (μm)	3.52±1.83 (1.19–7.95)	2.60±1.22 (1.36–4.74)	2.95±1.63 (0.81–6.58)	2.74±1.14 (1.46–5.09)	2.67±1.04 (1.71–4.35)	0.03
No. of eyes[a]	15	10	10	12	6	

RMS = root mean square. Definitions of each kind of corneal aberration: primary coma, Zernike terms $Z_3^{\pm 1}$; primary spherical aberration, Zernike term Z_4^0; residual aberrations, all Zernike terms except $Z_3^{\pm 1}$ and Z_4^0; spherical-like aberrations, Zernike terms fourth and sixth order; coma-like aberrations, Zernike terms third and fifth order.
Ranges are given in parentheses below each mean value.
[a]All patients completed a follow-up of at least 12 months. During the first year of follow-up no dropouts were found.

was necessary to achieve a greater effect. One of these repositioned ring segments was finally explanted because of the significant degradation of visual quality. No severe complications such as infections occurred. Ring extrusion was observed in only 1 eye at 6 months, and it was finally explanted. Mild channel deposits were observed in 4 eyes implanted with Intacs at 12 months.

Figure 4 shows a comparison of the preoperative refractive data of explanted (6 eyes) and nonexplanted eyes (28 eyes). Mean sphere and cylinder were higher preoperatively in the nonexplanted group, but differences did not reach statistical significance (all $P>0.17$, Mann–Whitney test) (Fig 4). Mean keratometry was 46.42±6.18 D in the nonexplanted group and 42.16±3.75 D in the explanted group. Differences in this parameter were not statistically significant ($P = 0.15$, Mann–Whitney test).

Because all the explanted cases were examined with the CSO topography system, a comparative analysis of the aberrometric and curvature parameters provided by this device was feasible. No statistically significant differences were found between groups in apical keratometry, Q45, Q8, AST3, AST6, and ISAI (all $P>0.16$, Mann–Whitney test). However, the ACG was significantly higher in the group of explanted eyes (7.89±4.89 nonexplanted vs. 19.04±11.14 explanted; $P = 0.03$, Mann–Whitney test) (Fig 5). In regard to corneal aberrations, all the aberrometric coefficients were on average higher in the group of explanted eyes (Fig 6), but the differences between groups did not reach statistical significance probably because of the small sample size (only 6 eyes were explanted) ($P = 0.14$, Mann–Whitney test).

Discussion

The insertion of extra material (ring segments) in the deep stroma induces a modification of the corneal curvature and corneal shape.[25] These mid-peripheral implants in a healthy cornea generate a central flattening because of the stromal

Table 6. Summary of Early Aberrometric Outcomes (1 Month Postoperative) in 2 Groups of Eyes: Those Implanted with Ring Segments Using the Mechanical Dissection for Corneal Tunnelization and Those Implanted Using Femtosecond Laser Technology

Parameter	Mechanical		IntraLase		*P* Value	
	Preoperative	*1 mo Postoperative*	*Preoperative*	*1 mo Postoperative*	*Preoperative*	*Postoperative*
Total RMS	17.30±18.14	17.62±17.91	15.94±20.60	13.22±9.57	0.30	0.56
RMS astigmatism	2.61±2.61	2.19±2.18	3.26±2.05	2.18±0.88	0.96	0.56
Primary coma RMS	3.53±2.57	2.69±0.97	2.75±1.56	2.50±1.50	0.30	0.52
Primary spherical aberration	−0.19±0.80	−0.19±2.11	−0.02±1.15	0.03±0.62	0.68	0.91
Residual RMS	1.61±0.67	3.05±1.95	1.59±0.63	1.88±0.94	0.28	0.20
Spherical-like RMS	1.19±1.35	2.69±1.63	1.35±0.69	1.21±0.41	0.26	0.03
Coma-like RMS	3.87±2.44	3.61±1.46	3.18±1.36	2.96±1.68	0.44	0.41

RMS = root mean square.
Comparative analysis of preoperative and early postoperative data is shown for each group.
Definitions of each kind of corneal aberration: primary coma, Zernike terms $Z_3^{\pm 1}$; primary spherical aberration, Zernike term Z_4^0; residual aberrations, all Zernike terms except $Z_3^{\pm 1}$ and Z_4^0; spherical-like aberrations, Zernike terms fourth and sixth order; coma-like aberrations, Zernike terms third and fifth order.

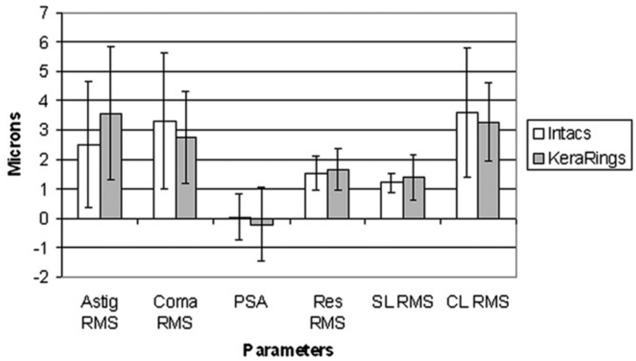

Figure 3. Comparative analysis of the initial postoperative aberrometric data in the group of eyes implanted with Intacs (24) (Addition Technology, Inc., Fremont, CA) and the group implanted with KeraRings (10) (Mediphacos, Belo Horizonte, Brazil). No statistically significant differences were found between both groups of eyes in any preoperative and 1-month postoperative corneal aberrometric parameter. Astig = astigmatism; CL = coma-like; PSA = primary spherical aberration; Res = residual; RMS = root mean square; SL = spherical-like. Definitions of each kind of corneal aberration: primary coma, Zernike terms $Z_3^{\pm1}$; primary spherical aberration, Zernike term Z_4^0; residual aberrations, all Zernike terms except $Z_3^{\pm1}$ and Z_4^0; spherical-like aberrations, Zernike terms fourth and sixth order; coma-like aberrations, Zernike terms third and fifth order.

collagen structure.[25] The magnitude of this flattening effect is in direct proportion to the thickness of the implant and in inverse proportion to its diameter.[25] This corneal flattening induced by the ICRS could be especially useful in the ectatic corneal disease for minimizing the corneal protrusion and consequently the refractive error. However, it should be considered that the stromal structure is altered in the ectatic cornea, with a nonorthogonal lamellar architecture.[30,31] Studies are necessary to define with precision the effect of this kind of implant in these weak corneas and how it can be predicted. In the specific case of the post-LASIK ectasia, the corneal structure is weakened by the laser tissue ablation, which breaks the balance between corneal biomechanics and intraocular pressure. However, it still remains unknown if the lamellar configuration in these specific cases is also altered. The present study attempts to characterize the refractive and corneal aberrometric effect of ICRS in this specific group of ectatic corneas. These changes would be the result of biomechanical modifications produced by the implants as a consequence of changes induced in the distribution of the corneal peripheral lamellae.

All the published studies on ICRS implantation for the management of post-LASIK ectasia are case reports or small series including a limited number of cases because of the complexity of finding such cases in clinical practice.[13,17–24] In this study, we collected data retrospectively from 2 ophthalmologic centers to achieve a large sample of cases, and we analyzed the refractive and aberrometric changes after the ICRS implantation during a 24-month follow-up. To the best of our knowledge, this study includes the largest reported series of cases of post-LASIK ectasia implanted with ICRS, 34 eyes.

Nonsignificant changes were found in sphere (mean change at 6 months, 0.52 D) and SE (mean change at 6 months, 0.93 D) after surgery, whereas a significant progressive reduction in cylinder was observed (mean change at 6 months, 0.83 D; mean change at 24 months, 1.56 D). On the contrary, other authors reported significant reductions in SE with ICRS.[18,22] An explanation for this difference could be the great variability in the preoperative SE observed in our sample, with a mean standard deviation of 3.66 D. In addition, a nonsignificant regression of the sphere and SE correction was observed in the period going from month 6 to month 24, suggesting that the ICRS did not stop the progression of the corneal ectasia. The significant astigmatic reduction found in our study supports the findings of previous studies.[19,20]

No significant changes were observed in UCVA during the follow-up, whereas a significant improvement in BSCVA was found. This best-corrected visual improvement was also reported in all previous series of post-LASIK ectasia with ICRS,[13,17–24] which confirms the adequate visual outcome provided by these implants in these ectatic corneas. In the current study, 38.89% of eyes gained 2 or more lines of BSCVA at 6 months after surgery, whereas this percentage increased to 60% at 24 months. Safety index in all visits was excellent (values >1), whereas the efficacy index was limited in the initial postoperative period, achieving values of ~1 at 12 and 24 months postoperatively.

In regard to changes in corneal curvature, a significant central corneal flattening was observed in the initial postoperative period (mean change, 1.54 D), with a posterior nonsignificant regression of this flattening effect (mean change, 1.74 D). This regression was consistent with the increase in myopia observed in the final part of the follow-up. However, Kymionis et al[18] found that mean keratometry remained stable postoperatively during a 5-year follow-up in a sample of 8 eyes. This difference in the keratometric evolution between both studies could be explained in part because significantly different samples of cases were evaluated. Mean preoperative keratometry was 45.76 D (range, 32.65–59.84 D) in our study, whereas it was 41.29 D (range, 37.79–46.15 D) in the study of Kymionis et al.[18] More moderate and advanced cases were included in our study,

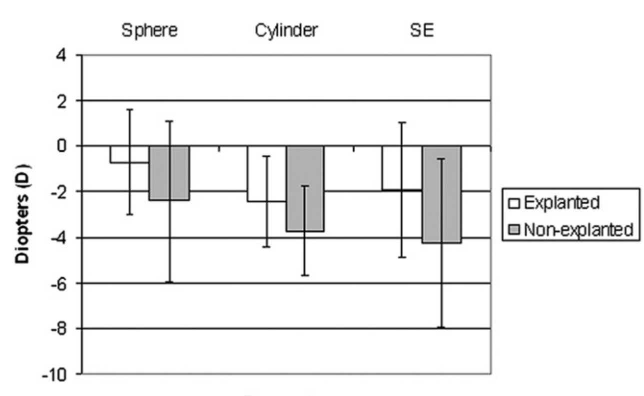

Figure 4. Comparison of preoperative refractive data in explanted and nonexplanted eyes. Mean sphere and cylinder were higher preoperatively in the nonexplanted eyes, but differences did not reach statistical significance. SE = spherical equivalent.

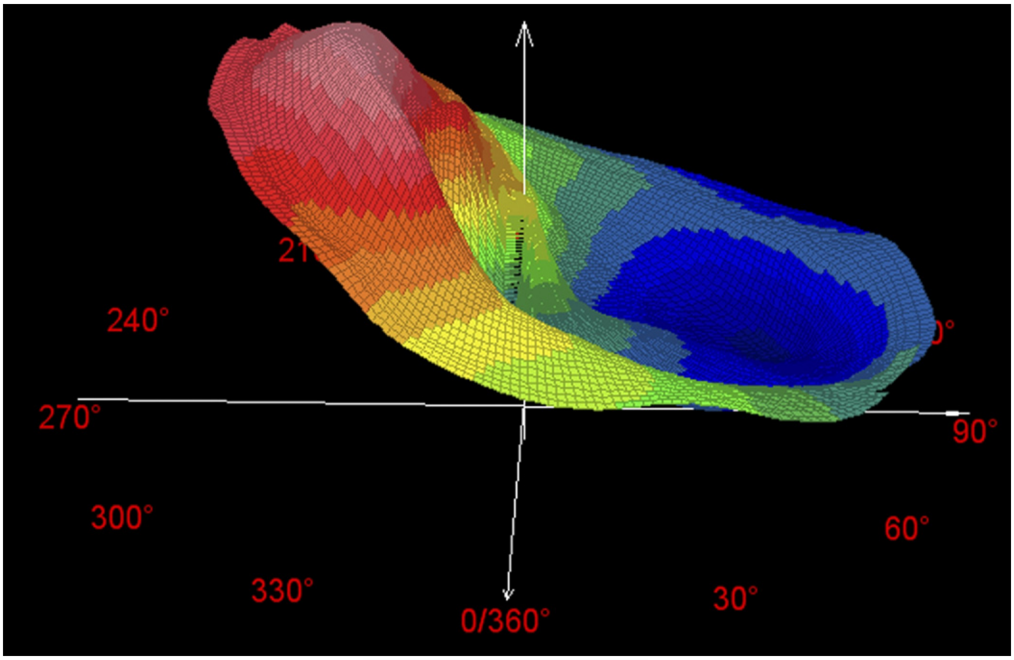

Figure 5. Three-dimensional preoperative corneal profile of a cornea in which ring segments were explanted. Preoperative apical gradient curvature was extremely high, 34.53 D. D = diopters.

and the ICRS effect probably was more unstable and unpredictable in these specific cases.

To the best of our knowledge, this is the first report on anterior corneal aberrometric outcomes after ICRS implantation in corneas with post-LASIK ectasia. Anterior corneal aberrometric analysis is an important tool in clinical practice for evaluating the ocular optical quality. It should be considered that the first refractive interface (air–cornea) is the most important contributor to the total power of the eye because of the large difference in refractive index existing at

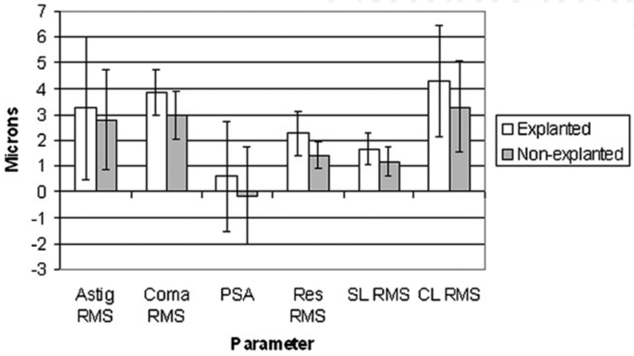

Figure 6. Comparative analysis of corneal aberrometric parameters in explanted and nonexplanted eyes. All aberrometric coefficients were on average higher in the group of explanted eyes, but differences did not reach statistical significance. Astig = astigmatism; CL = coma-like; PSA = primary spherical aberration; Res = residual; RMS = root mean square; SL = spherical-like. Definitions of each kind of corneal aberration: primary coma, Zernike terms $Z_3^{\pm1}$; primary spherical aberration, Zernike term Z_4^0; residual aberrations, all Zernike terms except $Z_3^{\pm1}$ and Z_4^0; spherical-like aberrations, Zernike terms fourth and sixth order; coma-like aberrations, Zernike terms third and fifth order.

this point. In highly aberrated corneas, such as in post-LASIK ectasia, the corneal aberrations of the anterior corneal surface are the most important source of optical errors in the eye. In the current study, we found that coma-like aberrations were significantly reduced with the implantation of ICRS. In addition, a nonsignificant reduction in primary coma was also observed. These modifications in the magnitude of coma-like aberrations were consistent with the postoperative improvement in BSCVA and the postoperative reduction in the inferosuperior asymmetry (although this change was not statistically significant). The primary and secondary comatic errors (the central Zernike terms from the third and fifth order, included in the coma-like RMS) have been demonstrated to have a negative impact on visual acuity because of the kind of optical blur that they induce.[32] These findings are consistent with those reported by Alió and Shabayek,[29] who also found a reduction of coma-like aberrations in keratoconic corneas implanted with KeraRings using the femtosecond technology, as well as a significant improvement in BSCVA. In addition to coma-like aberrations, a nonsignificant postoperative trend to more negative values of primary spherical aberration was observed. This finding was consistent with the negativization of the central corneal asphericity that was also observed.

No significant differences in corneal aberrometric outcomes between Intacs and KeraRings were found. However, there was a limitation for this analysis that should be considered: The sample of cases implanted with each ring segment type was small. On the contrary, the surgical technique used for ring segment implantation seemed to have an important role in the final outcome. A significantly higher magnitude of higher-order residual, coma-like, and spherical-like aberrations were found in those eyes that underwent operation with the mechanical procedure in the initial postoperative period. Therefore, it seems that the femtosecond technology is a better surgical procedure for implanting ICRS in post-LASIK ectatic corneas. The mechanical tunnelization may lack sufficient precision, and this may affect corneal aberrations leading to reduced optical performance. There are no previous studies comparing the aberrometric outcomes in eyes implanted with ICRS using the mechanical and the femtosecond-assisted procedures. Previously, only refractive and visual outcomes were compared between surgical techniques, and no statistically significant differences were observed in corneas with keratoconus and post-LASIK ectasia.[33]

We also studied whether preoperative aberrations could be used as a predictor for a good or bad visual prognosis. Preoperative primary coma and coma-like aberrations were inversely correlated with postoperative BSCVA. It seems that the presence of large corneal asymmetries inducing comatic aberrations is a limiting factor of the ICRS effect. In addition, corneas in which rings were explanted had on average higher preoperative values for all aberrometric coefficients. However, these aberrometric differences between explanted and nonexplanted eyes did not reach statistical significance. As happened with the comparison between Intacs and KeraRings, there was a limitation in this analysis because of the small sample of eyes compared. The ACG that defines the progression of curvature from the apex to the periphery (changes in diopters of curvature per millimeter) was significantly higher in the group of explanted eyes (Fig 5). Therefore, it seems that ectatic corneas with high irregularity and a pronounced conic protrusion are poor candidates for ICRS. This type of corneal configuration could be associated to a specific corneal structure limiting the ring segment effect and providing poorer results. It has been demonstrated that the keratoconic corneal structure is different compared with normal corneas with regions of more highly aligned collagen intermixed with regions in which there is little aligned collagen, and then a distortion of the orthogonal lamellar matrix.[30,31] In these cases with a significantly conic corneal protrusion, the distribution of lamellae in the cone area is highly irregular with a poor or unpredictable response to peripheral addition of material. In any case, future studies are required to understand how the configuration of ectatic corneal structure could influence the mechanism of action of the ICRS.

In conclusion, ICRS implantation, with Intacs or KeraRings, is a useful option for the treatment of corneal irregularity and astigmatism in post-LASIK corneal ectasia. Coma-like aberrations are significantly reduced with these implants, and a significant improvement in BSCVA is achieved. Anterior corneal aberrometry is a useful tool for achieving a better understanding of ICRS outcomes and as a screening factor for avoiding the implantation in those cases with poorer visual prognosis, eyes with high preoperative levels of corneal comatic aberrations. In addition, it seems that the use of the mechanical procedure for the implantation of ICRS limits the potential aberrometric correction of these implants, the procedure itself generating new aberrations.

The spherical correction and central flattening induced by ICRS are maintained during the initial postoperative period, but a regression of these effects is observed 12 months after surgery. This indicates that this kind of implant did not stop the progression of corneal ectasia in all cases. In any case, longer follow-ups are required to corroborate this refractive and keratometric instability in the long-term. Corneal collagen cross-linking could be another treatment option in those patients in whom the progression of the ectasia continues. It has been stated that corneal cross-linking is a therapeutic mean to arrest and partially reverse the progression of LASIK-induced iatrogenic keratectasia.[34] The combination of both techniques could have an important potential in post-LASIK ectasia treatment, and future studies should address this issue.

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Footnotes and Financial Disclosures

Originally received: September 22, 2008.
Final revision: May 15, 2009.
Accepted: May 22, 2009.
Available online: July 29, 2009. Manuscript no. 2008-1146.

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Financial Disclosure(s):
The author(s) have no proprietary or commercial interest in any materials discussed in this article.

Supported in part by a grant from the Spanish Ministry of Health, Instituto Carlos III, Red Temática de Investigación Cooperativa en Salud "Patología ocular del envejecimiento, calidad visual y calidad de vida," Subproyecto de Calidad Visual (RD07/0062).

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Corneal aberrometric and refractive performance of 2 intrastromal corneal ring segment models in early and moderate ectatic disease

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PURPOSE: To evaluate and compare visual, refractive, and corneal aberrometric outcomes after implantation of 2 types of intrastromal corneal ring segments (ICRS) in eyes with early to moderate ectatic disease.

SETTINGS: Vissum Corporation-Instituto Oftalmológico de Alicante, Alicante, Spain.

METHODS: This retrospective analysis comprised consecutive eyes with grade I or grade II corneal ectasia (keratoconus, pellucid marginal degeneration, ectasia after laser in situ keratomileusis) that had Intacs (Group I) or KeraRings (Group K) ICRS implantation using femtosecond technology. Visual, refractive, and corneal aberrometric outcomes were analyzed and compared between groups over a 6-month follow-up.

RESULTS: Group I had 17 eyes and Group K, 20 eyes. One month postoperatively, there was a statistically significant reduction in sphere in both groups ($P \leq .02$). At 6 months, there was a statistically significant reduction in manifest cylinder in Group K that was consistent with the significant reduction in corneal astigmatic aberration (both $P = .04$). The uncorrected distance visual acuity increased significantly in Group K ($P = .04$) but not in Group I; 41.18% of eyes in Group I and 52.94% in Group K gained 1 or more lines of corrected distance visual acuity. Both groups had significant corneal flattening ($P \leq .02$). At 1 month, the mean primary spherical aberration was -0.17 µm $\pm$ 0.52 (SD) in Group I and 0.40 $\pm$ 0.35 µm in Group K; the difference was statistically significant ($P < .01$).

CONCLUSION: Astigmatism correction in early to moderate ectatic corneas was more limited with the Intacs ICRS, which induced negative primary spherical aberration in the initial postoperative period.

Financial Disclosure: No author has a financial or proprietary interest in any material or method mentioned.

J Cataract Refract Surg 2010; 36:102–109 © 2010 ASCRS and ESCRS

Intrastromal corneal ring segment (ICRS) implantation has been evaluated as an additive surgical procedure for corneal ectasia resulting from keratoconus[1–20] or pellucid marginal degeneration (PMD)[21–27] or occurring after laser in situ keratomileusis (LASIK).[28–36] The procedure is an alternative in keratoconus cases, with the goal being to delay or prevent the need for corneal grafts.[7,8] Implantation of ICRS can improve visual acuity and reduce refractive errors and mean keratometry (K) values. The segments act as spacers between bundles of corneal lamellae, shortening the central arc length in a manner proportional to the thickness of the segment (Silvestrini TA, et al. IOVS 1994; 35:ARVO Abstract 3557). The arc-shortening effect flattens the central portion of the anterior corneal surface and steepens the peripheral area adjacent to the ring insertion site.[37,38] Segments with a short arc-length are effective in the correction of astigmatism,[1,8,17] inducing less corneal flattening and change in corneal toricity due to the structural configuration of corneal collagen (predicted by finite element modeling).[39]

Three types of ICRS have been evaluated in the management of keratoconus.[40] The first, Intacs segments (Addition Technology, Inc.), consist of a pair of semicircular pieces of poly(methyl methacrylate), each having a circumference arc length of 150 degrees and a hexagonal transverse shape. Each segment has an external diameter of 8.10 mm, an internal diameter of 6.77 mm, and variable thickness (0.25 to 0.45 mm in

Published by Elsevier Inc.
0886-3350/10/$—see front matter
doi:10.1016/j.jcrs.2009.07.030

0.05 mm increments) that allows modulation of the refractive effect.[41] Another Intacs design, Intacs SK, was recently developed. These ICRS have an inner diameter of 6.00 mm, an oval cross-section, and 2 thicknesses: 400 μm for K values of 57.0 to 62.0 diopters [D] and cylinder value <5.0 D and 450 μm for K values >62.0 D and cylinder value >5.0 D.[41] The other 2 ICRS types are Ferrara rings (Ferrara Ophthalmics) and KeraRings (Mediphacos, Ltda.). Both have a triangular cross-section that theoretically induces a prismatic effect to reduce photic phenomena[18] and are available in different thicknesses and arc lengths for customization based on the individual case. KeraRings ICRS have an external diameter of 4.40 mm, an internal diameter of 5.60 mm, and a thickness between 0.15 and 0.35 mm in 0.05 mm increments. An arc length of 90, 120, 160, and 210 degrees can be chosen depending on the topographic pattern and level of astigmatism. Good outcomes have been reported with all 3 types of ICRS[1–36]; however, to our knowledge, a comparison of results has not been published.

The aim of the present study was to evaluate and compare the visual, refractive, and corneal aberrometric outcomes after implantation of 2 types of ICRS using femtosecond laser technology in corneas with early to moderate ectatic disease. To our knowledge, this is the first study comparing the effect of the 2 ICRS in ectatic corneas.

PATIENTS AND METHODS

Consecutive eyes that had ICRS implantation for corneal ectasia from September 2006 to June 2007 at Vissum Corporation-Instituto Oftalmológico de Alicante were analyzed retrospectively. The institute's ethical board committee approved the study, and all patients provided informed consent that included approval for the use of clinical information in scientific studies.

The corneal ectasia in the study eyes was the result of keratoconus or PMD or occurred after LASIK. Cases were classified according to the Amsler-Krumeich and Alió-Shabayek[42] grading systems. The eyes were divided into 2 groups based on the type of ICRS implanted: Intacs (Group I) or KeraRings (Group K).

The keratoconus diagnosis was based on corneal topography and slitlamp observation (asymmetric bow-tie pattern with or without skewed axes; presence of stromal thinning, conical protrusion of the cornea at the apex, Fleischer ring, Vogt striae, or anterior stromal scar).[43] The PMD diagnosis was made according to slitlamp observation (inferior corneal thinning and ectasia above the area of maximum thinning), corneal topography (butterfly pattern, very steep contour in the peripheral inferior cornea with high keratometric powers radiating toward the center from the inferior oblique meridians), and refractive findings (significant against-the-rule astigmatism with a loss of corrected distance visual acuity [CDVA]).[43] Post-LASIK ectasia was diagnosed when the following findings were observed: corneal thinning on slitlamp examination, unstable topographic steepening (>1.0 D during each 6-month follow-up), progressive corneal thinning on ultrasound pachymetry, decreased distance visual acuity, and unstable refraction (>0.5 D spherical equivalent [SE] during each 6-month follow-up).[33] In all cases, the indication for ICRS implantation was reduced CDVA, contact lens intolerance, or both.

Preoperative and Postoperative Protocols

A comprehensive preoperative examination was performed that included Snellen uncorrected distance visual acuity (UDVA) and CDVA, manifest refraction, slitlamp biomicroscopy, Goldmann tonometry, fundus evaluation, ultrasound pachymetry, and corneal topographic and aberrometric analysis with the CSO topography system with EyeTop2005 software (Compagnia Strumenti Oftalmici). The topographer analyses 6144 corneal points in a circular annulus defined by an inner radius of 0.33 mm and an outer radius of 10.00 mm with respect to corneal vertex. The software converts the corneal elevation profile into corneal wavefront data using Zernike polynomials with expansion up to the 7th order. In this study, aberration coefficients and root-mean-square (RMS) values were calculated for a 6.0 mm pupil. The following topographic and aberrometric data from the topographer were evaluated and recorded: corneal dioptric power in the flattest meridian for the 3.0 mm central zone (K1); corneal dioptric power in the steepest meridian for the 3.0 mm central zone (K2); mean corneal power in the 3.0 mm zone (KM); astigmatism RMS; primary coma RMS computed for Zernike terms $Z(3,\pm1)$; coma-like RMS computed for 3rd-, 5th-, and 7th-order Zernike terms; spherical-like RMS computed for 4th- and 6th-order Zernike terms; and residual RMS computed for all Zernike terms except those corresponding to primary coma and spherical aberration. The Zernike coefficient for primary spherical aberration $Z(4,0)$ with its sign was also recorded.

Postoperative visits were scheduled for 1 day and 1, 3, and 6 months. On the first postoperative day, UCVA measurements and a slitlamp examination (ICRS position and corneal integrity) were performed. The remaining postoperative visits included UDVA and CDVA measurements, manifest refraction, a slitlamp examination, and corneal topographic and aberrometric analysis.

Submitted: February 2, 2009.
Final revision submitted: July 16, 2009.
Accepted: July 22, 2009.

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Supported in part by a grant from the Spanish Ministry of Health, Instituto Carlos III, Red Temática de Investigación Cooperativa en Salud Patología Ocular del Envejecimiento, Calidad Visual y Calidad de Vida, Subproyecto de Calidad Visual (RD07/0062).

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Table 1. Intacs nomogram.

Corneal Topography Pattern (Axial Map)	Indication*
Steepening area not involving 180-degree meridian of cornea (inferior cone)	1 segment: 0.45 mm thick
Steepening extending at least 1.0 mm above and beyond 180-degree meridian (central cone)	2 segments: 0.45 mm thick segment inferiorly and 0.25 mm thick segment superiorly

*The number and the thickness of the segments were selected based on the corneal topographic pattern of the inferior or central cone (axial or sagittal map).

Surgical Technique

The same experienced surgeon (J.L.A.) performed all procedures using topical anesthesia. The incision was placed on the steepest meridian. Corneal tunnelization was performed with a 30 kHz femtosecond system (IntraLase, IntraLase Corp.). Tunnels with an inner diameter of 6.6 mm and an outer diameter of 7.8 mm were used in Group I, and tunnels with diameters of 4.8 mm and 5.7 mm, respectively, were used in Group K. The number (1 or 2) and the thickness of ICRS in Group I were selected using previously defined criteria[44] (Table 1). In Group K, the manufacturer's nomogram[5] was used (Table 2). All ICRS in Group K had an arc length of 160 degrees.

All patients were prescribed topical ciprofloxacin every 8 hours for 2 days preoperatively. Postoperatively, topical tobramycin–dexamethasone eyedrops were used every 6 hours for 1 week and a topical lubricant was used every 6 hours for 1 month.

Statistical Analysis

Statistical analysis was performed using SPSS software for Windows (version 15.0, SPSS, Inc.). Normality of all data samples was first checked by the Kolmogorov-Smirnov test. When parametric analysis was possible, the Student *t* test for paired data was used for all comparisons between preoperative and postoperative parameter. The Student *t* test for unpaired data was used to compare outcomes between groups.

When parametric analysis was not possible, the Wilcoxon rank-sum test was used to assess the significance of differences between preoperative and postoperative data and the Mann-Whitney test was used for comparison between groups. A *P* value less than 0.05 was considered statistically significant in all comparisons.

In cases of ICRS explantation, data from visits after explantation were not included in the statistical analysis to prevent bias in the final results.

RESULTS

Patient Characteristics

The study evaluated 37 eyes of 28 patients; the corneal ectasia was unilateral in 28 cases and bilateral in 9 cases. The mean age of the 19 men (67.86%) and 9 women (32.14%) was 31.56 years ± 9.39 (SD) (range 15 to 56 years). The distribution of right eyes and left eyes was balanced (17 and 20, respectively). Group I comprised 17 eyes (44.74%) and Group K, 20 eyes (52.63%). One segment was implanted in 5 eyes (29.41%) in Group I and 8 eyes (40.00%) in Group K. Two segments were implanted in 12 eyes (70.59%) and 12 eyes (60.00%), respectively. No intraoperative complications occurred.

Cone opacity was observed in 1 eye (8.22%). The Amsler-Krumeich cone grade was I in 23 eyes (62.16%) and II in 14 eyes (37.84%); 11 eyes in Group I and 12 eyes in Group K had cone grade I, and 6 eyes and 8 eyes, respectively, had cone grade II. Based on corneal aberrations and the Alió-Shabayek system, 19 eyes (51.35%) had cone grade I and 18 eyes (48.65%), cone grade II. Keratoconus was present in 26 eyes (13 eyes in each group), PMD in 6 eyes (2 Group I; 4 Group K), and post-LASIK ectasia in 5 eyes (2 Group I; 3 Group K).

Group I

Figure 1 shows the sphere, cylinder, and SE in Group I over time. One month postoperatively, there was a statistically significant reduction in sphere and SE over preoperative values (both $P \leq .02$, paired Student *t* test). At 6 months, there was a statistically

Table 2. KeraRings nomogram.

	Superior Segment Thickness (mm)/Inferior Segment Thickness (mm)*			
Spherical Equivalent (D)	Ectasia Limited to One Half of Cornea	$^3/_4$ of Ectasia in One Half and $^1/_4$ in Other Half of Cornea	2/3 Ectasia in One Half and 1/3 in Other Half of Cornea	Ectasia Distributed Evenly in Both Halves of Cornea
Less than −10.0	25/35	25/35	30/35	35/35
−8.0 to −10.0	20/30	20/30	25/30	30/30
−6.0 to −8.0	15/25	15/25	20/25	25/25
−2.0 to −6.0	0/20	0/20	15/20	20/20

*The number and thickness of segments were selected based on the topographic distribution of the ectasia and the spherical equivalent. To define the distribution of the ectasia, the axial or sagittal topographic map was divided in half using the steepest meridian as axis of separation.

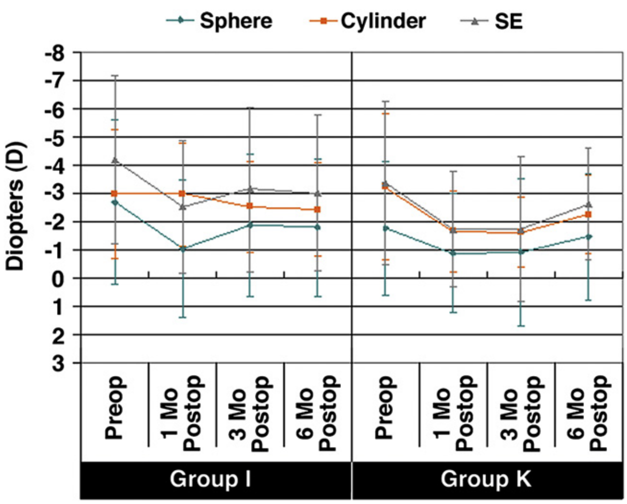

Figure 1. Postoperative changes in sphere, cylinder, and SE (SE = spherical equivalent).

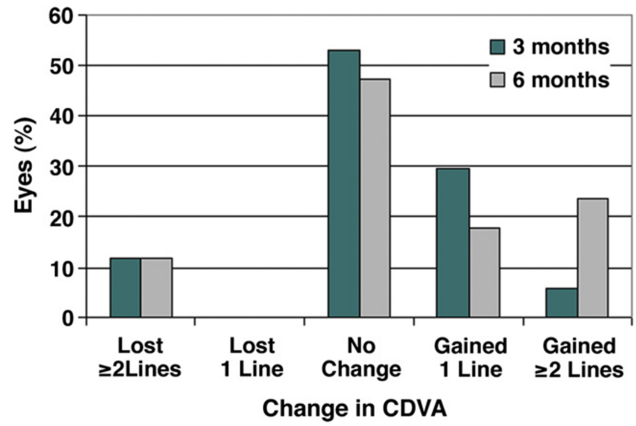

Figure 3. Postoperative changes in lines of CDVA in Group I (CDVA = corrected distance visual acuity).

significant regression in the achieved spherical correction ($P<.01$, paired Student *t* test). There were no statistically significant changes in cylinder at any postoperative follow-up ($P \geq .53$, paired Student *t* test).

There were no statistically significant changes in UDVA ($P \geq .72$, paired Student *t* test) or CDVA ($P \geq .32$, paired Student *t* test) at any postoperative follow-up (Figure 2). At 3 months, 6 eyes (35.29%) gained 1 or more lines of CDVA; by 6 months, 7 eyes (41.18%) had gained 1 or more lines of CDVA (Figure 3). Two eyes (11.76%) lost lines of CDVA at 3 months and 6 months.

Figure 4 shows the K readings over time. The mean, flattest, and steepest K readings were statistically significantly lower at 1 month than preoperatively ($P \leq .01$, paired Student *t* and Wilcoxon test). Although no further statistically significant changes occurred, there was slight regression of the achieved flattening at 3 months ($P \geq .12$, paired Student *t* test).

Figure 5 shows the corneal aberrometry results over time. The only statistically significant change was negativization of primary spherical aberration at 1 month ($P = .02$, paired Student *t* test). From 1 month to 6 months, there was a change in primary spherical aberration toward positive values ($P = .19$, paired Student *t* test) and a slight reduction in almost all aberrometric coefficients ($P \geq .38$, paired Student *t* test).

Group K

Figure 1 shows the sphere, cylinder, and SE in Group K over time. One month postoperatively, there was a statistically significant reduction in sphere and SE

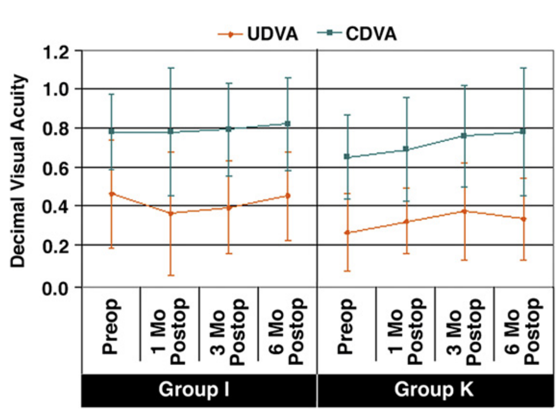

Figure 2. Changes in the UDVA and CDVA over time (CDVA = corrected distance visual acuity; UDVA = uncorrected distance visual acuity).

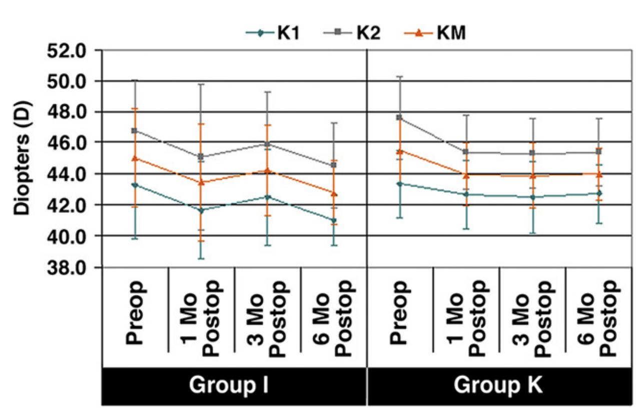

Figure 4. Changes in K values over time (K1 = corneal dioptric power in the flattest meridian in the 3.0 mm central zone; K2 = corneal dioptric power in the steepest meridian in the 3.0 mm central zone; KM = mean corneal power in the 3.0 mm zone).

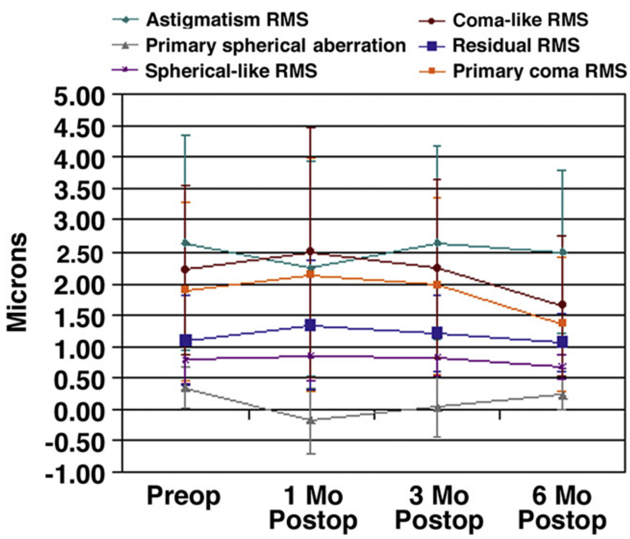

Figure 5. Changes in corneal aberration (6.0 mm pupil) over time in Group I (Coma-like RMS = 3rd- and 5th-order Zernike terms; Primary coma RMS = Zernike terms Z(3,±1); Primary spherical aberration = Zernike term Z(4,0); Residual RMS = all Zernike terms except Z(3,±1) and Z(4,0); RMS = root mean square; Spherical-like RMS = 4th- and 6th-order Zernike terms).

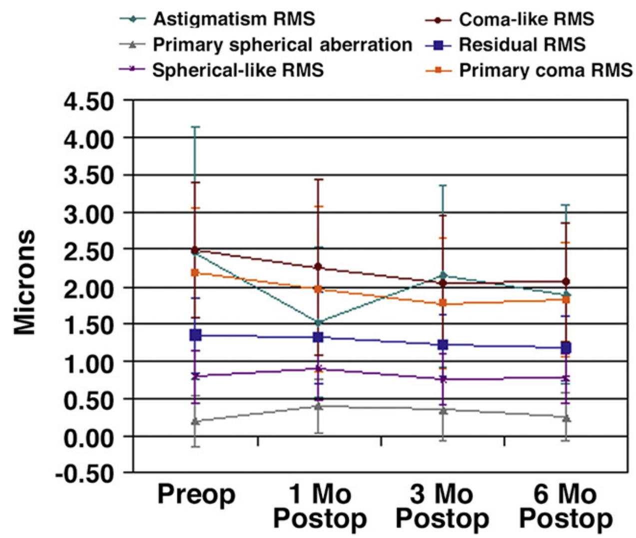

Figure 7. Changes in corneal aberration (6.0 mm pupil) over time in Group K (Coma-like RMS = 3rd- and 5th-order Zernike terms; Primary coma RMS = Zernike terms Z(3,±1); Primary spherical aberration = Zernike term Z(4,0); Residual RMS = all Zernike terms except Z(3,±1) and Z(4,0); RMS = root mean square; Spherical-like RMS = 4th- and 6th-order Zernike terms).

(both $P \leq .03$, Wilcoxon test). At 6 months, there was a slight, but not statistically significant, regression in the achieved spherical correction ($P = .17$, Wilcoxon test). There was a nonsignificant reduction in cylinder at 1 month ($P = .22$, Wilcoxon test). However, at 3 months, the reduction in cylinder was statistically significant ($P < .01$, Wilcoxon test). In addition, there was a statistically significant regression in cylindric correction from 3 months to 6 months ($P = .05$, Wilcoxon test).

The UDVA was statistically significantly better 1 month postoperatively than preoperatively ($P = .04$, paired Student *t* test); there were no further significant changes in UDVA ($P = .48$, paired Student *t* test) (Figure 2). The CDVA was statistically significantly better at 3 months ($P = .02$, Wilcoxon test); 10 eyes (55.55%) gained 1 or more lines of CDVA at 3 months and 9 eyes

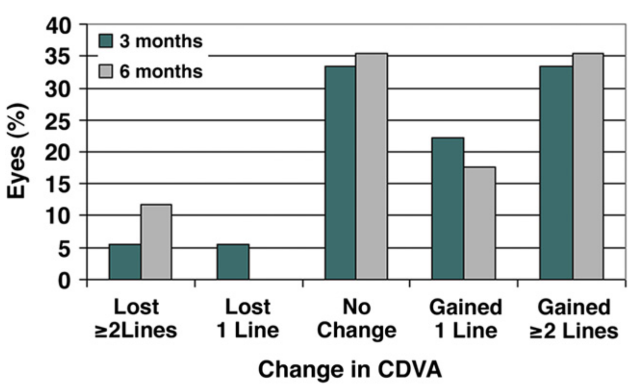

Figure 6. Postoperative changes in lines of CDVA in Group K (CDVA = corrected distance visual acuity).

(52.94%) gained 1 or more lines at 6 months (Figure 6). Two eyes (11.76%) lost lines of CDVA at 3 months and 6 months.

Figure 4 shows the K readings over time. The mean, flattest, and steepest K readings were statistically significantly lower at 1 month than preoperatively ($P \leq .02$, paired Student *t* and Wilcoxon test). No further statistically significant changes in K values occurred ($P \geq .64$, paired Student *t* test).

Figure 7 shows the corneal aberrometry results over time. The only statistically significant change was a reduction in astigmatism RMS at 1 month ($P = .04$, paired Student *t* test). Slight reductions in primary coma and coma-like RMS were also observed at 1 month ($P \geq .84$, paired Student *t* test). Primary spherical aberration and spherical-like RMS increased at 1 month and then decreased progressively over the subsequent follow-up ($P \geq .21$, paired Student *t* and Wilcoxon test).

Comparative Analysis

There were no statistically significant differences between Group I and Group K in any preoperative visual or refractive parameter ($P \geq .07$, unpaired Student *t* and Wilcoxon test). There was a statistically significant difference in primary spherical aberration between groups at 1 month ($P < .01$, unpaired Student *t* test), with a clear tendency toward negative spherical aberration in Group I. At 6 months, the K1 and safety index values were statistically significantly higher in Group K than in Group I ($P \leq .04$, unpaired Student *t* test).

There were no statistically significant differences between groups in cylinder or astigmatism RMS, probably due to high variability of these parameters and the small sample size ($P \geq .07$, unpaired Student t and Wilcoxon tests). At 1 month, the mean change in astigmatism RMS was -0.23 ± 0.74 μm in Group I and -0.99 ± 1.01 μm in Group K; the difference was statistically significant ($P = .04$, Wilcoxon test).

Complications

Explantation of the ICRS was performed in 3 eyes (8.11%), all in Group K. In 1 of the cases, the ICRS were explanted because of secondary extrusion after a bacterial keratitis that had been appropriately treated with an intensive fortified antibiotic–corticosteroid combination. In the other 2 cases, explantation was performed because of a poor postoperative visual outcome. Corneal melting and corneal neovascularization were not observed in any case.

DISCUSSION

In 2000, Colin et al.[20] reported the first results of ICRS implantation in eyes with keratoconus. They found a reduction in the corneal steepening and astigmatism associated with keratoconus. Since then, several studies[1–36] have confirmed the efficacy and safety of ICRS implantation in reducing spherocylindrical error and corneal steepening in the short term and long term. However, predicting the amount of flattening and refractive change induced by ICRS in ectatic corneas remains complicated. The mechanism of action of ICRS in ectatic corneas is not the same as in normal corneas. The stromal structure is altered in ectatic corneas, having a nonorthogonal lamellar architecture[45]; this makes it more difficult to predict the ICRS' mechanism of action. More studies of the effect of ICRS on the ectatic corneal structure are necessary to define a predictable ICRS implantation nomogram.

In the present study, we analyzed and compared the short-term refractive and aberrometric performance of 2 types of ICRS—Intacs (Group I) and KeraRings (Group K)—in ectatic corneas (keratoconus, PMD, post-LASIK ectasia). To our knowledge, this is the first study comparing the effect of the 2 types of ICRS.

Postoperatively, sphere and SE were significantly reduced in both groups. The spherical correction has been reported by others.[2,4,5,9,10,12] In addition, there was slight but not significant regression of the achieved spherical correction at 6 months in both groups, a finding also reported in medium-term studies of Intacs ICRS in keratoconic eyes.[7,8,11,15] Cylinder decreased significantly in Group K but not in Group I, indicating that Intacs ICRS are more limited in terms of correcting astigmatism. This supports findings in previous studies,[4,6] which found a nonsignificant change in manifest astigmatism after Intacs ICRS implantation in eyes with keratoconus. However, other studies[2,9–12,19,43] report significant changes in manifest astigmatism with this type of ICRS. The reason for the discrepancy could be the difference in the severity of the cases between our study and the previous studies. Our study included only mild to moderate cases, whereas many of the other studies included cases with keratoconus grade III and IV. In addition, we included only cases with low or moderate corneal asymmetry (Alió-Shabayek classification, low magnitude of coma-like aberrations).

In our study, Intacs ICRS were not as effective as KeraRings ICRS in controlling astigmatism. This finding is not surprising given that these ICRS are placed farther from the corneal center, reducing the effect of the segments. Patel et al.[38] predicted this, although it has not been proven in clinical practice. Ruckhofer et al.[17] proposed using short arc-length segments (120 degrees) for Intacs ICRS to achieve more effective astigmatism correction. This modification led to a -significant reduction in keratometric cylinder. KeraRings ICRS have 4 arc-length options (90 degrees, 120 degrees, 160 degrees, 210 degrees), allowing more accurate surgical planning and more effective astigmatism control. In addition, there was a statistically significant regression in cylindric correction from 3 months to 6 months in Group K ($P = .05$). One reason for the regression might be progression of the cone. If this is the case, the ICRS did not stop progression of the cone; however, longer follow-up is needed to confirm this.

The UDVA increased significantly in Group K but not in Group I, which is consistent with the higher magnitude of astigmatic correction in Group K. Furthermore, the CDVA increased significantly only in Group K, which is consistent with the significantly higher safety index in this group at 6 months. We found a significant increase in CDVA after KeraRings ICRS implantation in eyes with early, moderate, or advanced keratoconus.[5] Other studies[2,8–12,15,22,44] report a significant increase in CDVA after Intacs ICRS implantation in different and heterogenous groups of ectatic eyes. In our study, safety was good with both types of ICRS, with 41.18% of eyes in Group I and 52.94% in Group K gaining 1 or more lines of CDVA at 6 months.

Regarding corneal curvature, the mean K values were significantly lower with both types of ICRS, which supports the changes in corneal curvature reported by other studies of ICRS.[2,4–12,15,22,29,33,44] Therefore, both ICRS induce significant central flattening, which explains the significant reduction in the spherical error. In our series, this flattening effect was maintained during the 6-month follow-up.

In addition to visual and refractive outcomes, we analyzed the aberrometric changes at the anterior corneal surface. This is the first refractive interface (air–cornea) and is the most important contributor to the total power of the eye due to the large difference in the refractive index at this point. In highly aberrated corneas, such as in cases of corneal ectasia, the anterior corneal surface is the most important source of optical aberrations in the eye. Thus, analysis of these optical errors is mandatory to gain a better understanding of patients' visual complaints after ICRS implantation. We observed different aberrometric changes in the short term with both types of ICRS. Intacs ICRS induced significant negativization of the primary spherical aberration, whereas KeraRings ICRS induced a slight and nonsignificant increase, but with a positive sign. The significant difference in this aberration between the groups lessened progressively during the subsequent follow-up. There are significant differences between the 2 types of ICRS, including the cross-section shape (hexagonal versus triangular) and inner diameter (6.6 mm versus 4.8 mm). These factors might account for the differences in aberrometry.

With both types of ICRS, primary coma and coma-like aberrations were lower 6 months postoperatively than preoperatively; however, the changes did not reach statistical significance. The reduction in coma-like errors occurred at 6 months in Group I but immediately after implantation in Group K. This could explain why Group K had a significant improvement of CDVA at 3 months but Group I did not. Primary coma has a very negative impact on visual acuity because it induces optical blur.[46] In a previous study,[5] we found a significant reduction of higher-order aberrations after KeraRings ICRS implantation using the femtosecond laser technology in eyes with keratoconus; however, the reduction was significant only in eyes with a magnitude of coma aberration greater than 3.0 μm.

In conclusion, both types of ICRS used in our study were safe and effective in reducing spherical error and inducing central corneal flattening in early to moderate ectatic corneas (eyes with low levels of coma-like aberrations). However, the ability of Intacs ICRS to correct astigmatism in these eyes was more limited; this ICRS model induced negative primary spherical aberration in the early postoperative period, although this tendency disappeared by 6 months. In addition, coma-like aberrations tended to decrease after ICRS implantation, and the change occurred more rapidly with the KeraRings ICRS. Studies with a longer follow-up are needed to confirm the stability of visual, refractive, and aberrometric outcomes over the long term. Also, more studies of refractive and aberrometric results with short arc-length ICRS are needed to confirm their effectiveness in correcting astigmatism.

The reduction in segment diameter seems to be key to more effective control of astigmatism. However, if the segments are nearer from the pupil margins, visual quality can be adversely affected because scattered rays of light by the ICRS could reach the retina, inducing blur and glare sensation. Therefore, a compromise between ring effect and visual quality should be defined to achieve more efficacious control of the spherocylindrical error without inducing photic phenomena.

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Corneal Biomechanics, Refraction, and Corneal Aberrometry in Keratoconus: An Integrated Study

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Purpose. To evaluate the relationship of corneal biomechanical properties to refraction and corneal aberrometry in keratoconic eyes.

Methods. A total of 81 consecutive keratoconic eyes of 81 patients ranging in age from 11 to 58 years were included in the study. Three groups were differentiated according to the severity of keratoconus: mild (37 eyes), moderate (24 eyes), and severe (20 eyes). Visual acuity, refraction, corneal topography, and corneal aberrations were evaluated. In addition, corneal biomechanics were analyzed in relation to two parameters: corneal hysteresis (CH) and corneal resistance factor (CRF). Correlations between these biomechanical factors and the remaining clinical parameters were investigated.

Results. CH and CRF in the severe keratoconus group were significantly lower than those in the other two groups ($P \leq 0.01$). A significant difference in CRF was found between mild and moderate cases ($P = 0.04$). A moderate correlation was found between the CRF and mean keratometry in the overall sample ($r = -0.564$). In addition, a significant, strong correlation was found between the spherical-like root mean square (RMS) and the CRF only in the severe keratoconus group ($r = -0.655$). Multiple regression analysis revealed that CRF correlated significantly with keratometry and the corneal spherical-like RMS ($R^2 = 0.40$, $P < 0.01$).

Conclusions. The CRF correlates with the magnitude of corneal spherical-like aberrations, especially in severe keratoconus. It should be considered an additional factor in keratoconus grading. (*Invest Ophthalmol Vis Sci.* 2010;51:1948–1955) DOI:10.1167/iovs.09-4177

Keratoconus is an ectatic corneal disorder characterized by progressive corneal thinning that results in corneal protrusion, irregular astigmatism, and decreased vision.[1] Its incidence varies depending on several factors, such as the ethnic group analyzed or the diagnostic criteria used (most estimates are between 50 and 230 per 100,000 in the general population).[1] The hallmark of this ectatic disorder is the presence of an irregular corneal astigmatism. This significant irregularity is the consequence of changes occurring in the anterior corneal geometry, which can be assessed by means of corneal topography: increased area of corneal power surrounded by concentric areas of decreasing power, inferior–superior power asymmetry, and skewing of the steepest radial axes above and below the horizontal meridian.[2,3] For this reason, corneal topography has become an indispensable tool for keratoconus diagnosis. In addition, the anterior corneal aberration analysis has been demonstrated to be an effective tool for detecting and grading keratoconus.[4–8] Higher amounts of vertical coma and larger values of coma-like root mean square (RMS) are usually present in patients with keratoconus or suspected keratoconus.[5–8]

All these topographic and aberrometric alterations in keratoconic eyes appear as a consequence of the biomechanical changes that occur in the corneal structure. Corneal elasticity and rigidity are severely affected in keratoconic eyes,[9,10] due to the structural alterations of the cornea. It should be considered that the keratoconic stromal structure is not based on an orthogonal lamellar matrix, as in normal corneas. In keratoconus, there are regions of highly aligned collagen intermixed with regions in which there is little aligned collagen.[11,12] These structural alterations lead to a weakening of the cornea, which becomes more susceptible to the effect of any pressure on it, such as intraocular pressure. As a consequence, corneal shape can be distorted more easily (corneal steepening and aberrometric increase).

The in vivo study of corneal biomechanical properties is not an easy task. To date, only one clinical device has been developed for the purpose (Ocular Response Analyzer [ORA]; Reichert, DePew, NY).[13] Two biomechanical parameters are provided by this instrument: corneal hysteresis (CH) and the corneal resistance factor (CRF). Other studies have demonstrated that these two parameters are significantly reduced in keratoconic eyes,[9,10] as would be expected. The purpose of the present study was to define the relationship between the biomechanical parameters provided by this system (i.e., CH and CRF), and other clinical data such as refraction, corneal topography, or aberrometry in keratoconus. The knowledge of these relations will allow the clinician to achieve a better understanding of the changes that occur in this ectatic disease and to obtain an integrated criterion for keratoconus diagnosis. In addition, it will provide information about the key clinical parameters representing the severity of this disease.

Methods

Patients

A total of 81 consecutive keratoconic eyes of 81 patients with diagnosed keratoconus were retrospectively analyzed in two Spanish ophthalmology centers: Vissum Instituto Oftalmológico de Alicante and Centro de Oftalmología Barraquer in Barcelona. The age of patients

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Supported in part by a grant from the Spanish Ministry of Health, Instituto Carlos III, Red Temática de Investigación Cooperativa en Salud "Patología ocular del envejecimiento, calidad visual y calidad de vida," and Subproyecto de Calidad Visual Grant RD07/0062.

Submitted for publication June 18, 2009; revised August 20 and October 27, 2009; accepted November 6, 2009.

Disclosure: **D.P. Piñero**, None; **J.L. Alio**, None; **R.I. Barraquer**, None; **R. Michael**, None; **R. Jiménez**, None

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ranged from 11 to 58 years (mean, 31.81 ± 10.34); 56.8% were male and 43.2% were female. Keratoconus diagnosis was based on corneal topography and slit lamp observation. In all cases, clinical findings characteristic of keratoconus were evident: corneal topography revealing an asymmetric bowtie pattern, with or without skewed axes and at least one keratoconus sign on slit lamp examination, such as stromal thinning, conical protrusion of the cornea at the apex, Fleischer ring, Vogt striae, or anterior stromal scar.[1] Only keratoconus cases with no previous ocular surgery and no other active ocular disease were included in the study. Ethics board committee approval from our institution was obtained for the investigation. All patients were informed about inclusion in the study and signed an informed consent in accordance with the Declaration of Helsinki.

Examination Protocol

A comprehensive examination was performed in all cases and included: logMAR uncorrected visual acuity (UCVA), logMAR best spectacle-corrected visual acuity (BSCVA), manifest refraction, slit lamp biomicroscopy, Goldmann tonometry, fundus evaluation, ultrasonic pachymetry, and corneal topographic analysis. As topographic data were collected from two different centers, two different corneal topography systems were used for corneal examination: the CSO (CSO [Costruzione Strumenti Oftalmici], Firenze, Italy) and the Orbscan IIz (Bausch & Lomb, Rochester, NY). The first device is a Placido-based system, and the Orbscan II is a combined scanning-slit and Placido disc topography system. Although the agreement between these specific devices has not been reported, Orbscan and Placido-based devices have been shown to provide similar accuracy and precision on calibrated spherical test surfaces.[14] In this study, the following topographic data were evaluated and recorded with all corneal topographic devices: corneal dioptric power in the flattest meridian for the 3-mm central zone (K1), corneal dioptric power in the steepest meridian for the 3-mm central zone (K2), and mean corneal power in the 3-mm zone (KM).

Corneal aberrometry was also recorded and analyzed only in those patients examined with the CSO topography system (55 eyes), because this device was the only one of those used in this study with the capability of direct calculation of this specific information. The system analyzes 6144 corneal points of a corneal area enclosed in a circular annulus defined by an inner radius of 0.33 mm and an outer radius of 10 mm with respect to corneal vertex. The software of the CSO (EyeTop2005; CSO) automatically performs the conversion of corneal elevation profile into corneal wavefront data by using the Zernike polynomials with an expansion up to the seventh order. In this study, the aberration coefficients and root mean square (RMS) values were calculated for a 6-mm pupil in all cases. The following parameters were analyzed and recorded: higher order RMS, RMS for corneal astigmatism, primary coma RMS (computed for the Zernike terms $Z_3^{\pm 1}$), coma-like RMS (computed for third-, fifth-, and seventh-order Zernike terms), spherical-like RMS (computed for fourth- and sixth-order Zernike terms), and higher order residual RMS (computed considering all Zernike terms, except those corresponding with primary coma and spherical aberration). The corresponding Zernike coefficient for primary spherical aberration (Z_4^0) was also reported with its sign.

Corneal biomechanics was characterized by means of the ORA (Reichert). This device delivers to the eye an air pulse that causes the cornea to move inward, achieving a specific applanation state or flattening (P1). Milliseconds after the first applanation, the pressure decreases, and the cornea passes through a second applanated state (P2), while returning from concavity to its normal convex curvature. Two different pressures are then recorded (P1 and P2) and the difference between them is considered to be the CH. In addition, the software of this instrument provides the CRF, which is calculated by using a proprietary algorithm, and it is said to be predominantly related to the elastic properties of the cornea.[13] These parameters, CH and CRF, were shown to be reproducible in nonsurgical, healthy eyes.[15]

The patients wearing contact lenses for the correction of the refractive error were instructed to discontinue their use for at least 2 weeks before the examination for soft lenses and at least 4 weeks before the examination for rigid gas-permeable lenses.

Statistical Analysis

The normality of all data samples was first checked by means of the Kolmogorov-Smirnov test. When parametric analysis was possible, the Student's *t*-test for unpaired data (two samples) or the one-way analysis of variance (ANOVA) with Bonferroni post hoc analysis (more than two samples) was used to compare the outcomes between specific groups (i.e., comparison between keratoconus grades). When parametric analysis was not possible, the Mann-Whitney test (two samples) or the Kruskal-Wallis test (more than two samples) was used for the comparison between groups. Statistical significance was set at a α level of 0.05 (SPSS, ver. 15.0 for Windows; SPSS, Chicago, IL).

Correlation coefficients (Pearson or Spearman depending on whether a normality condition could be assumed) were used to assess the correlation between different variables. In addition, linear regression analysis was performed to obtain a bivariate linear model characterizing the relationship between those pairs of parameters showing good and significant correlation. Furthermore, a multiple regression equation (backward-elimination method) was derived by using different clinical data (visual acuity, refraction, keratometry, and corneal aberrations) to predict the biomechanical properties those measured by the ORA device (CH and CRF). All model assumptions were evaluated by analyzing residuals, normality of unstandardized residuals (homoscedasticity), multicollinearity, and Cook's distance, to detect influential points or outliers.

Results

The contribution of the two participating centers to the present study was as follows: 58 eyes from Vissum Alicante and 23 eyes from Centro de Oftalmología Barraquer. There was a balanced distribution of right and left eyes: 43 versus 38, respectively. Cone opacity was observed in six (7.4%) eyes. According to the Amsler-Krumeich grading system, 37 (45.7%) eyes had cone grade I, 24 (29.6%) cone grade II, 4 (4.9%) cone grade III, and 16 (19.8%) cone grade IV. Considering the corneal aberrations and according to the Alió-Shabayek grading system, 25 (44.6%) eyes had a cone grade I, 12 (21.4%) cone grade II, 7 (12.5%) cone grade III, and 12 (21.4%) cone grade IV. Table 1 shows a summary of the visual, refractive, keratometric, corneal aberrometric, pachymetric, and biomechanical data of the sample of keratoconic eyes analyzed in the study.

A significant but weak correlation was found between the ORA biomechanical parameters and the logMAR BSCVA (CH, $r = -0.354$; CRF, $r = -0.431$; $P < 0.01$). As shown in Figure 1, there was a significant variability in the relationship between biomechanical and visual data, which could explain the limited correlation between them. Regarding keratometry, moderate negative correlations were found between keratometric readings and the CRF (K1, $r = -0.554$; K2, $r = -0.558$; KM, $r = -0.564$; $P < 0.01$; Fig. 2). In addition, weak but significant correlations were found between the CRF and the corneal aberrometric parameters (all $P < 0.01$) higher order ($r = -0.484$), primary coma ($r = -0.487$), spherical-like ($r = -0.482$), and coma-like ($r = -0.487$) RMS (Fig. 3).

Multiple regression analysis revealed that the CRF correlated significantly with K1, higher order RMS, spherical-like RMS, and coma-like RMS ($P < 0.01$). For this relation, a linear model with predictability (R^2) of 0.40 and adjusted R^2 of 0.38 was found (Durbin-Watson statistic = 2.38; multicollinearity tolerance = 1.62):

$$CRF = 15.47 - 0.16 \times \mathrm{K1} - 0.71 \times \mathrm{RMS}_{\mathrm{sph-1}}$$

Table 1. Summary of Data from the Sample of Keratoconic Eyes

Parameter	Mean ± SD (Range)
Visual parameters	
LogMAR UCVA	0.97 ± 0.57 (0.01 to 2.78)
LogMAR BSCVA	0.28 ± 0.25 (0.00 to 1.30)
Refractive parameters	
Sphere, D	−3.06 ± 5.22 (−19.75 to +4.00)
Cylinder, D	−4.03 ± 2.98 (−14.00 to 0.00)
Spherical equivalent, D	−5.08 ± 5.13 (−19.75 to +1.12)
Keratometric parameters	
K1, D	47.82 ± 5.04 (39.90 to 68.49)
K2, D	52.59 ± 6.80 (44.95 to 84.61)
KM, D	50.20 ± 5.75 (43.25 to 75.79)
Corneal aberrometric parameters	
Higher-order RMS, μm	3.17 ± 1.86 (0.48 to 10.30)
RMS astigmatism, μm	3.16 ± 2.52 (0.33 to 15.14)
Primary coma RMS, μm	2.72 ± 1.82 (0.33 to 9.01)
Z_4^0, μm	−0.21 ± 0.71 (−1.80 to 1.31)
Residual RMS, μm	1.28 ± 0.78 (0.26 to 4.71)
Spherical-like, μm	0.96 ± 0.62 (0.11 to 3.69)
Comalike, μm	2.98 ± 1.82 (0.47 to 9.62)
Pachymetric parameters	
Central pachymetry, μm	470.13 ± 56.39 (341.00 to 590.00)
Biomechanical parameters	
CH, mm Hg	8.06 ± 1.36 (4.90 to 10.90)
CRF, mm Hg	6.89 ± 1.56 (3.70 to 10.70)

Data are expressed as the mean ± SD (range).

K1, corneal dioptric power in the flattest meridian for the 3-mm central zone; K2, corneal dioptric power in the steepest meridian for the 3-mm central zone; KM, mean corneal power in the 3-mm zone; aberrometric definitions, primary coma, terms $Z_3^{\pm 1}$; primary spherical aberration, term Z_4^0; residual aberrations, all Zernike terms except $Z_3^{\pm 1}$ and Z_4^0; spherical-like, terms from fourth and sixth order; comalike: terms from third, fifth and seventh orders.

where K1 is the dioptric power in the flattest corneal meridian for the 3-mm central zone measured in diopters and RMS_{sph-l} is the RMS corresponding to the corneal spherical-like aberrations measured in micrometers.

The homoscedasticity of the model was confirmed by the normality of the unstandardized residuals distribution and the absence of influential points or outliers (mean Cook's distance = 0.02 ± 0.04). In this model, 26.71% of unstandardized residuals were higher than 1.5 mm Hg.

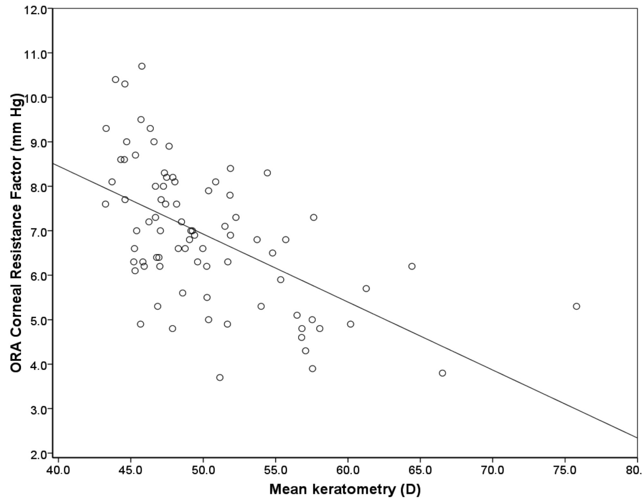

Figure 2. Scattergram showing the relationship between the CRF and KM. The adjusting line to the data obtained by means of the least-squares fit is shown. This linear predicting model showed a limited predictability (*straight line*, R^2 = 0.316).

On the contrary, the multiple regression analysis showed a weaker linear predictive model for the CH parameter (R^2 = 0.21, adjusted R^2 = 0.13). Specifically, the CH was found to correlate minimally with K1 and with higher order, spherical-like, and coma-like RMS values.

Besides this analysis, a comparison between keratoconus grades was performed. As only four eyes with keratoconus grade III (Amsler-Krumeich grading system) were included in our sample, a larger group including keratoconic eyes with either grade III and IV was created. This group was designated as the severe keratoconus group (20 eyes), and it was compared with keratoconic eyes of grades I (37 eyes) and II (24 eyes). No significant differences were present in age among these three groups of eyes (grade I, grade II, and severe keratoconus; $P = 0.42$, Kruskal-Wallis test). Table 2 summarizes the visual, refractive, and keratometric data obtained for the three

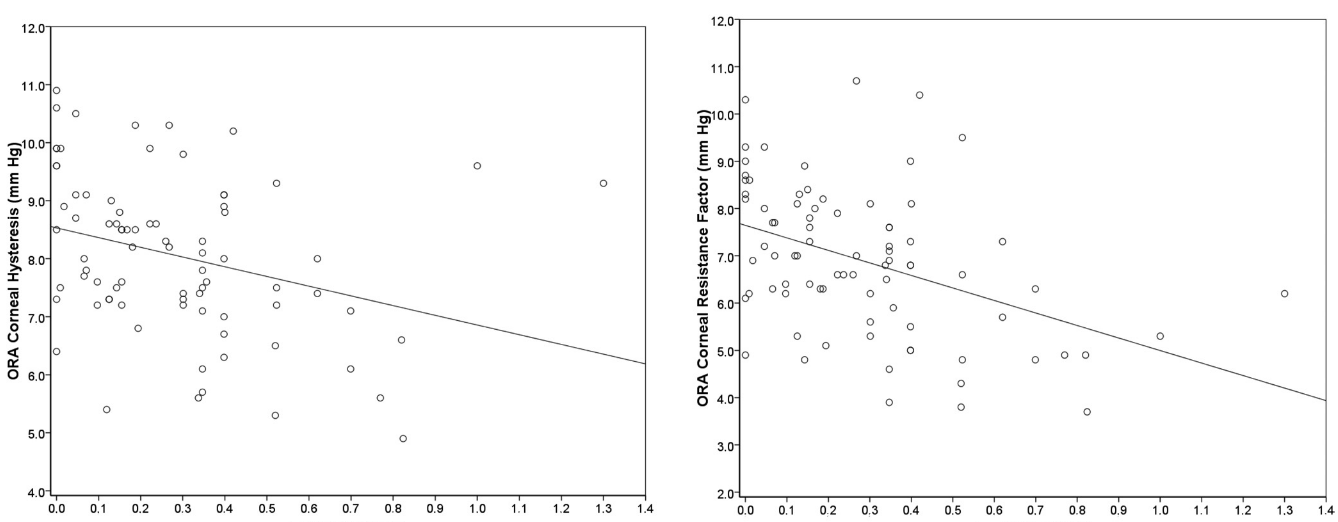

Figure 1. Scattergrams showing the relationship between the ORA biomechanical parameters and the logMAR BSCVA. *Left*: relationship between CH and logMAR BSCVA; *right*: relationship between the CRF and the logMAR BSCVA. In both graphs, the adjusting line to the data obtained by means of the least-squares fit is also shown. The two linear predicting models obtained showed a very low predictability (CH-BSCVA, *straight line*, R^2 = 0.10; CRF-BSCVA, *dotted line*, R^2 = 0.18).

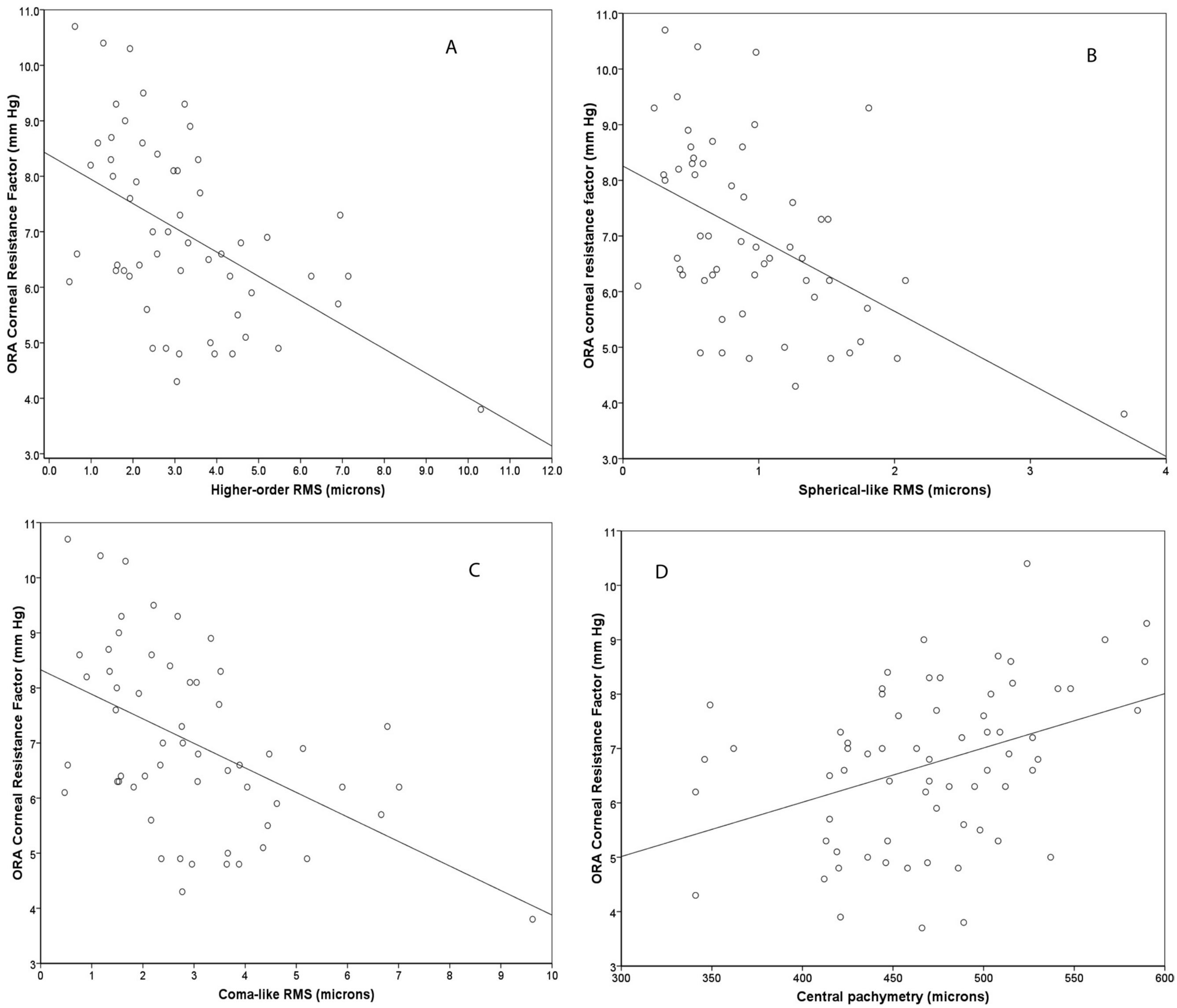

FIGURE 3. Scattergrams showing the relationship between the CRF and other clinical parameters: **(A)** higher order RMS; **(B)** spherical-like RMS; **(C)** coma-like RMS; and **(D)** central pachymetry. The adjusting line to the data obtained by means of the least-squares fit is shown in the four graphs: **(A)** CRF (mm Hg) = −0.44 × higher order RMS (μm) + 8.38 (R^2 = 0.25); **(B)** CRF (mm Hg) = −1.30 × spherical-like RMS (μm) + 8.26 (R^2 = 0.24); **(C)** CRF (mm Hg) = −0.45 × coma-like RMS (μm) + 8.33 (R^2 = 0.24); and **(D)** CRF (mm Hg) = 0.01 × central pachymetry (μm) + 2.02 (R^2 = 0.15).

groups of eyes analyzed. As expected, significant differences were found between the keratoconus groups in logMAR UCVA, logMAR BSCVA, and keratometry (Kruskal-Wallis test, all $P < 0.01$). In addition, in eyes with keratoconus grade I, cylinder was significantly lower than in eyes with grade II and severe keratoconus (Mann-Whitney, $P \leq 0.03$).

TABLE 2. Summary of Visual, Refractive, Keratometric, and Pachymetric Data Obtained from the Three Groups of Eyes

Parameter (Range)	Grade I (37 Eyes)	Grade II (24 Eyes)	Grades III and IV Severe Keratoconus (20 Eyes)	*P*
LogMAR UCVA	0.72 ± 0.48 (0.01 to 1.78)	1.01 ± 0.46 (0.02 to 2.00)	1.37 ± 0.64 (0.05 to 2.78)	<0.01
Sphere, D	−2.18 ± 4.51 (−18.00 to +3.50)	−2.46 ± 4.16 (−10.00 to +4.00)	−5.44 ± 6.87 (−19.75 to +3.00)	0.27
Cylinder, D	−2.93 ± 2.47 (−9.50 to 0.00)	−5.05 ± 3.01 (−14.00 to 0.00)	−4.85 ± 3.23 (−12.00 to 0.00)	0.01
SE, D	−3.64 ± 4.48 (−19.50 to +1.12)	−4.98 ± 4.42 (−14.50 to +1.00)	−7.86 ± 6.09 (−19.75 to 0.00)	0.02
LogMAR BSCVA	0.16 ± 0.18 (0.00 to 0.70)	0.30 ± 0.19 (0.02 to 0.82)	0.50 ± 0.29 (0.00 to 1.30)	<0.01
K1, D	44.18 ± 1.72 (39.90 to 47.53)	47.59 ± 1.96 (43.50 to 50.60)	54.83 ± 4.37 (48.31 to 68.49)	<0.01
K2, D	47.72 ± 1.96 (44.95 to 52.35)	52.45 ± 1.50 (49.65 to 56.90)	61.75 ± 7.11 (55.52 to 84.61)	<0.01
KM, D	45.97 ± 1.38 (43.25 to 48.58)	49.95 ± 1.41 (47.64 to 51.88)	58.32 ± 5.40 (52.26 to 75.79)	<0.01
Central pachymetry, μm	499.93 ± 48.16 (413.00 to 90.00)	462.70 ± 53.01 (349.00 to 41.00)	437.35 ± 51.08 (341.00 to 509.00)	<0.01

Data are the mean ± SD (range). Abbreviations are defined in Table 1.

Table 3. Summary of Corneal Aberrometric Data for the Three Groups of Eyes Keratoconic Eyes

Parameter	Grade I (37 Eyes)	Grade II (24 Eyes)	Grades III and IV Severe Keratoconus (20 Eyes)	*P*
Higher order RMS	1.91 ± 0.87 (0.48 to 4.32)	3.69 ± 1.28 (2.08 to 7.14)	5.04 ± 2.01 (3.05 to 10.30)	<0.01
RMS astigmatism	2.10 ± 1.35 (0.48 to 5.36)	2.99 ± 1.48 (0.33 to 5.76)	5.41 ± 3.62 (1.18 to 15.14)	<0.01
Primary coma RMS	1.51 ± 0.88 (0.33 to 3.98)	3.42 ± 1.24 (1.72 to 6.90)	4.31 ± 2.13 (0.37 to 9.01)	<0.01
Z_4^0	+0.06 ± 0.46 (−1.26 to +0.70)	−0.24 ± 0.38 (−1.03 to +0.35)	−0.73 ± 1.06 (−1.80 to 1.31)	<0.01
Residual RMS	0.98 ± 0.43 (0.26 to 1.92)	1.26 ± 0.48 (0.58 to 2.27)	1.90 ± 1.17 (0.60 to 4.71)	0.01
Spherical-like RMS	0.71 ± 0.39 (0.11 to 1.81)	0.79 ± 0.32 (0.30 to 1.35)	1.64 ± 0.71 (0.51 to 3.69)	<0.01
Comalike RMS	1.74 ± 0.84 (0.47 to 4.04)	3.59 ± 1.27 (1.92 to 7.01)	4.75 ± 1.93 (2.76 to 9.62)	<0.01

Data are expressed as mean micrometers ± SD (range). Definitions are defined in Table 1.

Table 3 summarizes the corneal aberrometric data for the three groups of keratoconic eyes. Significantly lower levels of higher order, primary coma, coma-like, and higher order residual aberrations were present in eyes with keratoconus grade I in comparison with levels in the other two groups (Bonferroni and Mann-Whitney test, all $P < 0.01$). The spherical-like RMS was significantly higher in the severe keratoconic eyes compared with mild and moderate cases (Bonferroni test, $P < 0.01$). The primary spherical aberration was significantly more negative in those eyes with severe keratoconus (Mann-Whitney test, all $P < 0.05$). Regarding the RMS for corneal astigmatism, it was significantly higher in moderate and severe cases than in the mild cases (Bonferroni test, $P \leq 0.01$).

Figure 4 shows the differences in the corneal biomechanical parameters provided by the ORA between keratoconus groups. No significant differences in CH were found between mild and moderate keratoconus cases (Bonferroni, $P = 0.86$) or between moderate and severe cases (Bonferroni test, $P = 0.07$). However, significant differences in the CRF were found between all keratoconus groups (Bonferroni test; mild-moderate, $P = 0.04$; mild-severe, $P < 0.01$; moderate-severe, $P = 0.02$), with the lowest values in the most advanced cases (Fig. 4). Regarding corneal pachymetry, mild keratoconus corneas were significantly thinner than those with the diagnosis of moderate and severe keratoconus (Bonferroni test, $P \leq 0.04$).

Several correlations were found to be significant (although not all of them strong) when the relationship between different visual, refractive, keratometric, pachymetric, and aberrometric parameters and the ORA biomechanical parameters was investigated. In the mild keratoconus group, a positive correlation was found between the ORA biomechanical parameters and central pachymetry (CH, $r = 0.530$; CRF, $r = 0.481$; $P = 0.01$). However, in the moderate keratoconus group, a negative correlation was found between the ORA biomechanical parameters and logMAR BSCVA (CH, $r = -0.610$; CRF, $r = -0.587$; $P < 0.01$). In addition, a moderate correlation was found between the CRF and the RMS for spherical-like aberrations ($r = -0.502$, $P = 0.05$; Fig. 5). This correlation between CRF and spherical-like RMS became statistically significant and stronger in the severe keratoconus group ($r = -0.655$, $P = 0.01$; Fig. 5). Besides these correlations, in this group of eyes, a moderate and significant negative correlation was found between the steepest keratometric reading and the CRF ($r = -0.501$, $P = 0.03$).

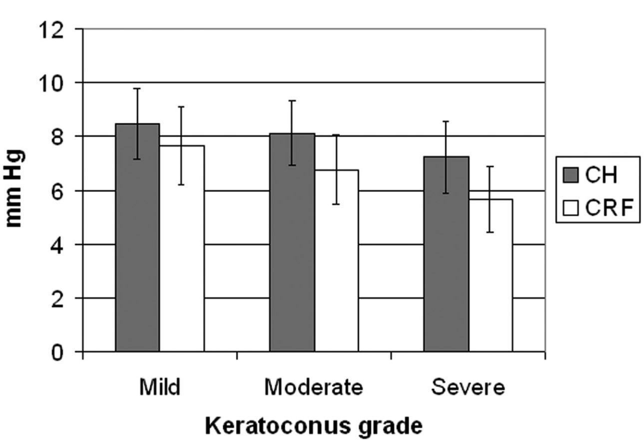

Figure 4. Differences in the biomechanical parameters provided by the ORA between keratoconus grades. CH and CRF were significantly lower in the group of eyes with severe keratoconus.

Discussion

The human cornea is a viscoelastic tissue[13,16] that responds to the presence of any force. This response is not only dependent on the magnitude of the force, but also on the velocity of the force application. As a viscoelastic element, two main properties can be identified in corneal tissue: static resistance or elasticity and viscous resistance or damping.[13] The first property describes the proportionality between the magnitude of tissue deformation and the applied force. The second property represents the dependence on time of the relationship between deformation and applied force. These properties describing the viscoelasticity of the cornea are in relation with its biomechanical behavior.[17]

Many studies have been conducted in an attempt to characterize corneal biomechanics,[13,18–22] but to do it in vivo is not an easy task. Invasive techniques have been described for this purpose, such as the injection of saline solution into the anterior chamber[18] or corneal imaging by central indentation.[19] However, Luce[13] presented in 2005 a noninvasive device for characterizing the corneal biomechanics in vivo, the ORA (Bausch & Lomb). This instrument uses a dynamic bidirectional applanation process to provide a new two measurements of corneal biomechanics: CH and the CRF.[13] Several studies have been performed with the ORA, most of them attempting to define the changes induced in corneal biomechanics after different kinds of surgeries[10,23–25] as well as in some pathologic processes.[9,13,26,27] Specifically, a reduction in the ORA biomechanical parameters was found in keratoconic corneas.[9,10] As commented before, this biomechanical limitation seems to be the consequence of those changes occurring in the collagen lamellar structure of these kinds of corneas (distortion of the orthogonal lamellar matrix).[11,12] Besides this biomechanical limitation, a corneal steepening and an aberrometric corneal increase can also be observed in keratoconic corneas.[1–8] The purpose of the present study was to analyze the degree of correlation between the biomechanical parameters provided by the ORA (CH and CRF) and other clinical data such as refraction, corneal topography, and aberrometry in keratoconus. In addition, we investigated whether there are visual, refractive, keratometric, pachymetric, or aberrometric param-

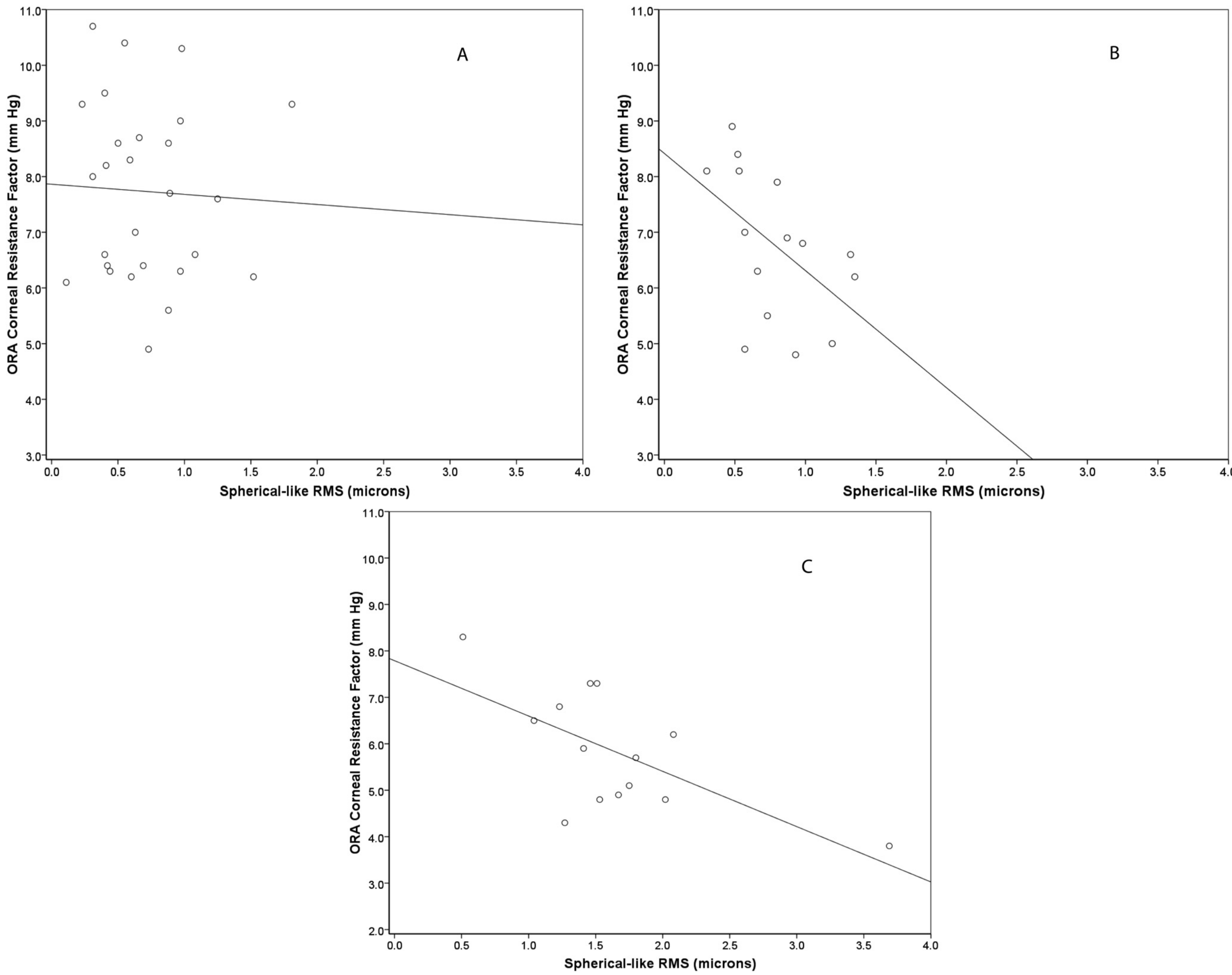

FIGURE 5. Scattergrams showing the relationship between the CRF and the RMS for spherical-like aberrations in the three groups of keratoconic eyes analyzed: **(A)** Mild keratoconus (grade I). **(B)** Moderate keratoconus (grade II) group. **(C)** Severe keratoconus (grades III and IV). The adjusting line to the data obtained by means of the least-squares fit is shown in the three graphs: **(A)** CRF (mm Hg) = −0.18 × spherical-like RMS (μm) + 7.86 ($R^2 < 0.01$); **(B)** CRF (mm Hg) = −2.10 × spherical-like RMS (μm) + 8.41 ($R^2 = 0.25$); and **(C)** CRF (mm Hg) = −1.19 × spherical-like RMS (μm) + 7.79 ($R^2 = 0.43$).

eters that enable prediction of the corneal biomechanical properties of keratoconic eyes. The knowledge of these relations will allow the clinician to achieve a better understanding of the changes that occur in this ectatic disease and to obtain an integrated criterion for keratoconus diagnosis. Furthermore, it will provide information about the key clinical parameters representing the severity of the disease.

In the present study, we found significant but weak correlations between the CRF and the various aberrometric coefficients (higher order, primary coma, spherical-like, and coma-like aberrations). All the correlation coefficients corresponding to these relationships were negative, indicating that the higher the aberration, the lower the CRF. One factor that could explain the weakness of these correlations was the high variability observed, especially in those eyes with moderate CRF (6–7 mm Hg; Fig. 3). In addition, a moderate negative correlation between CRF and mean curvature was found. It should be remembered that mean keratometric measures have always been used as a parameter for classifying the level of severity in keratoconus.[6] Curiously, the CH did not correlate significantly with any refractive, keratometric, pachymetric, or aberrometric parameters. Therefore, it seems that the CH is a parameter with less ability to characterize the clinical changes occurring in keratoconic corneas. This finding is consistent with a previous experience in which a viscoelastic biomechanical model of the cornea was used to describe the effect of viscosity and elasticity on CH and showed that the CH was a more variable parameter, with theoretically less diagnostic ability.[17] A low CH value could be present in a cornea with a high or low elastic modulus, depending on the associated viscosity.[17] Shah et al.[9] demonstrated that a clear separation of normal and keratoconic eyes was not possible with CH used as a screening criterion, because the ranges overlapped.

The manufacturer stated that CH may reflect mostly corneal viscosity, whereas the CRF may predominantly relate to the elastic properties of the cornea.[10] However, the exact physical meaning of these parameters is still not well understood. They are said to represent the viscoelastic properties of the cornea, but there is no study proving whether these parameters correlate with the standard mechanical properties used for the description of the elastic materials (Young's modulus). The CRF is calculated as a linear function of the two pressures recorded during the ORA measurement procedure (P1 and P2). It is said to be an indicator of the overall resistance of the cornea. From a mathematical point of view, the CRF places more emphasis on P1, and so it is more heavily weighted by the underlying corneal elastic properties.[17] However, despite not knowing the exact physical meaning of the parameters CH and CRF, they have been very useful for characterizing the biomechanical properties of the cornea.

Multiple regression analysis revealed that 40% of the variance in the CRF could be explained by the corneal flattest curvature and the levels of corneal spherical-like aberrations. Therefore, changes in the viscoelastic properties of the cornea seem to be in part responsible for the keratometric and aberrometric changes in keratoconus. This finding supports previous ones stating that the keratometric and aberrometric analysis are crucial for keratoconus diagnosis.[5–7] For example, our research group developed a keratoconus grading system in which mean keratometric measurements and the coma-like RMS were used as the main discriminating factors (Alió-Shabayek classification).[6] Regarding visual and refractive data, no correlations of these factors with the ORA biomechanical parameters were found. An explanation of this fact is the variability of these subjective measurements in keratoconus patients due to the difficulty in finding a clear focus in such patients.[28] It should be considered that the spherocylindrical refraction in keratoconus can be easily biased by the loss of retinal image quality induced by the significant aberrometric increase.

When the sample was divided into mild (grade I), moderate (grade II), and severe (grade III and IV) keratoconus cases, significant differences were found in the ORA biomechanical parameters, as expected. Significantly lower values of CH were found only in the severe ectatic cases. Regarding the CRF, the higher the keratoconus grade, the lower the CRF was, with significant differences between all keratoconus groups. It seems that the corneal elastic component, theoretically represented by the CRF, is greatly affected in severe keratoconus as a consequence of the structural changes. However, it seems that changes in the general viscoelastic properties (viscosity+elasticity), theoretically represented by CH, are more variable in keratoconic corneas.

A strong correlation was found between the magnitude of spherical-like aberrations and the CRF in severe keratoconic eyes. This correlation was negative and then, the higher the CRF, the lower the magnitude of spherical-like aberrations was. Therefore, corneas with lower CRF values were associated with a more aberrant corneal profile. We cannot find a simple explanation of this fact in our results, because the ectatic process is multifactorial, with several interacting variables. Probably, this biomechanical alteration represented by the low CRF makes the cornea more susceptible to deformation by intraocular pressure or the eyelid effect, leading to a more significant level of corneal irregularity. More studies on this issue are necessary, to obtain more precise information about the ectatic procedure and how the biomechanical alterations can affect the corneal profile. This study is preliminary, but it shows a potential relationship between corneal irregularity and corneal biomechanical changes. Our results support the previous scientific evidence that there are more levels of higher order corneal aberrations in keratoconic corneas.[4–8]

The correlation between the CRF and corneal higher order aberrations was limited in moderate keratoconus and very weak in mild keratoconus cases. In these cases, the CRF can be reduced, but with few alterations in corneal topography and aberrations. This fact indicates that a biomechanical alteration could be present before topographic and clinical changes become apparent and would explain the significant variability in topographic and aberrometric alterations that could be observed, especially in mild keratoconus, which make the detection of the most incipient cases sometimes difficult.

In summary, the ORA biomechanical parameters are significantly reduced in severe keratoconus, with significant differences between mild and moderate cases only for the CRF. Keratometry and the magnitude of corneal spherical-like aberrations are factors in relation with the biomechanical changes that occur in keratoconus. Therefore, all these factors should always be considered when diagnosing this ectatic corneal condition. Furthermore, it was demonstrated that corneas with a more reduced CRF (measured by the ORA system) were more irregular, with higher levels of corneal higher order aberrations, especially of spherical-like aberrations. This reduction in the CRF represents the biomechanical change that occurs in keratoconus. This parameter seems to correlate with changes in the elastic component of the cornea according to the manufacturer and previous studies, but the relation should be proven with accuracy in the future.

In future studies, the role of the CRF as a predictive parameter for keratoconus progression and the success of intracorneal ring segment implantation for the management of keratoconus should be evaluated. A better understanding of the CH and CRF and their exact contribution to the elastic and viscous components is necessary to achieve a more comprehensive characterization of the ectatic process of the cornea.

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TRABAJO 7: ***Piñero DP, Alio JL, Teus MA, Barraquer RI, Michael R, Jiménez R. Modification and refinement of astigmatism in keratoconic eyes implanted with intracorneal ring segments. J Cataract Refract Surg 2010 (accepted for publication)***

Date: 04/19/2010
To: "Jorge L. Alio" jlalio@vissum.com
From: "Journal of Cataract and Refractive Surgery" jcrs@ASCRS.org
Subject: Your Submission, "MODIFICATION AND REFINEMENT OF ASTIGMATISM IN KERATOCONIC EYES IMPLANTED WITH INTRACORNEAL RING SEGMENTS"

Ref.: Ms. No. JCRS-09-1107R3
MODIFICATION AND REFINEMENT OF ASTIGMATISM IN KERATOCONIC EYES IMPLANTED WITH INTRACORNEAL RING SEGMENTS
Journal of Cataract & Refractive Surgery

Dear Dr. Alio,

The Editorial Board has accepted your (revised) manuscript

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(JCRS-09-1107R3)

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Associate Editor
Journal of Cataract & Refractive Surgery

MODIFICATION AND REFINEMENT OF ASTIGMATISM IN KERATOCONIC EYES IMPLANTED WITH INTRACORNEAL RING SEGMENTS

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The authors have no proprietary or commercial interest in the medical devices that are involved in this manuscript.

This study has been supported in part by a grant from the Spanish Ministry of Health, Instituto Carlos III, Red Temática de Investigación Cooperativa en Salud "Patología ocular del envejecimiento, calidad visual y calidad de vida", Subproyecto de Calidad Visual (RD07/0062)

Abstract

PURPOSE: To analyze by means of the Alpins vectorial method the corneal astigmatic changes occurring after KeraRing implantation in keratoconic eyes

SETTING: Vissum Corporation, Alicante, Spain

PARTICIPANTS: 35 eyes of 30 patients with the diagnosis of keratoconus and implanted with KeraRing segments were included. All surgeries were performed by three surgeons using the femtosecond technology and following the same protocol. Visual, refractive, keratometric and corneal aberrometric changes were evaluated during a 12-month follow-up. Additionally, corneal astigmatic changes were analyzed using the Alpins vectorial method: targeted induced astigmatism (TIA), surgically induced astigmatism (SIA), difference vector (DV), magnitude of error (ME), flattening effect (FE) and torque (TRQ).

RESULTS: A significant visual improvement (p=0.03) and central flattening was found after surgery. Manifest astigmatism was reduced significantly after surgery (p<0.01). The magnitude of SIA vector was significantly lower than the TIA postoperatively (p≥0.02). Mean magnitude of DV was -2.96 ± 1.68 D at 3 months postoperatively. Mean ME remained negative and unchanged during the follow-up (p≥0.10). Mean magnitude of FE was also significantly lower than TIA at all postoperative visits (p≥0.01). Mean magnitude of TRQ vector was 1.21 ± 0.98 D at 3 months postoperatively. Significant negative correlations were found between corneal astigmatism preoperatively and postoperative ME and DV at all postoperative visits.

CONCLUSIONS: The magnitude of corneal astigmatism is significantly reduced with KeraRing, but there is a trend to undercorrection and the meridian of correction is not the appropriate in all cases. Nomograms should be implemented in the future.

Introduction

Intrastromal corneal ring segments (ICRS) have been proposed and investigated as an additive surgical procedure for keratoconus correction[1-21], providing an interesting alternative aiming at delaying and preventing corneal graft in keratoconus patients[7,8]. These ring segments have been demonstrated to be a very effective therapeutic option for improving visual acuity, reducing the refractive error and also for reducing the corneal curvature in keratoconic eyes[1-21]. Several authors reported significant reductions in the magnitude of manifest astigmatism after ICRS implantation in keratoconic corneas[1,2,4-6,8-12,14,15,19,20]. However, changes in the axis of astigmatism were not analyzed in any of these studies. It should be remembered that the astigmatism is a vectorial variable and then it has associated a magnitude and an axis. The vectorial character of astigmatism should be considered if a precise and complete analysis of astigmatic changes after ICRS is pretended to be done. The only previous experience of vectorial analysis of astigmatic correction after the implantation of ICRS (130º arc-length) was performed by Ruckhofer et al[22], but in healthy astigmatic corneas, not in keratoconus.

The Alpins method is a vectorial analysis that allows determining the effectiveness of a specific astigmatic treatment[23,24]. It considers the magnitude and orientation of astigmatism. Three fundamental vectors are used in this analysis: target induced astigmatism (TIA), surgically induced astigmatism (SIA), and difference vector (DV)[23,24]. The various relationships among these three vectors provide a complete description of the astigmatic correction achieved with a specific modality of treatment. It can be known whether the treatment was on axis or off axis and whether too much or too little effect was achieved. The Alpins method has been used by several authors to analyze the astigmatic changes induced with different surgical and non-surgical options (relaxing incisions[25,26], excimer laser refractive surgery[27-31], cataract surgery[32], vitrectomy[33], orthokeratology[34]). However, to the best of our knowledge, it has never been used to analyze the astigmatic changes occurring after ICRS implantation in ectatic corneas. The information obtained with this vectorial analysis would be of great value to optimize the nomograms for ICRS implantation and to detect predictive factors for a good visual outcome after this kind of surgery.

One additional problem for the analysis of astigmatic changes in keratoconus is the poor accuracy of subjective refraction in this kind of eyes[35]. Manifest astigmatism (considering all ocular optics) is measured by proving several spherocylindrical lenses and detecting which of them provides the best focus according to the subject criteria. However, in keratoconic eyes the higher-order aberrations become very important as a consequence of corneal shape deformation, and then the perceived blur is not only due to the spherocylindrical error. Therefore, the subjective determination of the spherical and cylindrical components of the refraction can be easily biased by the focus variability introduced by other optical aberrations. Astigmatism measured by keratometry or corneal topography is a more objective measurement, but it only considers the effect of corneal optics. In any case, it should be remembered that anterior corneal astigmatism accounts for a large percentage of total ocular astigmatism, especially in cases with moderate and high astigmatism such as happens in keratoconus. The first refractive interface (air-cornea) is the most important contributor to the total power of the eye due to the large difference in refractive index existing at this point.

The aim of the present study was to analyze by means of the Alpins vectorial method the corneal astigmatic changes occurring after KeraRing implantation in keratoconic eyes and to determine the relationship among these changes and the final visual, refractive and corneal aberrometric outcome.

Material and methods

Patients

Data from patients who underwent ICRS implantation for keratoconus treatment from March 2005 to June 2008 in three different Spanish ophthalmologic centers (Vissum Alicante, Vissum Madrid and Centro de Oftalmología Barraquer) were retrospectively reviewed and analyzed. Only keratoconus cases implanted with KeraRings using the femtosecond laser technology and with a 12-month postoperative follow-up were included in the current study (no ring segment explantation or reposition). We preferred to include only cases operated with one technique because it was demonstrated that the type of stromal dissection has a significant impact on the corneal aberrometric outcome with ICRS[36]. Table 1 summarizes the contribution of each participating centre to the current study. A total of 35 consecutive eyes of 30 patients diagnosed with keratoconus (30 unilateral and 5 bilateral cases) were finally included.

Keratoconus diagnosis was based on corneal topography and slit-lamp observation. In all cases, preoperative findings characteristic of keratoconus were evident: corneal topography revealing an asymmetric bowtie pattern with or without skewed axes and at least one keratoconus sign on slit-lamp examination, such as stromal thinning, conical protrusion of the cornea at the apex, Fleischer ring, Vogt striae or anterior stromal scar[37]. The Alió-Shabayek classification[38] was used for grading the keratoconus cases. In all cases ICRS implantation was indicated due to the existence of reduced BSCVA and/or contact lens intolerance. Cases with other previous ocular surgery or active ocular disease were not implanted with ICRS.

Ethical board committee approval of our institution was obtained for this investigation. In addition, during the process of consent for this surgery, consent was taken to later include clinical information in scientific studies.

Examination protocol

A comprehensive examination was performed in all cases which included: uncorrected visual acuity (UCVA) (LogMAR), Snellen best-spectacle corrected visual acuity (BSCVA) (LogMAR), manifest refraction, slit-lamp biomicroscopy, Goldman tonometry, fundus evaluation, ultrasonic pachymetry and corneal topographic analysis. As topographic data were collected from three different centers, a total of two different corneal topography systems were used for corneal examination: the CSO (CSO, Firenze, Italy) and the Orbscan IIz systems (Bausch & Lomb, Rochester, NY). The first device is a Placido-based system and the Orbscan II is a combined scanning-slit and Placido-disc topography system. Although the agreement between these specific devices has not been reported, Orbscan and Placido-based devices have been proved to provide similar accuracy and precision on calibrated spherical test surfaces[39]. In any case, each case of the study was evaluated with the same topographic instrument during all follow-up. The following topographic data were evaluated and recorded with all corneal topographic devices: corneal dioptric power in the flattest meridian for the 3 mm central zone (K1), corneal dioptric power in the steepest meridian for the 3 mm central zone (K2), mean corneal power in the 3 mm zone (KM) and corneal astigmatism (AST), calculated as the difference between K2 and K1.

Corneal aberrometry was also recorded and analyzed only in those patients examined with the CSO topography system (CSO, Firenze, Italy) (20 eyes), because this device was the only one with the capability to calculate directly this specific information. This topography system analyzes a total of 6144 points of a corneal area enclosed in a circular annulus defined by an inner radius of 0.33 and an outer radius of 10 mm respect to corneal vertex. The software of the CSO, the EyeTop2005 (CSO, Firenze, Italy), automatically performs the conversion of corneal elevation profile into corneal wavefront data using the Zernike polynomials with an expansion up to the 7^{th} order. In this study, the aberration coefficients and root mean square (RMS) values were calculated for a 6-mm pupil in all cases. The following parameters were analyzed and recorded: higher order root mean square (RMS), primary coma RMS (computed for the Zernike terms $Z_3^{\pm 1}$), coma-like RMS (computed for third, fifth, and seventh order Zernike terms), spherical-like RMS (computed for fourth and sixth order Zernike terms) and higher order residual RMS (computed considering all Zernike terms except those corresponding with primary coma and spherical aberration). The corresponding Zernike coefficient for primary spherical aberration (Z_4^0) was also reported with its sign.

The patients wearing contact lenses for the correction of the residual refractive error were instructed to discontinue the use of contact lenses for at least 2 weeks before each examination for soft contact lenses and at least 4 weeks before examination for rigid gas permeable contact lenses

Surgery

Surgical procedures were performed by a total of three experienced surgeons (JLA from Vissum Alicante, MAT from Vissum Madrid and RIB from Centro de Oftalmología Barraquer). In all cases an antibiotic prophylaxis before surgery consisting of topical ciprofloxacin (Oftacilox; Alcon Cusí, Barcelona, Spain) every eight hours for two days was prescribed to be applied. All procedures were performed under topical anaesthesia.

In all cases incision was placed on the steepest meridian (no more than 3 degrees of deviation from it). The femtosecond technology was used in all cases for corneal tunnelization (30 kHz IntraLase femtosecond system, Intralase Corp, Irvine, California, USA) following a protocol previously described[5,36]. The selection of the number (1 or 2), arc-length and thickness of KeraRing segments was performed following the nomogram defined by the manufacturer[5,36]. In 26 eyes (74.3%) two ring segments were implanted whereas in the remaining 9 eyes (25.7%) only one segment was necessary.

No intraoperative complications occurred. Topical tobramycin and dexamethasone eye drops (TobraDex; Alcon Laboratories, Inc, Fort Worth, Texas, USA) were used postoperatively every six hours for one week and stopped. Topical lubricants were also prescribed to be applied every six hours for one month (Systane, Alcon Laboratories, Inc, Fort Worth, Texas, USA).

Follow-up evaluation

Postoperative visits were scheduled for the first postoperative day and for months 1, 3, 6 and 12 postoperatively. On the first postoperative day, UCVA measurement and slit-lamp examination (intracorneal rings position and corneal integrity) were performed. Snellen UCVA and BSCVA measurement, manifest refraction, slit lamp examination and corneal topography were performed in the rest of postoperative examinations. All patients completed the 12-month follow-up, attending to all visits.

Vectorial analysis of corneal astigmatic changes

As commented previously, the Alpins method of vector analysis was used to evaluate corneal astigmatic changes[23,24]. This vectorial analysis was only performed for corneal astigmatism (objective parameter) due to the high variability observed in the ocular astigmatism obtained by means of subjective refraction (difficult to select the best focus because of the poor visual quality). All calculations were performed using the ASSORT software (ASSORT Pty. Ltd, Cheltenham, Australia) which is especially designed for using the Alpins vectorial analysis.

The following vectors were determined and evaluated: targeted induced astigmatism (TIA) as the vector of intended change in cylinder for each treatment, surgically induced astigmatism (SIA) as the vector of the real change achieved and difference vector (DV) as the additional astigmatic change that would enable the initial surgery to achieve its intended target. Additionally, the following parameters derived from the relationship between these vectors were calculated and analyzed in each postoperative visit:

-Magnitude of error (ME): the arithmetic difference between the magnitudes of the SIA and TIA

-Angle of error (AE): the angle described by the vectors of the achieved correction (SIA) and the intended correction (TIA)

-Flattening effect (FE): the amount of astigmatism reduction achieved by the effective proportion of the SIA at the intended meridian. It was calculated using a previously described mathematical relationship[23].

-Torque (TRQ): the amount of astigmatic change induced by the SIA, due to nonalignment of the treatment, that has been ineffective in reducing astigmatism at the intended meridian but causes rotation and a small increase in the existing astigmatism. It was calculated using a previously described mathematical relationship[40].

Statistical analysis

SPSS statistics software package version 15.0 for Windows (SPSS, Chicago, Illinois, USA) was used for statistical analysis. Normality of all data samples was firstly checked by means of Kolmogorov-Smirnov test. When parametric analysis was possible, the Student t test for paired data was performed for all parameters comparisons between preoperative and postoperative examinations or consecutive postoperative visits. On the contrary, when parametric analysis was not possible, the Wilcoxon Rank Sum test was applied to assess the significance of differences between preoperative and postoperative data, using in all cases the same level of significance ($p<0.05$). Correlation coefficients (Pearson or Spearman depending if normality condition could be assumed) were used to assess the correlation between different variables.

Results

A total of 35 eyes of 30 patients with a mean age of 34.00 ± 12.75 years (ranging from 15 to 68 years) were included. 25 patients were male and 25 were female. 15 cases (42.9%) were right eyes and 20 left eyes (57.1%). No opacity of the cone area was observed in any case. According to the Amsler-Krumeich grading system, 15 eyes had a cone grade I (42.9%), 15 eyes grade II (42.9%), 2 eyes grade III (5.7%), and 3 eyes grade IV (8.6%). Considering the corneal aberrations and according to the Alió-Shabayek grading system, 7 eyes had a cone grade I (35.0%), 7 eyes grade II (35.0%), 2 eyes grade III (5.7%), and 4 eyes grade IV (11.4%).

Visual and refractive outcomes

Table 2 summarizes the visual and refractive outcomes. A statistically significant improvement in logMAR UDVA was observed at 3 months after surgery ($p=0.03$, Wilcoxon test), with no significant changes afterwards ($p\geq0.80$, Wilcoxon test). Sphere was reduced at 3 months after surgery and this change was in the limit of statistical significance ($p=0.05$, Wilcoxon test). Regarding the magnitude of manifest cylinder, a statistically significant reduction was found at 3 months ($p<0.01$, Wilcoxon test). No significant changes in sphere and cylinder were observed during the remaining follow-up ($p\geq0.90$, Wilcoxon test). In addition, an improvement of the logMAR CDVA was observed at 3 months ($p<0.01$, Wilcoxon test), with no significant changes in the rest of follow-up ($p\geq0.70$, Wilcoxon test).

Keratometric and corneal aberrometric outcomes

All the keratometric readings were significantly reduced at 3 months (K1, $p=0.01$, paired Student t test; K2, $p<0.01$, Wilcoxon test; KM, $p<0.01$, paired Student t test) (Table 3). No significant keratometric changes were detected during the rest of follow-up ($p\geq0.49$, paired Student t and Wilcoxon tests). Regarding corneal aberrometry (Table 4), a statistically significant reduction was only found in the RMS for corneal astigmatism at 3 months ($p=0.01$, Wilcoxon test). The remaining RMS values also decreased at 3 months, but changes did not reach statistical significance (higher order RMS $p=0.15$, coma RMS $p=0.39$, residual RMS $p=0.36$, spherical-like RMS $p=0.57$, coma-like RMS $p=0.07$; Wilcoxon test). No significant changes were detected during the rest of follow-up ($p\geq0.56$, Wilcoxon and paired Student t tests), instead of the decrease of some aberrometric parameters at the final part of the follow-up.

Vectorial analysis of corneal astigmatic changes

Table 5 summarizes changes in the different vectors analyzed with the Alpins vectorial method during the follow-up. Mean magnitude of TIA was 5.59 ± 2.90 D whereas the mean magnitude of SIA was always lower (Figure 1). Therefore, an undercorrection of the corneal astigmatism was present with the ICRS (in an ideal complete correction, SIA and TIA would have the same value). Indeed, a statistically significant difference was present between TIA and SIA at all postoperative visits ($p\geq0.02$, Mann-Whitney test) (in an ideal and perfect correction TIA and SIA would be identical). In addition, no significant changes in this vector were detected during the postoperative follow-up ($p\geq0.09$, Wilcoxon test).

Regarding DV, its mean magnitude was equal to or lower than 3.53 D at all visits of the follow-up (Table 5), with no significant changes among them ($p\geq0.10$, Wilcoxon and paired Student t tests). There was a significant variability in this parameter, as shown in figure 2. Therefore, the effect on corneal astigmatism of ring segments was very variable and it was dependent on the specific conditions of each case. The ME was also negative (undercorrection) and it remained unchanged during the follow-up ($p\geq0.16$, Wilcoxon and paired Student t tests). In any case, an increase of variability (standard deviation) in this vector could be observed with time (1 month, -2.36 ±2.88 D; 3 months, -1.56 ± 2.34 D; 6 months, -1.65 ± 3.08 D; 12 months, -1.44 ± 4.46 D).

The module of FE was also significantly lower than TIA at all postoperative visits ($p \geq 0.01$, Mann-Whitney test). It did not change significantly throughout the follow-up ($p \geq 0.19$, paired Student t test) (Table 5). Regarding the torque vector, its magnitude was always positive. It did not change significantly during all the follow-up ($p \geq 0.55$, paired Student t test), presenting a mean magnitude around 1 at all postoperative visits (Table 5).

In addition, the angle of error and its changes after surgery were evaluated. The mean magnitude of this angle was negative (achieved correction is clockwise to the intended axis) at all postoperative visits, but a significant variability was observed (Figure 3). Mean AE became progressively more negative with time, but changes did not reach statistical significance ($p \geq 0.59$, paired Student t test). In addition, mean absolute means (considering mean absolute values of AE) were also calculated: 1 month 11.31 ± 8.68, 3 months 10.77 ± 9.07, 6 months 8.04 ± 6.66, and 12 months 11.35 ± 6.67. No significant differences were observed in this parameter between postoperative visits ($p \geq 0.35$, Wilcoxon test).

Correlation of corneal astigmatic changes with other clinical parameters

We only report those correlations that were moderate or good and with statistical significance. A statistically significant negative correlation was found at all postoperative visits between the magnitude of corneal astigmatism preoperatively and the postoperative ME (1 month r=-0.572; 3 months r=-0.780; 6 months r=-0.728; 12 months r=-0.744; all $p<0.01$). Therefore, the higher the corneal astigmatism, the more negative the postoperative ME was (Figure 4). In addition, a positive significant correlation was found between the preoperative corneal astigmatism and the magnitude of the DV at all postoperative visits (1 month r=0.534, p=0.01; 3 months r=0.592, $p<0.01$; 6 months r=0.692, $p<0.01$; 12 months r=0.636, $p<0.01$). This correlation between preoperative corneal toricity and postoperative DV was moderate in the initial postoperative period and it became better at the end of the follow-up.

As could be expected according to the previous relationships, significant correlations were found between preoperative and postoperative corneal astigmatism (1 month r=0.527; 3 months r=0.601; 6 months r=0.700; 12 months r=0.635; all $p<0.01$) and also between the magnitude of the TIA vector and postoperative ME (1 month r=-0.563; 3 months r=-0.597; 6 months r=-0.686; 12 months r=-0.687; all $p<0.01$). At 1 month postoperatively, significant positive correlations were found between higher order residual RMS and the magnitude of the SIA (r=0.647, $p<0.01$), between higher order residual RMS and the module of the FE (r=0.692, $p<0.01$), between spherical-like RMS and the magnitude of the SIA (r=0.611, $p<0.01$) and also between spherical-like RMS and the magnitude of the FE (r=0.683, $p<0.01$). However, these correlations were lost during the remaining follow-up (6 and 12 months $r \leq 0.50$, $p \geq 0.05$) (Figure 5).

Discussion

ICRS were developed and investigated initially as an alternative option for myopia correction due to the significant central flattening induced by the implants[41-45]. However, the preliminary success of this refractive option was overshadowed and overtaken by the rapid rise in popularity of laser in situ keratomileusis (LASIK). This refractive technology was then redirected and it was found to be a useful therapeutic option for the correction of the refractive error and irregularity present in the ectatic corneal disease[21]. Several studies have confirmed the efficacy and safety of these implants for the reduction of spherocylindrical error and corneal steepening in keratoconus in both short and long term[1-22]. In all these studies the astigmatism was not considered as a vector and only changes in the magnitude of astigmatism were evaluated. However, it is important to analyze changes in the axis of cylinder and if the astigmatic correction is induced in the targeted meridian. Errors in the axis of the astigmatic correction could be the responsible for some induced aberrations and for a poor predictability of the spherocylindrical correction. The purpose of the current study was to analyze by means of the Alpins vectorial method the corneal astigmatic changes occurring after KeraRing implantation in keratoconic eyes and to determine the relationship among these changes and the final visual, refractive and corneal aberrometric outcome. We preferred to analyze only vectorial changes of corneal astigmatism because it is an objective variable that cannot be biased by the patient's criteria. It should be considered that the accuracy of subjective refraction is poor in keratoconus[35]. The perceived blur in keratoconic eyes is the consequence of both second (sphere and cylinder) and higher order aberrations. Therefore, the subjective determination of the spherical and cylindrical components of the refraction can be easily biased by the focus variability introduced by other optical aberrations. Additionally, it should be considered that the anterior corneal astigmatism accounts for a large percentage of total ocular astigmatism, especially in cases with moderate and high astigmatism such as happens in keratoconus.

In the present study, a reduction in the limit of statistical significance was found for the sphere at 3 months after surgery. The mean reduction of this refractive parameter was 1.13 D at 12 months after surgery. Previous studies have also reported a significant reduction of the spherical component of the manifest refraction[2,4,6,9,10,12], but a great variability in the change reported in each study can be observed (mean change from 0.43 to 5.00 D depending on the author)[1-21]. Several facts could explain such discrepancy between studies, such as the different types of keratoconic eyes analyzed in each study or the poor predictability of manifest refraction in keratoconus. Regarding the magnitude of manifest astigmatism (ocular astigmatism), a statistically significant reduction of this parameter was observed after surgery, as in other previous studies[1,2,4-6,8-12,14,15,20] (mean change from 0.75 to 2.88 D). However, the magnitude of this astigmatism was undercorrected. These refractive changes were consistent with the observed visual outcomes. Significant improvements in logMAR UDVA (mean change of 3 lines) and CDVA (mean change of 1 line) were found after surgery.

Regarding corneal curvature, central keratometric readings (mean, steepest, flattest K's) were reduced significantly. This outcome supports previous findings reported with KeraRing and Intacs, showing also a significant central flattening effect[1-12,14,17]. This keratometric reduction was the responsible for the change in refraction and the visual improvement. In addition, significant changes were observed in corneal higher order aberrations. As expected according the change in manifest astigmatism, a significant reduction of the RMS value for corneal astigmatism was achieved with segments. On average, a reduction around 31% was found for this parameter. This fact was also consistent with the reduction observed in the magnitude of corneal astigmatism. Besides astigmatic changes, a non-significant reduction of corneal coma-like aberrations was observed in our sample (mean reduction at 12 months of 24.5%). This trend was consistent with the non-significant reduction of the RMS value corresponding to the corneal higher order aberrations (mean reduction at 12 months 22.5%). This limited aberrometric reduction could be in relation with the significant improvement found on average in logMAR CDVA. It should be remembered that primary coma has been demonstrated to have a very negative impact on visual acuity due to the optical blur that it induces[46]. In a previous study of our research group a significant reduction of higher order aberrations was also found after KeraRing implantation using the femtosecond laser technology in keratoconus, but only in those eyes with a magnitude of coma aberration larger than 3 microns[5].

The Alpins vectorial analysis method was used for evaluating the changes occurring with surgery in corneal astigmatism. To the best of our knowledge, this is the first study that applies the Alpins method to analyze the changes occurring in the magnitude and meridian of corneal astigmatism after ICRS implantation in keratoconic corneas. If the treatment is ideal and perfect, the magnitude of TIA and SIA should be coincident and then the DV and the ME should be zero. In our sample we have found a SIA vector with a magnitude significantly different from the magnitude of TIA. Specifically, the magnitude of SIA was significantly lower than the magnitude of the TIA vector. This implies that the ICRS generated an undercorrection of corneal astigmatism (mean value of 1.82 D at 12 months), which was maintained throughout the follow-up. It should be considered at this point that corneal and manifest astigmatism are not the same and then the mean undercorrection of 1.82 D cannot be extrapolated literally to manifest astigmatism. However, the trend to undercorrection was similar for both kinds of astigmatisms because they were directly related.

The magnitude of DV was higher than 1 D in a large percentage of eyes, as shown in Figure 2. Regarding the orientation of DV, a significant variability could be observed, with significant differences even between postoperative visits in the same eye. This variability implies that the nomogram was not predictive for all cases and then additional parameters should be considered in future developments of the nomogram in order to achieve a better predictability of the outcomes. It should be remembered that only refractive and topographic parameters are considered in the current nomogram when selecting the segment to implant, but the biomechanical properties of the cornea are not considered at all. A best knowledge of the structure where the segments are going to be implanted is necessary if more predictable outcomes are desirable. On the other hand, the variability in the orientation of this vector during the last period of the follow-up could be due to biomechanical changes still occurring in some eyes in spite of being implanted with KeraRings. It seems that progress of the ectatic process could be possible in some cases implanted with ICRS.

Mean ME was negative and this confirms again the difference between the surgically induced and the targeted induced astigmatism vectors and the undercorrection of corneal astigmatism. However, there were specific cases with a positive ME after surgery and then showing the opposite trend. This is consistent with the variability of DV and then it confirms the poor predictability of the nomogram for some cases. The flattening effect and torque vectors (FE and TRQ) were also studied. The FE vector represents the amount of astigmatism reduction achieved by the effective proportion of the SIA at the intended meridian[23]. If the treatment would have achieved a perfect and total correction, SIA and TIA would be coincident and SIA and FE vectors would be equal. However, this situation did not occur and then part of the astigmatic correction was not induced at the intended meridian. The TRQ vector represents the amount of astigmatic change induced by the SIA, due to nonalignment of the treatment, that has been ineffective in reducing astigmatism at the intended meridian but causes rotation and a small increase in the existing astigmatism[23]. If the treatment would have been totally effective, the TRQ vector would be zero. However, mean magnitude of TRQ vector was around 1. As with the other vectors analyzed, there was a significant variability, with cases with TRQ vector of zero and cases with a magnitude of TRQ over 2 D. Therefore, the nomogram is not optimized and it should consider additional factors in relation with the properties of the corneal tissue. In all cases the magnitude of TRQ was positive and then the vector lied 45 degrees counter clockwise to the SIA. Finally, the mean angle of error was negative, indicating that the achieved correction was clockwise to its intended axis. In any case, a significant variability was observed and cases with more than 20º of AE (negative or positive) could be observed.

Finally, we analyzed the level of correlation between some clinical parameters and corneal astigmatic changes analyzed by means of the Alpins vectorial method. Negative significant correlation was found between preoperative corneal astigmatism and postoperative ME and positive correlation was found between the magnitude of DV and preoperative corneal astigmatism at all postoperative visits. These correlations were initially moderate and it became stronger with time. Therefore, the higher the corneal astigmatism, the more significant the ME (with negative sign) and DV were. Therefore, it seems clear that corneal astigmatism in keratoconus is a factor that allows predicting a good or poor corneal astigmatic correction with ICRS. Keratoconic corneas with a significant astigmatic configuration could be associated to a specific corneal structure limiting the effect of ring segments and providing poorer outcomes. It was demonstrated that lamellar structure of keratoconic corneas is different compared to normal corneas with regions of more highly aligned collagen intermixed with regions in which there was little aligned collagen (distortion of the orthogonal lamellar matrix)[47,48]. Probably in these keratoconic cases with a significant astigmatic configuration the distribution of corneal lamellae is highly irregular with poor or unpredictable response to a peripheral addition of tissue. In any case, future studies are required in order to understand how the configuration of ectatic corneal structure is modified or altered with the ICRS. In addition, significant positive correlations were found between the magnitude of SIA and FE vectors and the magnitude of residual higher order and spherical-like aberrations. The higher the surgically induced astigmatism (the astigmatism induced for correcting the existing), the higher the corneal aberrations were. This trend was observed in the initial period of the follow-up, but not at the end. Therefore, if more corneal astigmatism was intended to be corrected, more corneal higher order aberrations were induced. It should be considered that little misalignments of high astigmatic corrections will have more impact on corneal optical quality and they could an important source of optical errors. The lost of correlation between the magnitude of SIA and aberrations at the end of the follow-up could be explained by biomechanical changes occurring in spite of the effect of the segments. These biomechanical changes could also generate changes in the magnitude of corneal higher order aberrations.

In conclusion, KeraRing implantation is a useful option for reducing the spherocylindrical error and corneal irregularity in keratoconus. The magnitude of corneal and refractive astigmatism are significantly reduced with the implants, but there is a trend to undercorrection. Therefore, a significant difference can be observed between the target and the surgically induced astigmatism by corneal values. A mean value of undercorrection between 1.5 and 2 D was found, although a significant variability among cases was observed, confirming the necessity of a more refined nomogram including more variables, such as corneal biomechanics or keratoconus severity. Indeed, this undercorrection is more significant for those corneas with larger levels of astigmatism. Therefore, a corrective factor accounting for this undercorrection should be considered in future implantations using the manufacturer's nomogram. Regarding the meridian of corneal astigmatism, there is trend of the achieved correction to be clockwise to its intended axis, although a significant variability in the angle of error can be observed depending on the case. In a significant percentage of cases an amount of the corneal astigmatic change induced by the implants is ineffective in reducing astigmatism at the intended meridian due to nonalignment of the treatment. In addition, the surgically induced corneal astigmatism is in relation with the magnitude of corneal higher order aberrations postoperatively. The current nomogram should be implemented in order to attempt to minimize these errors in the astigmatic correction. The variability observed in the corneal astigmatic outcome is indicative of the need of including more variables in the nomogram, not only refractive and topographic parameters. The biomechanical properties of the corneal tissue should be also considered when choosing the segment to implant in a specific case. Finally, in future studies on ICRS the astigmatic outcomes require a vectorial analysis of the astigmatic changes to be presented to avoid wrong or incomplete conclusions.

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Figure 1.- Vectorial display of surgically induced astigmatism (SIA) by corneal values during the postoperative follow-up (blue, 1 month; green, 3 months; orange, 6 months; red, 12 months). Abbreviations: D, diopters.

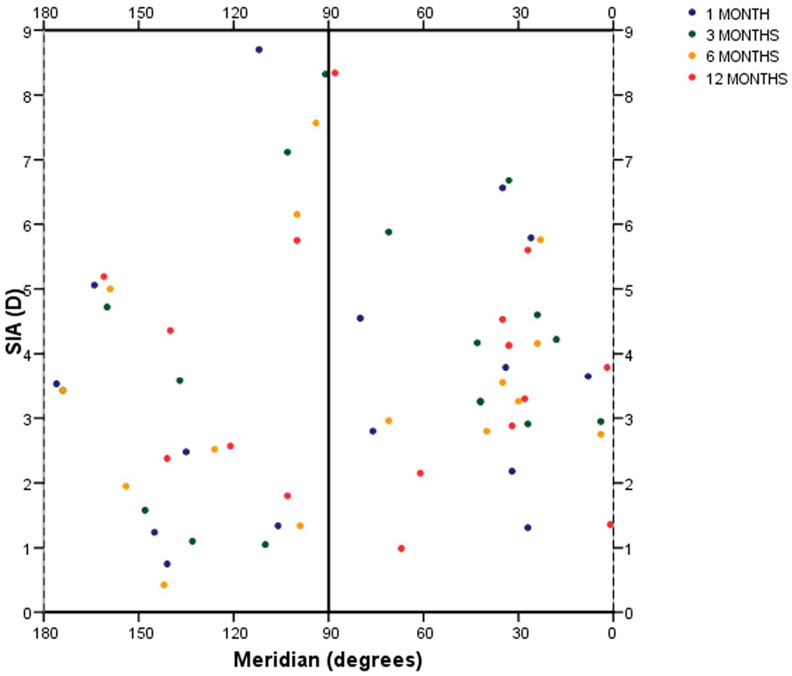

Figure 2.- Vectorial display of the difference vector (DV) during the postoperative follow-up (blue, 1 month; green, 3 months; orange, 6 months; red, 12 months). It represents the astigmatism that should be induced additionally to achieve the intended target in each case. Abbreviations: D, diopters.

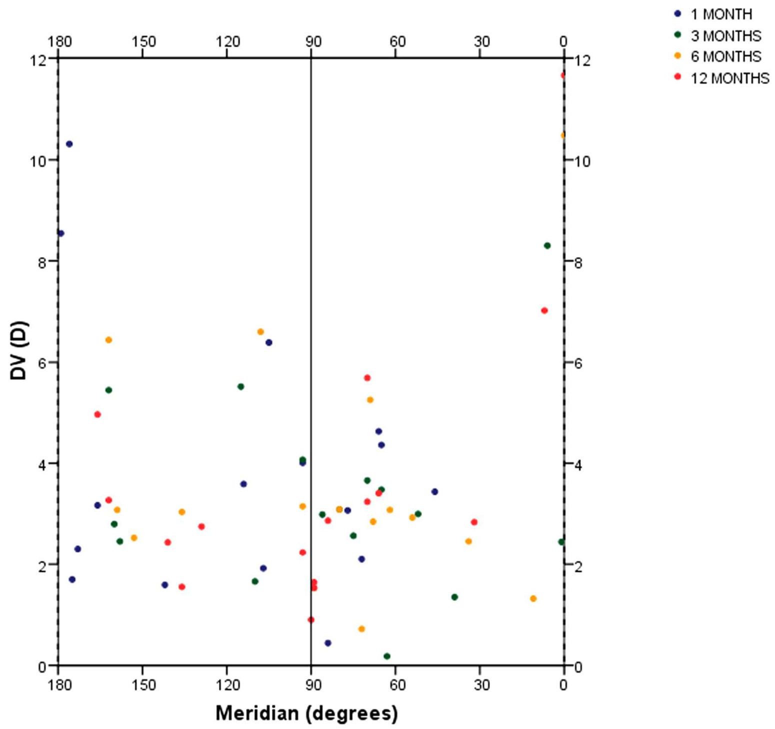

Figure 3.- Changes in the angle of error during the follow-up in all cases. A significant variability can be observed.

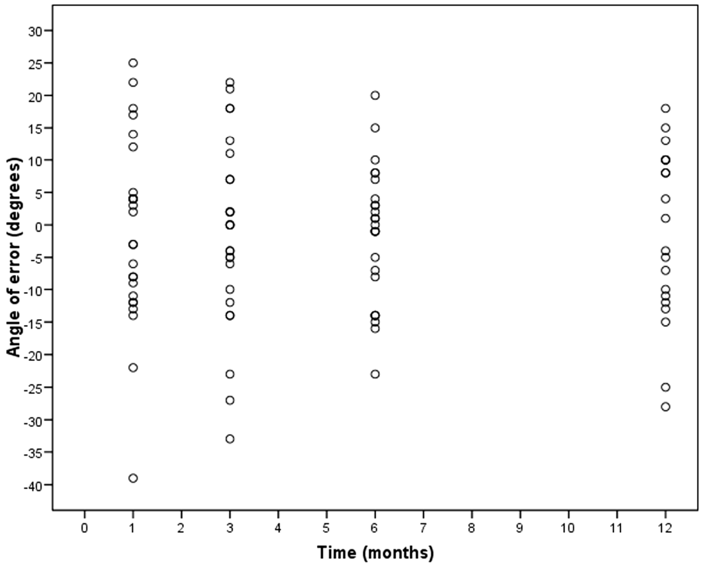

Figure 4.- Scattergram showing the relationship between the preoperative corneal astigmatism and the 3-month postoperative magnitude of error (ME). The adjusting line to the data obtained by means of the least-squares fit is shown. This linear predicting model showed a good predictability (R^2: 0.63). Abbreviations: D, diopters.

$$ME_{post} = 1.72 - 0.61 \times CA_{preop}$$

,where ME_{post} is the magnitude of error at 3 months after surgery and CA_{preop} the preoperative corneal astigmatism

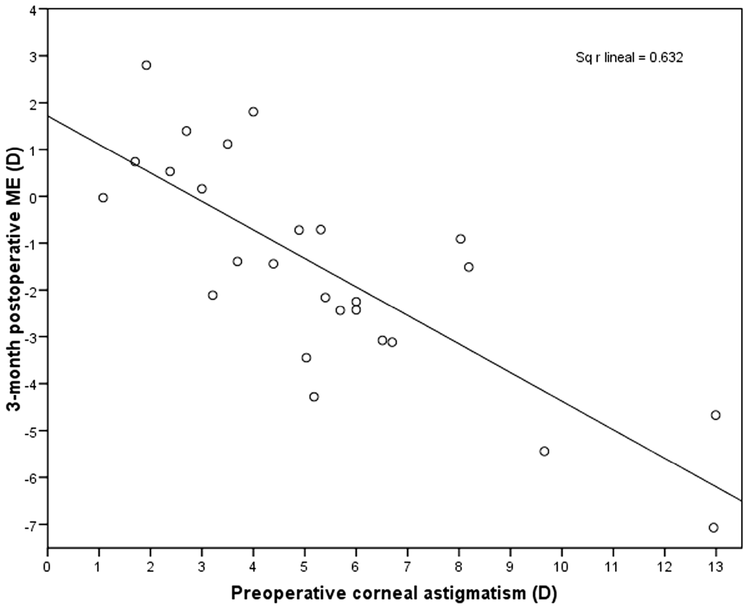

Figure 5.- Scattergrams showing the relationship between the module of SIA vector and the root mean square (RMS) for spherical-like aberrations at 1 (up) and 12 months (down) after surgery. The adjusting lines to the data obtained by means of the least-squares fit are shown. Abbreviations: D, diopters.

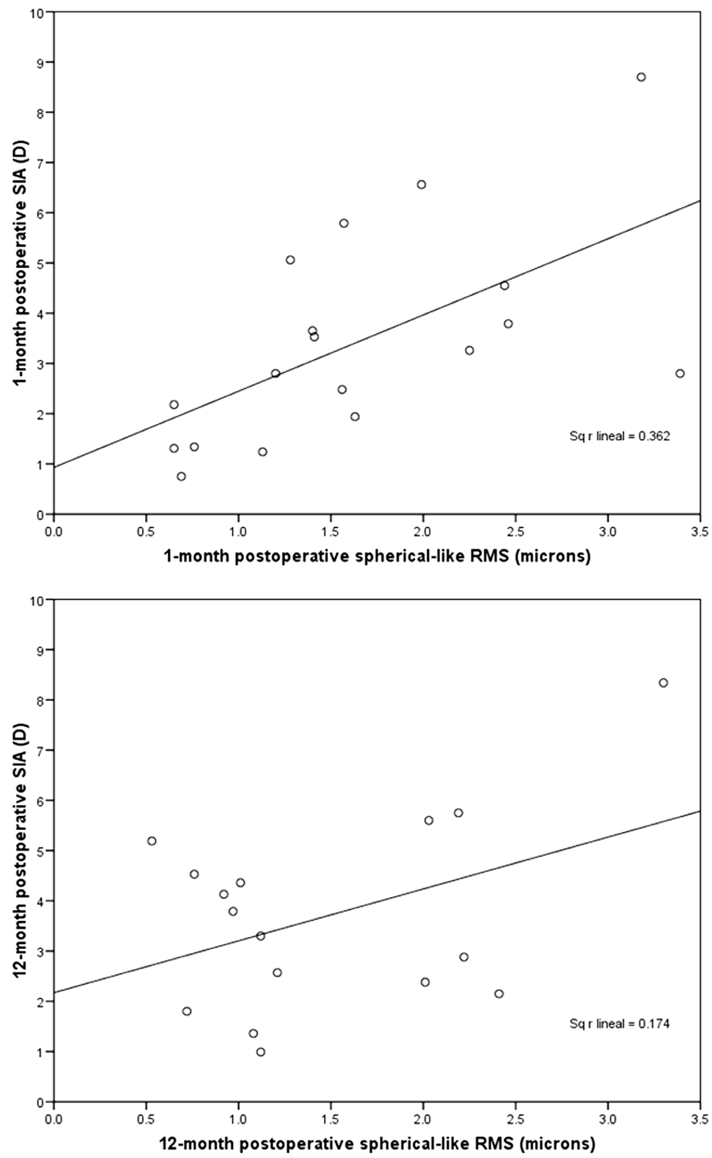

Table 1.- Contribution of each participating ophthalmologic centre to this retrospective study.

INVESTIGATOR	SURGEON	OPHTHALMOLOGIC CENTER	EYES IMPLANTED WITH ICRS
1	Dr Alió	Vissum Alicante	16
2	Dr Barraquer	Centro de Oftalmología Barraquer	13
3	Dr Teus	Vissum Madrid	6

* Abbreviations: ICRS, intracorneal ring segments.

Table 2.- Summary of the visual and refractive outcomes. Ranges are shown in brackets below each mean value.

Parameter (range)	Preop	1 Month	3 Months	6 Months	12 months
LogMAR UDVA	0.96 ± 0.45 (0.15,1.60)	0.71 ± 0.33 (0.15,1.30)	0.72 ± 0.34 (0.05,1.30)	0.66 ± 0.37 (0.15,1.30)	0.69 ± 0.39 (0.15,1.30)
Sphere (D)	-2.21 ± 3.56 (-9.00,+6.50)	-1.90 ± 4.72 (-17.00,+9.50)	-1.89 ± 3.66 (-16.00,+4.00)	-1.44 ± 2.94 (-8.50,+2.50)	-1.08 ± 2.39 (-6.00,+2.00)
Cylinder (D)	-4.72 ± 2.41 (-9.00,0.00)	-2.56 ± 1.84 (-6.75,0.00)	-2.57 ± 1.67 (-6.50,0.00)	-2.72 ± 1.71 (-7.50,-1.00)	-2.39 ± 1.49 (-6.50,0.00)
LogMAR CDVA	0.37 ± 0.32 (0.05,1.48)	0.30 ± 0.32 (0.00,1.30)	0.26 ± 0.28 (0.02,1.00)	0.26 ± 0.27 (0.00,1.00)	0.26 ± 0.27 (0.00,1.00)

* Abbreviations: UDVA, uncorrected distance visual acuity; SE, spherical equivalent; CDVA, corrected distance visual acuity; D, diopters.

Table 3.- Summary of the keratometric outcomes. Ranges are shown in brackets below each mean value.

Parameter (range)	Preop	1 Month	3 Months	6 Months	12 months
K1 (D)	46.13 ± 4.75 (34.93,60.20)	45.34 ± 5.56 (32.44,59.21)	45.49 ± 5.23 (34.85,59.18)	45.07 ± 5.32 (34.85,59.17)	44.85 ± 5.39 (35.17,58.54)
K2 (D)	51.77 ± 4.47 (45.11,65.89	48.82 ± 4.77 (42.75,63.22)	48.41 ± 4.99 (40.29,63.25)	48.17 ± 4.69 (41.29,62.32)	48.31 ± 4.81 (40.13,61.41)
KM (D)	48.95 ± 4.41 (41.43,63.20)	46.68 ± 5.34 (37.60,61.17)	46.21 ± 4.87 (37.57,60.71)	46.57 ± 4.88 (38.07,60.59)	46.49 ± 5.04 (36.95,59.83)

* Abbreviations: K1, corneal dioptric power in the flattest meridian for the 3 mm central zone; K2, corneal dioptric power in the steepest meridian for the 3 mm central zone; KM, mean corneal power in the 3 mm zone; D, diopters.

Table 4.- Summary of the corneal aberrometric outcomes. Ranges are given in brackets below each mean value.

Parameter	Preop	1 Month	3 Months	6 Months	12 Months
Higher-order RMS (microns)	3.65 ± 1.90 (1.26,8.85)	3.19 ± 1.03 (1.52,5.50)	3.06 ± 1.19 (1.50,6.57)	2.79 ± 0.95 (1.65,5.84)	2.83 ± 0.83 (1.55,4.41)
RMS astigmatism (microns)	4.05 ± 3.04 (0.48,10.87)	2.45 ± 1.68 (0.33,7.04)	2.57 ± 1.78 (0.14,6.82)	2.80 ± 2.29 (0.29,9.05)	2.79 ± 2.36 (0.34,9.05)
Primary coma RMS (microns)	2.67 ± 1.50 (0.33,5.80)	2.49 ± 1.00 (0.47,4.84)	2.37 ± 1.29 (0.43,6.08)	1.94 ± 0.88 (0.43,3.48)	2.09 ± 0.88 (0.62,3.77)
Z_4^0 (microns)	-0.32 ± 1.06 (-2.06,2.69)	-0.35 ± 0.71 (-1.51,0.80)	-0.19 ± 0.68 (-1.75,1.10)	0.09 ± 0.97 (-1.65,2.62)	-0.22 ± 0.66 (-1.47,0.90)
Residual RMS (microns)	1.85 ± 1.69 (0.64,8.10)	1.65 ± 0.83 (0.65,3.39)	1.53 ± 0.85 (0.52,3.27)	1.56 ± 0.92 (0.52,3.89)	1.48 ± 0.78 (0.53,3.30)
Spherical-like RMS (microns)	1.41 ± 1.32 (0.40,6.38)	1.29 ± 0.81 (0.54,3.30)	1.21 ± 0.75 (0.43,2.73)	1.27 ± 0.81 (0.46,3.59)	1.19 ± 0.74 (0.33,3.22)
Coma-like RMS (microns)	3.27 ± 1.59 (0.40,6.13)	2.84 ± 0.92 (1.42,5.06)	2.73 ± 1.15 (1.44,6.21)	2.41 ± 0.80 (1.20,4.60)	2.47 ± 0.80 (1.33,4.13)

* Abbreviations: RMS, root mean square.

* Aberrometric definitions: primary coma, terms $Z_3^{\pm 1}$; primary spherical aberration, term Z_4^0; residual aberrations, all Zernike terms except $Z_3^{\pm 1}$ and Z_4^0; spherical-like aberrations, terms from fourth and sixth order; coma-like aberrations, terms from third, fifth and seventh order.

Table 5.- Summary of the different vectors analyzed with the Alpins vectorial method during the follow-up of the current study. The objective of this vectorial analysis was to evaluate the corneal astigmatic changes that occurred after the implantation of ICRS in keratoconic corneas. Ranges are shown in brackets below each mean value.

Magnitude (meridian)	1 Month	3 Months	6 months	12 months
SIA (D)	3.80 ± 2.27 (0.75, 8.92)	3.83 ± 1.85 (0.90, 8.32)	4.06 ± 2.25 (0.42, 11.32)	3.77 ± 1.92 (0.99, 8.34)
DV (D)	3.46 ± 2.29 (0.44, 10.31)	2.96 ± 1.68 (0.18, 8.30)	3.09 ± 2.27 (0.61, 10.49)	3.53 ± 2.44 (0.90, 11.66)
FE (D)	3.50 ± 2.33 (0.29, 8.87)	3.46 ± 1.93 (0.77, 8.07)	3.87 ± 2.28 (0.37, 11.25)	3.12 ± 2.02 (0.58, 8.25)
TRQ (D)	1.17 ± 0.79 (0.09, 3.13)	1.21 ± 0.98 (0.00, 2.89)	0.92 ± 0.74 (0.00, 2.59)	1.15 ± 0.55 (0.18, 2.26)

* Abbreviations: SIA, surgically induced astigmatism; DV, difference vector; ME, magnitude of error; FE, flattening effect; TRQ, torque; D, diopters.

<u>TRABAJO 8:</u> ***Piñero DP, Alio JL, Teus MA, Barraquer RI, Uceda-Montañés A. Modelling the intracorneal ring segment effect in keratoconus using refractive, keratometric and corneal aberrometric data. Invest Ophthalmol Vis Sci 2010 (in press).***

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MODELLING THE INTRACORNEAL RING SEGMENT EFFECT IN KERATOCONUS USING REFRACTIVE, KERATOMETRIC AND CORNEAL ABERROMETRIC DATA

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None of the authors have any financial interests to disclose

This study has been supported in part by a grant from the Spanish Ministry of Health, Instituto Carlos III, Red Temática de Investigación Cooperativa en Salud "Patología ocular del envejecimiento, calidad visual y calidad de vida",

Abstract

PURPOSE: To characterize the refractive, keratometric and corneal aberrometric effect of a specific type of intracorneal ring segment (ICRS) as a function of its thickness and the preoperative conditions of the cornea.

METHODS: A total of 72 consecutive keratoconic eyes of 57 patients ranging in age from 15 to 68 years were retrospectively analyzed and included in the study. All cases were diagnosed with keratoconus and implanted with 160º arc-length KeraRing segments (Mediphacos), using the femtosecond laser technology. Correlations between ring segment thickness and several clinical parameters were investigated. In addition, a multiple regression analysis was performed in order to characterize all factors influencing on the ring segment effect.

RESULTS: Significant reductions in central curvature, corneal astigmatism and coma-like aberrations were found postoperatively ($p \leq 0.03$). Moderate and limited correlations were found between ring segment thicknesses and changes in mean keratometry and higher order aberrations ($r \leq 0.50$, $p < 0.01$). A consistent linear relationship of the superior ring segment thickness to the induced corneal changes, the preoperative cylinder and the difference in thickness between inferior and superior segments was found ($p < 0.01$, R^2: 0.91). An almost identical model was obtained for the inferior ring segment thickness with the only distinction in the factor accounting for the thickness difference between segments ($p < 0.01$, R^2: 0.64).

CONCLUSIONS: The selection of the ring segment to implant in keratoconus should not be based not only on refraction and subjective appearance of the corneal topographic pattern but also on corneal aberrometry. This highly customized selection would allow a more predictable outcome.

FINANCIAL DISCLOSURE: None of the authors have any financial interest to disclose

Introduction

Intracorneal ring segments (ICRS) have been demonstrated to be effective in improving visual acuity, reducing the refractive error and mean keratometry in keratoconic eyes[1-22]. These segments act as spacer elements between the bundles of corneal lamellae producing a shortening of the central arc length (arc shortening effect), which is proportional to the thickness of the implant[23]. 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 insertion is displaced forward[24,25]. In non-pathological corneas, there is a nearly linear relationship between the degree of central corneal flattening and the thickness of the implanted ring segments[26,27]. However, this mechanism of action is not reproduced exactly in the keratoconic cornea. It should be considered that the well-organized lamellar structure of the cornea is lost when the corneal tissue degenerates, as it happens in keratoconus[28]. The regular orthogonal arrangement of the collagen fibrils is destroyed within the apical scar of the keratoconus[28]. Therefore, the effect induced by the ICRS in keratoconus may be different than the effect induced in normal corneas because the structural properties of the corneal collagen framework are also different.

Several nomograms for ICRS implantation in keratoconus have been developed, all of them intuitive or based on poor and subjective empirical data[3,5,7-22,29]. A nomogram based on objective data or following an accurate mathematical model characterizing the ICRS effect has still not been developed or reported. Different limited approaches have been proposed as nomograms for ICRS implantation in keratoconus, some of them based on spherical equivalent refraction or on the subjective appearance of the corneal topographic profile (decentred o not decentred cones). Good visual and refractive outcomes have been reported with all of them[3,5,7-22,29]. However, there are still anecdotal cases of ICRS implantation with minimal keratometric reductions or with no keratometric effect in spite of following the indications provided by these nomograms. It has been demonstrated that the preoperative manifest refraction or best corrected visual acuity are factors with a limited ability to predict the postoperative visual outcome[30]. In contrast, corneal aberrometry was found to have a great potential of prediction for the postoperative visual outcome[2]. Therefore, there is a need for readjusting the nomograms using objective clinical data or more complex mathematical corneal modelizations in order to obtain more predictable results.

The final aim of the current study was to characterize the refractive, keratometric and aberrometric effect of one specific type of intracorneal implants as a function of the thicknesses used and the preoperative conditions of the cornea. To the best of our knowledge, this is the first study that attempts to develop a modelization of the ICRS effect based on objective data and considering also corneal aberrometry as an additional influencing factor.

Patients and methods

Patients

Eyes with the diagnosis of keratoconus and implanted with 160º arc length KeraRing (Mediphacos, Belo Horizonte, Brazil) segments (Figure 1) were retrospectively analyzed in four Spanish ophthalmologic centres: 3 centres from Vissum Corporation (Alicante, Seville and Madrid) and the Barraquer Ophthalmologic

Centre in Barcelona. A total of 72 consecutive keratoconic eyes of 57 patients ranging in age from 15 to 68 years old were included (mean age: 32.93 ± 11.20 years). A total of 59.6% of patients included in this study were male and 40.4% were female. Fifteen of these keratoconic cases were bilateral and 57 were unilateral.

Only keratoconus cases implanted with KeraRing (Figure 1) using the femtosecond laser technology and with no other previous ocular surgery and active ocular disease were included in this study. Keratoconus diagnosis was based on corneal topography and slit-lamp observation. In all cases, preoperative findings characteristic of keratoconus were evident: corneal topography revealing an asymmetric bowtie pattern with or without skewed axes and at least one keratoconus sign on slit-lamp examination, such as stromal thinning, conical protrusion of the cornea at the apex, Fleischer ring, Vogt striae or anterior stromal scar[31]. The Alió-Shabayek classification[32] was used for grading keratoconus in those cases where corneal aberrations were evaluated. In all cases ICRS implantation was indicated due to the existence of reduced BSCVA and/or contact lens intolerance.

Ethical board committee approval of the institutions participating in this study was obtained for this investigation. In addition, during the process of consent for this surgery, consent was taken to later include clinical information in scientific studies, following the tenets of the Helsinki declaration.

Examination protocol

A comprehensive examination was performed preoperatively in all cases which included: Snellen uncorrected visual acuity (UCVA) (LogMAR scale), Snellen best-spectacle corrected visual acuity (BSCVA) (LogMAR scale), manifest refraction, slit-lamp biomicroscopy, Goldman tonometry, fundus evaluation, ultrasonic pachymetry and corneal topographic analysis. As topographic data were collected from four different centers, a total of two different corneal topography systems were used for corneal examination: the CSO (CSO, Firenze, Italy) and the Orbscan IIz systems (Bausch & Lomb, Rochester, NY). The first device is a Placido-based system and the Orbscan II is a combined scanning-slit and Placido-disc topography system. Although the agreement between these specific devices has not been reported, Orbscan and Placido-based devices have been proved to provide similar accuracy and precision on calibrated spherical test surfaces[33]. In this study, the following topographic data were evaluated and recorded with all corneal topographic devices: corneal dioptric power in the flattest meridian for the 3 mm central zone (K1), corneal dioptric power in the steepest meridian for the 3 mm central zone (K2) and mean corneal power in the 3 mm zone (KM).

Corneal aberrometry was also recorded and analyzed only in those patients examined with the CSO topography system (CSO, Firenze, Italy) (59 eyes, Vissum Alicante and Vissum Madrid), because this device was the only one with the capability to calculate directly this specific information. This topographic system analyzes a total of 6144 points of a corneal area enclosed in a circular annulus defined by an inner radius of 0.33 and an outer radius of 10 mm respect to corneal vertex. The software of the CSO, the EyeTop2005 (CSO, Firenze, Italy), automatically performs the conversion of corneal elevation profile into corneal wavefront data using the Zernike polynomials with an expansion up to the 7th order. In this study, the aberration coefficients and root mean square (RMS) values were calculated for a 6-mm pupil in all cases. The following parameters were analyzed and recorded: higher order root mean square (RMS), primary coma RMS (computed for the Zernike terms $Z_3^{\pm1}$), coma-like RMS (computed for third, fifth, and seventh order Zernike terms), spherical-like RMS (computed for fourth and sixth order Zernike terms) and higher order residual RMS (computed considering all

Zernike terms except those corresponding with primary coma and spherical aberration). The corresponding Zernike coefficient for primary spherical aberration (Z_4^0) was also reported with its sign.

Surgery

Surgical procedures were performed by a total of four experienced surgeons (JLA from Vissum Alicante, AUM from Vissum Sevilla, MAT from Vissum Madrid and RIB from Centro de Oftalmología Barraquer) using the same femtosecond technology for corneal tunnelization (30 kHz IntraLase femtosecond system, IntraLase Corp, Irvine, California, USA) and following in all cases the same surgical protocol, which was the standard procedure described in detail by many authors in previous works[2,4,6-8,13].

In all cases an antibiotic prophylaxis before surgery consisting of topical ciprofloxacin (Oftacilox; Alcon Cusí, Barcelona, Spain) every eight hours for two days was prescribed to be applied.

Regarding the location of the incision, two different criteria were used. The former cases included in the study were operated on using a temporal incision which was the initial standard procedure. A total of 21 eyes were included following this modality of incision (in 7 cases incision was near the flattest meridian whereas in the rest it was oblique to the flattest and steepest corneal meridian). In contrast, the most recent cases were operated on using an incision on the steepest corneal meridian (51 eyes, 70.8%), which is the most currently accepted incision criterion for this type of surgical procedure. In any case, the geometric centre of the ring segment was always placed on the flattest corneal meridian.

The selection of the number (1 or 2) and thickness of KeraRing (Figure 1) segments to implant was performed following the nomogram defined by the manufacturer[2,8]. In 24 eyes (33.3%) only one ring segment was implanted whereas in the remaining 48 eyes (66.7%) two segments were necessary.

No intraoperative complications occurred. Topical tobramycin and dexamethasone eye drops (TobraDex; Alcon Laboratories, Inc, Fort Worth, Texas, USA) were used postoperatively every six hours for one week and stopped. Topical lubricants were also prescribed to be applied every six hours for one month (Systane, Alcon Laboratories, Inc, Fort Worth, Texas, USA).

Follow-up evaluation

Visual, refractive and corneal aberrometric outcomes were evaluated 3 months after surgery. No longer follow-up was included because we wanted to analyze the real effect of the ring segments, not changes with time once they had been implanted. It should be considered that corneal biomechanical changes and a progression of the ectatic corneal process can still occur in spite of the implantation of ring segments[2,34]. No explantation or reposition cases were detected during these first three postoperative months.

Statistical analysis

SPSS statistics software package version 15.0 for Windows (SPSS, Chicago, Illinois, USA) was used for statistical analysis. Normality of all data samples was firstly checked by means of Kolmogorov-Smirnov test. When parametric analysis was possible, the Student t test for paired data was performed for all parameters comparisons between preoperative and postoperative examinations or consecutive postoperative visits. On the contrary, when parametric analysis was not possible, the Wilcoxon Rank Sum test was applied to assess the significance of differences between preoperative and postoperative data, using in all cases the same level of significance ($p<0.05$).

For simplifying the statistical analysis the following notations and criteria were used: superior segment was considered any segment whose geometric center was located on the superior half of the cornea, inferior segment was considered any segment whose geometric center was located on the inferior half of the cornea and a thickness of zero was considered when a specific segment was not implanted (superior or inferior). With these criteria, the bivariate correlations of visual, refractive and corneal aberrometric changes with superior and inferior ring segment thicknesses were evaluated (Pearson or Spearman correlation coefficients depending if normality condition could be assumed or not). Furthermore, a multiple regression analysis was performed using the backward elimination method with the aim of obtaining a mathematical expression relating the different kind of changes induced by each ring segment, superior and inferior, separately. Model assumptions were evaluated by analyzing residuals, the normality of unstandardized residuals (homoscedasticity), and the Cook's distance in order to detect influential points or outliers. In addition, the lack of correlation between errors and multicollinearity was assessed by means of the Durbin-Watson test and the calculation of the collinearity tolerance and the variance inflaction factor (VIF).

Results

The contribution of the four participating centres to the current study was as follows: 60 eyes from the Vissum Corporation centres (Alicante, Seville and Madrid) and 12 eyes from the Barraquer Ophthalmologic Centre. There was a balanced distribution of right and left eyes (35 eyes vs. 37 eyes). Cone opacity was observed only in 5 cases (6.9%). Considering the corneal aberrations and according to the Alió-Shabayek grading system, 14 eyes had a cone grade I (26.9%), 16 eyes a cone grade II (30.8%), 8 eyes a cone grade III (15.4%) and 14 eyes a cone grade IV (26.9%).

Visual, refractive and corneal changes

Table 1 summarizes the visual and refractive data preoperatively and 3 months after KeraRing implantation. As shown in the table, manifest sphere and cylinder were reduced significantly with the implants ($p<0.01$, Wilcoxon test). A mean improvement in UCVA of three lines was found that was statistically significant ($p<0.01$, Wilcoxon test). Regarding the BSCVA, a statistically significant improvement of around 1 line was also observed ($p<0.01$, Wilcoxon test).

All keratometric readings were reduced significantly 3 months after surgery ($p<0.01$, Wilcoxon tests) (Figure 2). Specifically, a mean central flattening effect of 2.45 ±2.45 D was obtained. Regarding corneal aberrations, a significant decrease was observed in the RMS values for coma-like aberrations ($p=0.03$, Wilcoxon test) and corneal astigmatism ($p=0.01$, Wilcoxon test) at 3 months after surgery (Table 2). The primary spherical aberration term became on average more positive postoperatively, although the change did not reach statistical significance (Table 2).

Correlation between ring segment thickness and visual, keratometric and refractive changes

Table 3 summarizes the statistically significant correlations of the postoperative outcome to different preoperative and ring segment parameters. As shown in this Table, the thicknesses of the superior and inferior ring segments were found to be inversely correlated to the change achieved in mean keratometry (Figure 3) and positively correlated to the change induced in corneal residual higher-order aberrations (Figure 4). The change in mean keratometry was found to be significantly correlated to other preoperative clinical parameters, as the UCVA, BSCVA, mean keratometry and the manifest sphere. Furthermore, the change achieved with the implants in manifest refraction was found to be significantly correlated to the preoperative or baseline refractive status.

Multiple regression analysis

According to the correlation analysis, several factors seem to be implicated on the ring segment effect and this requires a more complex analysis. For this reason, a multiple linear regression was performed in order to find the appropriate mathematical expression relating all the influencing factors. The aim was to find a model predicting the superior and inferior ring segment thicknesses required for achieving a specific postoperative clinical change with a specific baseline conditions. Table 4 summarizes the predictability and goodness of fit of the different models obtained. First, two models were calculated considering only the visual, refractive and keratometric data, which were available in all the participating centers:

Model 1: $SST(\mu m) = 102.84 - 13.48 \times CYL_p - 21.27 \times DifKM - 0.65 \times DifIST$ (R^2: 0.84, $p<0.01$)

Model 2: $IST(\mu m) = 102.84 - 13.48 \times CYL_p - 21.27 \times DifKM + 0.35 \times DifIST$ (R^2: 0.62, $p<0.01$)

where *SST* is the thickness of the superior segment, IST the thickness of the inferior segment, CYL_p the preoperative cylinder, *DifKM* the change in mean keratometry after surgery, and *DifIST* the difference between the thickness of the inferior and superior ring segments.

These models revealed that the thicknesses of both ring segments were inversely correlated to the preoperative manifest astigmatism and the change in mean keratometry. The only difference between these two models was the factor accounting for the difference in thickness between the inferior and superior ring segments.

When the multiple regression analysis was performed introducing also corneal aberrometric data (59 eyes), two new models with an increased predictability were obtained in spite of using a smaller sample size:

Model 3 (R^2: 0.91, $p<0.01$):

$$SST(\mu m) = 132.20 - 12.14 \times CYL_p - 20.47 \times DifKM + 24.37 \times DifRMSHOA - 0.74 \times DifIST$$

Model 4 (R^2: 0.64, $p<0.01$):

$$IST(\mu m) = 132.20 - 12.14 \times CYL_p - 20.47 \times DifKM + 24.37 \times DifRMSHOA + 0.26 \times DifIST$$

,where *SST* is the thickness of the superior segment, IST the thickness of the inferior segment, CYL_p the preoperative cylinder, *DifKM* the change in mean keratometry after surgery, *DifRMSHOA* the change in the

RMS value for corneal higher order aberrations, and *DifIST* the difference between the thickness of the inferior and superior ring segments.

These two new implemented models also revealed an inverse correlation of the thicknesses of both ring segments to the preoperative manifest astigmatism and the change in mean keratometry. In addition, these thicknesses were found to be positively correlated to change in corneal higher-order aberrations. The difference in thickness between the inferior and superior ring segments was also the differential factor between these two predictive models.

Homoscedasticity of the four models was confirmed by the normality of the unstandardized residuals distribution (p=0.09) and the absence of influential points or outliers (mean cook's distance, 0.12 ± 0.31). The lack of correlation between errors and multicollinearity was also confirmed (Tolerances between 0.57 and 0.77; VIFs between 1.30 and 1.74) was also confirmed. With the model for the thickness of the superior segment, 92.68% of unstandardized residuals were lower than 100 µm and 75.61% lower than or equal to 50 µm. With the model for the thickness of the inferior segment, 90.24% of unstandardized residuals were lower than 100 µm and 68.29% lower than or equal to 50 µm.

Homoscedasticity of these models was confirmed by the normality of the unstandardized residuals distribution (p≥0.09) and the absence of influential points or outliers. The lack of multicollinearity and the independence of the residuals were also confirmed (Table 4).

A statistically significant negative correlation was found between the unstandardized residuals for the four developed linear models and the magnitude of the preoperative sphere (Models 1 and 2, r=-0.32, p=0.04; Models 3 and 4, r=-0.47, p<0.01). In addition, statistically significant differences in some corneal aberrometric coefficients were found between cases with residuals higher than 50 µm and those with residuals lower than or equal to 50 µm for the first two developed models (Model 1 and 2, RMS for astigmatism p=0.02, RMS for residual higher order aberrations p=0.01, RMS for coma-like aberrations p=0.02; Wilcoxon tests). In the two linear models which considered corneal higher order aberrations, differences between cases with residuals higher than 50 µm and those with residuals lower than or equal to 50 µm were near the limit of statistical significance for the RMS values corresponding to corneal astigmatism and spherical-like aberrations (p=0.06, Wilcoxon tests) (Figure 5). It should be considered that only 13 cases had residuals higher than 50 µm, whereas the remaining cases presented lower residuals. This trend for corneal astigmatism and spherical-like aberrations was also observed in the other two linear models.

Discussion

A significant central flattening was also observed after KeraRing implantation. A mean change of around 2.5 D was found. This outcome supports the previous findings reported after KeraRing and Intacs, implantation showing also a significant flattening effect[1-15,20,29]. This keratometric reduction was the main reason for the change in refraction and the increase in UCVA. However, this keratometric change was dependent on several preoperative factors as keratometry and BSCVA. As previously commented, the ring segments implanted in the mid-periphery has been proven to induce a shortening of the central arc length (arc shortening effect)[23] and then a flattening of the central portion of the anterior corneal surface[24,25]. Regarding corneal aberrometric changes, significant changes were found in corneal astigmatism and coma-like aberrations. This aberrometric improvement could be in relation with the significant improvement found on average in LogMAR BSCVA. It should be remembered that primary coma has been demonstrated to have a very negative impact on visual acuity due to the optical blur that it induces[34]. In a previous study of our research group a significant reduction of higher order aberrations was found after KeraRing implantation using the femtosecond laser technology in keratoconus, but only in those eyes with a magnitude of coma aberration larger than 3 microns[8]. In addition, it should be mentioned that a non-significant change of the primary spherical aberration towards less negative values was observed. This change in primary spherical aberration and also the reduction in coma-like errors were consistent with the reduction of the localized corneal steepening which was present in these keratoconic eyes.

Correlations between the ring segment thicknesses and the refractive, keratometric and corneal aberrometric changes were also investigated. A specific criterion was used for defining the concept of superior and inferior ring segment in order to simplify the statistical analysis: superior segment was considered any segment whose geometric center was located on the superior half of the cornea and inferior segment was considered any segment whose geometric center was located on the inferior half of the cornea. In addition, a non-implanted ring segment (superior or inferior) was considered as an implant with thickness zero. Several statistically significant weak and moderate correlations were found between the thickness of the superior and inferior ring segments and some clinical changes (Table 3). For example, these thicknesses were inversely correlated with the change in mean keratometry and positively correlated with the change in the RMS value corresponding to the corneal higher order residual aberrations. As previously commented, a nearly linear relationship between the degree of central corneal flattening and ring thickness was found in normal corneas[26,27]. Besides these moderate relationships, we found that some clinical changes were also significantly correlated with some preoperative conditions, as the magnitude of the spherocylindrical error or the corneal curvature. Therefore, it seems clear that some factors are influencing on the visual and refractive outcomes achieved with the KeraRing segments. In other words, this process cannot be represented by means of a simple linear model with two variables. The effect achieved with each KeraRing segment is a multifactorial process depending on the ocular preoperative conditions as well as on the thickness of the implant. It should be considered that all segments were implanted using the same surgical criteria (inner and outer diameter of 4.8 mm and 5.7 mm, ring placed at approximately 80% of the depth of the cornea). The diameter and the depth of the implant are also factors in relation with the final effect achieved with the ring segments[25], but these factors have not been modified in the current study. It should be considered that corneal changes induced by the ICRS must be in relation to the structural properties of the collagen framework in the corneal stroma. The stroma accounts for 90% of corneal thickness, and evidently its mechanical properties define for the most part the mechanical properties of the whole corneal structure. In the normal cornea, there is a preferred orientation of collagen lamellae along the horizontal and vertical directions, but this trend is maintained to within about 1 mm from the limbus, where a circular or tangential disposition of fibrils occurs[35]. However, this well organized lamellar structure is lost when the corneal tissue degenerates, as it happens in keratoconus[28]. The regular orthogonal arrangement of the collagen fibrils is destroyed within the apical scar of the keratoconus[28]. Therefore, the ICRS effect in keratoconus seems to be a more complicated phenomenon that needs a more complex mathematical modelling. The current investigation was aimed at defining an approach to this mathematical modelling using a multiple linear regression analysis. A more accurate model should be defined in the future considering clinical parameters and also accurate measurements of the structural and mechanical properties of the corneal tissue.

A consistent linear model relating the thickness of superior and inferior ring segments with the achieved clinical changes and the ocular preoperative conditions was obtained. This analysis was first performed considering only visual, refractive and keratometric data which were available in all the participating centers. We found that the thicknesses of the inferior and superior ring segments were significantly correlated with the preoperative manifest cylinder, the change in mean keratometry and the difference in thickness between the inferior and superior segments. Thicknesses were inversely correlated with the preoperative cylinder and the keratometric change. This means that the thicker the segment, the higher the keratometric change was. However, this effect was limited by the preoperative manifest cylinder of the eye which seems to be in relation with the instability of the keratoconic cornea. The third implicated factor, the difference in thickness between the inferior and superior segments represents the interaction between both ring segments and it was positively correlated with the thickness of the inferior ring segment, but inversely correlated with the thickness of the superior ring segment. This means that the most positive combination for KeraRing consists of a superior ring segment thinner than the inferior implant. The goodness of fit of these models was confirmed by testing the homoscedasticity of the models, the correlation between residuals and the multicollinearity. The predictability of the superior ring segment thickness model was good, with 91.23% of unstandardized residuals below 100 μm and 63.16% below or equal to 50 μm. However, the predictability of the inferior ring segment thickness model was moderate, with 87.72% of unstandardized residuals below 100 μm and 63.16% below or equal to 50 μm.

Furthermore, a new multiple regression analysis was performed including only the sample of eyes with examination of corneal aberrations, which was smaller because this kind of exam was only performed in two of the participating centers in this study. In spite of using a smaller sample, the predictability of the models for the thicknesses of the superior and inferior ring segments improved. For both models the same influencing factors were detected (preoperative cylinder, keratometric change and difference in thickness between inferior and superior ring segments), but an additional aberrometric parameter was included, the change in the RMS value corresponding to the corneal higher order aberrations (negative correlation). Thinner segments would be necessary in those cases where the required reduction in corneal higher order aberrations is lower (cases with lower preoperative levels of higher order aberrations). In contrast, thicker segments would be necessary in the most highly aberrated corneas. It has been previously demonstrated that the visual outcome with ICRS implanted using a standard nomogram for all cases was inversely correlated with the magnitude of some corneal higher order aberrations[2,36]. It should be considered that larger amounts of corneal higher order aberrations are present in the more advanced keratoconic corneas[32,37]. In such cases, the biomechanical alteration seems to be more pronounced. Indeed, in a previous work of our research group we found a significant correlation between the CRF parameter measured with the Ocular Response Analyzer (ORA) and the magnitude of corneal spherical-like aberrations[37]. All the topographic and aberrometric alterations in keratoconic eyes are the consequence of the biomechanical changes which occur in the corneal structure. Therefore, the improvement in the predictability of the models for the ring segment thicknesses when including the corneal higher order aberrations could be the consequence of introducing an additional factor in relation with the corneal biomechanical status. In other words, the introduction of the aberrometric factor could be an indirect manner of considering part of the corneal biomechanical factor. In any case, this indirect contribution of aberrometry to corneal biomechanics is limited and it is not accounting for the total biomechanical effect. The predictability of the superior ring segment thickness model including corneal aberrations was quite good, with 92.68% of unstandardized residuals below 100 μm and 75.61% below or equal to 50 μm. The predictability of the model for the thickness of the inferior segment was also good but a little bit more limited, with 90.24% of unstandardized residuals below 100 μm and 68.29% below or equal to 50 μm.

Finally, we performed the analysis of the residuals for the four developed multiple linear models. Although the predictability was acceptable for all models, there were few cases with residuals of 100 μm or more. In such cases, the use of this nomogram would not be appropriate, leading to poorly predictable result. Specifically, we have found that those cases with residuals higher than 50 microns presented higher levels of corneal higher order aberrations. Higher RMS values for corneal spherical-like aberrations were found in those cases with the highest residuals. This aberrometric parameter was found to be inversely correlated with one biomechanical parameter provided by the ORA system, the CRF[37]. Therefore, it seems clear that the corneal biomechanical status is a limiting factor for the developed nomogram and would have significant relevance in the more advanced keratoconic cases. Currently, there is no nomogram for ICRS implantation considering the specific biomechanical properties of the cornea. One reason for this fact is that the analysis of the corneal biomechanical properties of the cornea in vivo is not an easy task in the clinical practice. To this date, only one device has been developed for the clinical evaluation of corneal biomechanics, the ORA system from Reichert[38]. This device is an adaptation of a noncontact tonometer, which allows the measurement of the intraocular pressure as well as two new metrics referred to as hysteresis (CH) and corneal resistance factor (CRF). The exact differences between these two biomechanical parameters, CH and CRF, as well as the exact contributions of the elastic and viscous components to the magnitude of these parameters are not still completely understood. However, in spite of not knowing the exact physical meaning of these parameters, CH and CRF have been proven to be very useful for characterizing the biomechanical properties of the cornea in the clinical practice[39]. Indeed, as previously commented, the keratometry and the magnitude of corneal higher order aberrations have been proven to be inversely correlated with the CRF in keratoconus[37].

Limitations of the current investigation should be also mentioned. One limitation is the retrospective character of this investigation, with no possibility of including cases following the same controlled postoperative protocol of measurements. For example, as commented, corneal aberrations were not obtained in all cases because different topographic devices were used and one of them was not able to derive aberrations directly. This fact limited the sample size available for the analysis of some clinical parameters. A second limitation was the two different incision criteria used in the study. It should be considered that there is no general agreement about which location for corneal incision is the better option. Different reference points have been described in the literature, such as the temporal position, the 12 o'clock position (superior), the axis of positive cylinder if it was not 90º away from topographic axis or the steepest topographic meridian[40]. To this date, there are no published studies comparing the visual, refractive and keratometric outcomes after ICRS implantation using some of these incision locations. Theoretically, the ideal location would be the steepest corneal meridian, as most of surgeons do currently, because this kind of incision would reduce the corneal power of the steepest meridian and it would increase the flattest keratometric reading. This would minimize the corneal and manifest astigmatism. However, significant reductions in manifest cylinder have been also achieved in eyes with the incision located on other locations[40]. In our study, an incision on the steepest corneal meridian was used in the great majority of cases, with very few cases with the incision distant from the steepest corneal meridian. We think that this factor could have introduced a very little variability in the outcome. Indeed, we have obtained very predictable models for the selection of the ring segments according to the intended corneal change and the preoperative conditions of the eye. Furthermore, the most important issue was the position of the ring segments and it was always parallel to the flattest corneal meridian.

In conclusion, KeraRing are useful for corneal modelling in keratoconus but their effect is not the same in all cases. The thickness of the implants are in relation with the keratometric change, but there are other factors accounting for the final effect, as the preoperative astigmatism or the preoperative level of corneal higher order aberrations. The selection of the ring segment to implant should not be based only on refraction and the subjective appearance of the corneal topographic pattern. Corneal aberrometry is an additional factor that should be considered in the selection of the ring segments to implant. Specifically, the thicknesses of the superior and inferior 160º arc-length KeraRing segments that should be implanted in a keratoconic case are significantly correlated with the preoperative manifest cylinder, the intended changes in mean keratometry and in the RMS value for corneal higher order aberrations, and also with the selected difference in thickness between the inferior and superior ring segments. We have obtained a consistent multiple linear model relating all these factors which only fails in the most highly aberrated or the most advanced cases. The predictability in these advanced cases are limited with the proposed nomograms and it seems the underlying significant biomechanical alteration necessitates a more complex mathematical model for characterizing the ring segment effect. In future studies the inclusion of a precise factor in the ICRS model accounting for the real biomechanical status should be performed. To achieve this, future developments in the field of corneal biomechanics are necessary in order to obtain an accurate instrument for evaluating corneal biomechanics, utilizing the standard physical concepts used for the description of the viscoelastic materials. In addition, the applicability of this modelization for the development of a new optimized nomogram for the clinical practice should be addressed in the future.

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Figure Legends

Figure 1.- Keratoconic cornea implanted with KeraRing segments with an arc-length of 160º. Upper figure: high resolution corneal image obtained by means of the Visante optical coherence tomography system (Zeiss). Lower figure: frontal image obtained with a slit-lamp biomicroscope.

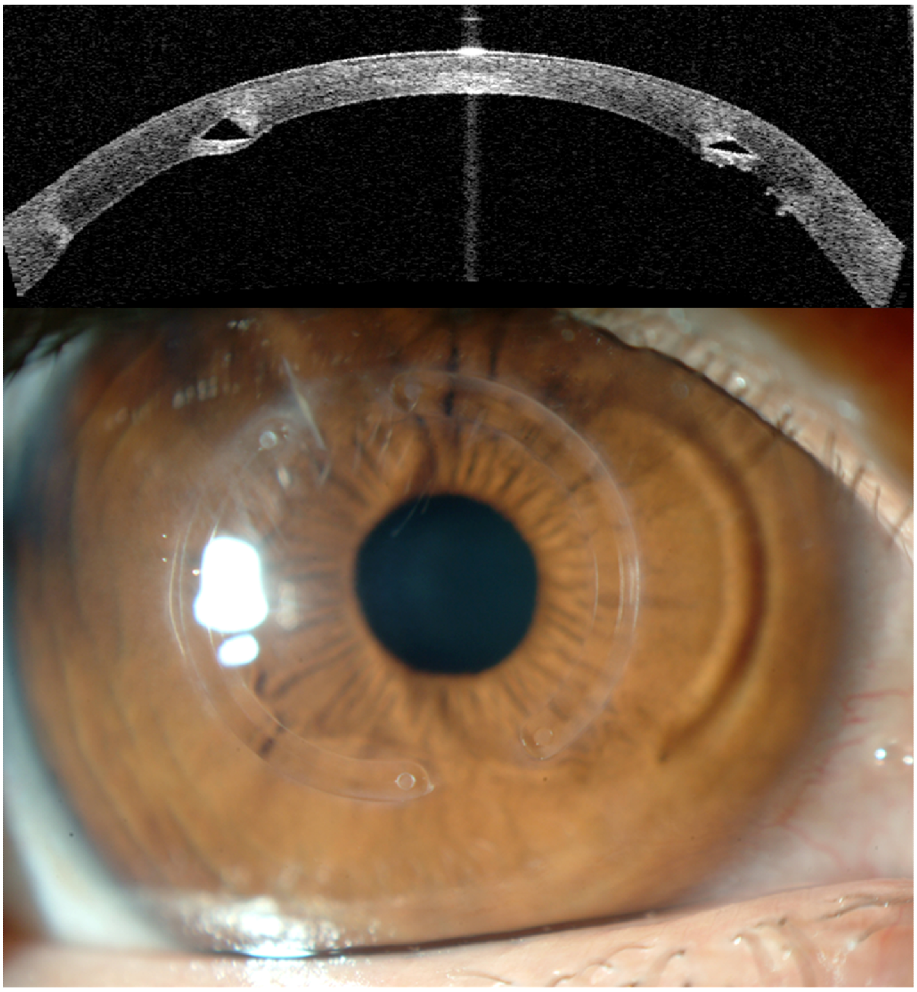


Figure 2.- Changes in keratometric parameters during the follow-up: corneal dioptric power in the flattest meridian for the 3-mm central zone (K1), corneal dioptric power in the steepest meridian for the 3-mm central zone (K2), and mean corneal power in the 3-mm zone (KM). A statistically significant reduction was observed in all keratometric parameters.

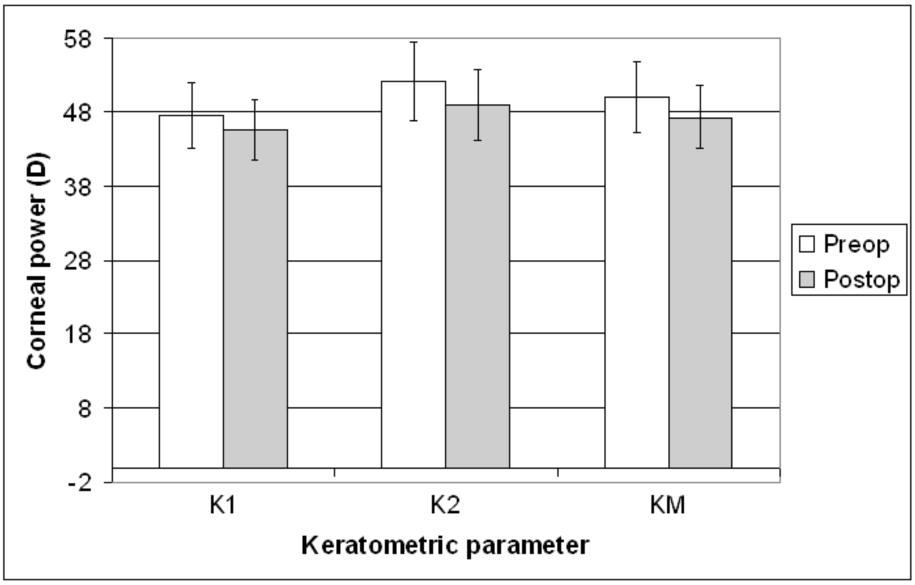


Figure 3.- Scattergrams showing the relationship between the change in mean keratometry (postop-preop) and the thickness of the superior (left) and inferior (right) ring segment. The adjusting line to the data obtained by means of the least-squares fit is shown in both graphs:

Change in mean keratometry (D) = -0.007 x Superior segment thickness (μm) - 1.239 (R^2: 0.129)

Change in mean keratometry (D) = -0.008 x Inferior segment thickness (μm) - 0.433 (R^2: 0.079)

Abbreviations: diopters, D.

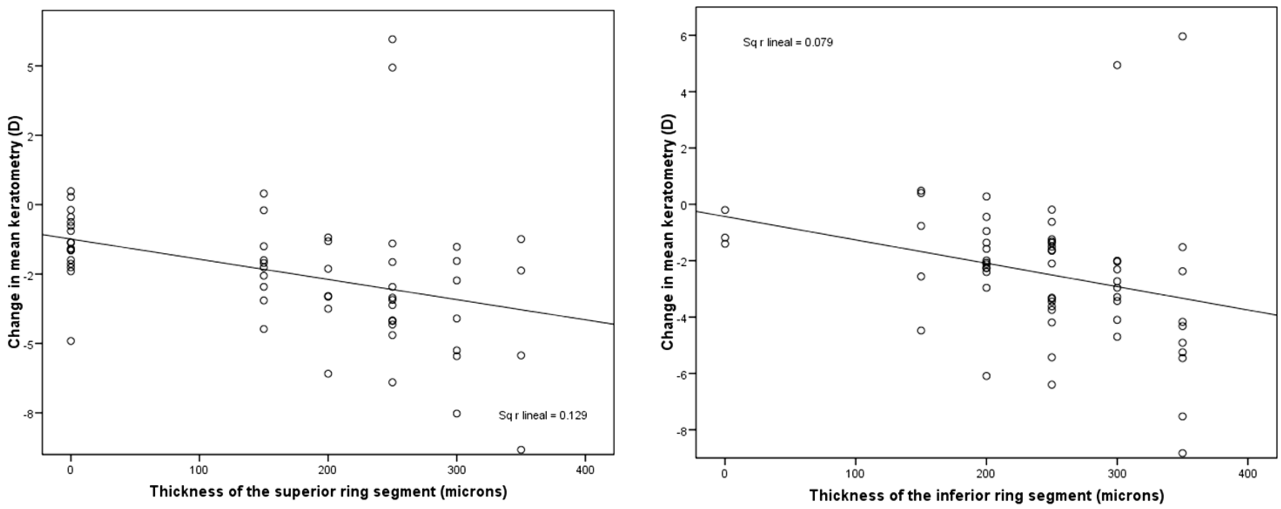
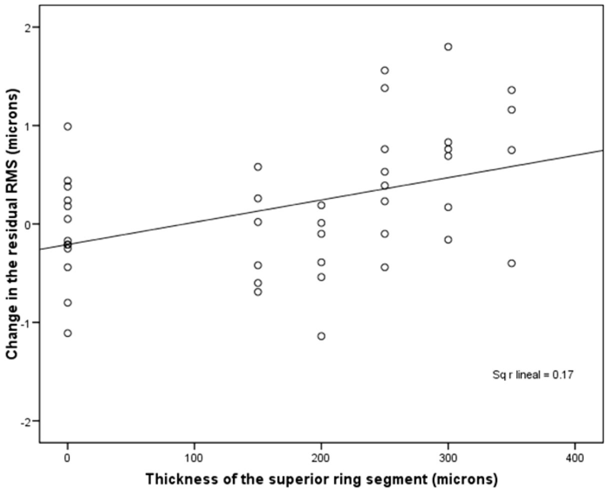


Figure 4.- Scattergrams showing the relationship between the change (postop-preop) in the RMS value for the corneal residual higher order aberrations (computed considering all Zernike terms except those corresponding with primary coma and spherical aberration) and the thickness of the superior (left) and inferior (right) ring segment. The adjusting line to the data obtained by means of the least-squares fit is shown in both graphs:

Change in residual RMS (μm) = 0.002 x Superior segment thickness (μm) - 0.209 (R^2: 0.170)

Change in residual RMS (μm) = 0.005 x Inferior segment thickness (μm) - 1.057 (R^2: 0.308)

Abbreviations: root mean square, RMS.



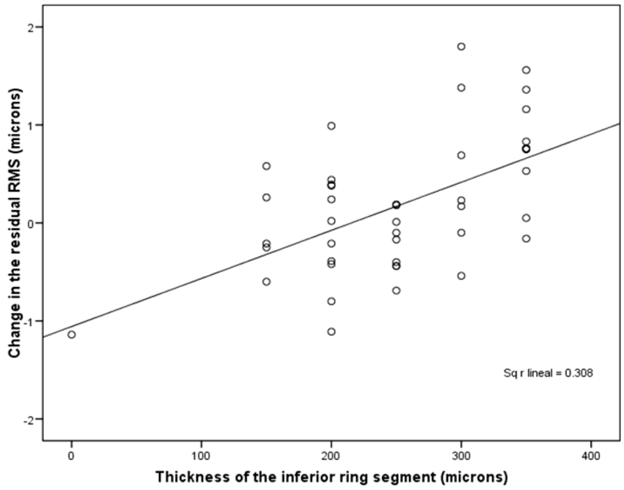
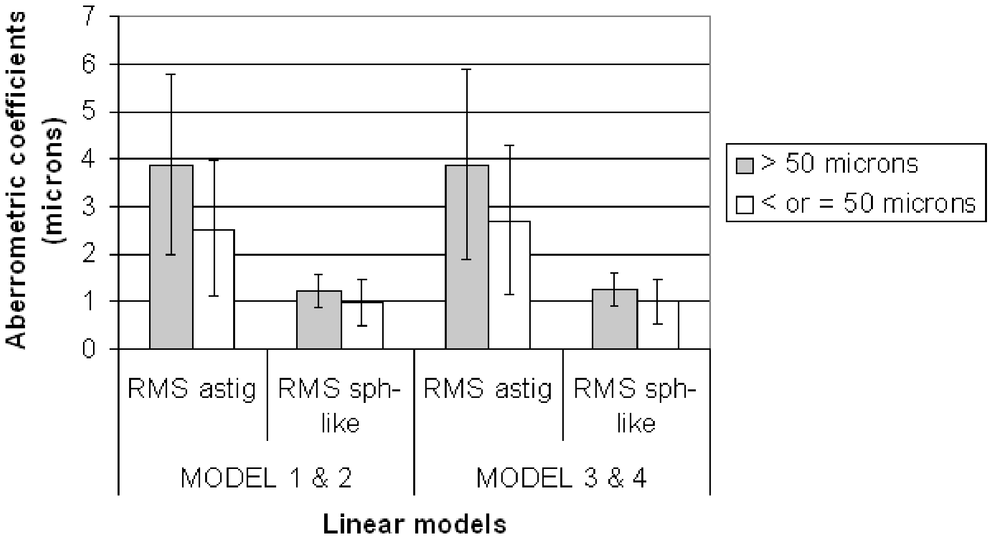


Figure 5.- Differences in corneal astigmatism and spherical-like aberrations between cases with unstandardized residuals higher than 50 microns (grey bars) and cases with residuals below or equal to 50 microns (white bars) for the four developed linear models in the current study (Model 1 & 2, models for the superior and inferior ring segment thickness without considering corneal aberrations; Model 3 & 4, models for the superior and inferior ring segment thickness considering the corneal aberrometric factor).



<u>TRABAJO 9:</u> ***Alió JL, Piñero DP, Sogutlu E, Kubaloglu A. Intracorneal ring segment reimplantation in keratoconus eyes with previous unsuccessful implants. J Cataract Refract Surg 2010 (accepted for publication)***

Ref.: Ms. No. JCRS-09-1185R2 Intracorneal ring segment reimplantation in keratoconus eyes with previous unsuccessful implants Journal of Cataract & Refractive Surgery

Dear Dr. Pinero,

The Editorial Board has accepted your (revised) manuscript Intracorneal ring segment reimplantation in keratoconus eyes with previous unsuccessful implants (JCRS-09-1185R2) for publication in the journal. As soon as it is scheduled for a particular issue, you will receive typeset pages to check.

Sincerely,

William J. Dupps, MD, PhD
Associate Editor
Journal of Cataract & Refractive Surgery

INTRACORNEAL RING SEGMENT REIMPLANTATION IN KERATOCONUS EYES WITH PREVIOUS UNSUCCESSFUL IMPLANTS

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None of the authors have any financial interests to disclose

This study has been supported in part by a grant from the Spanish Ministry of Health, Instituto Carlos III, Red Temática de Investigación Cooperativa en Salud "Patología ocular del envejecimiento, calidad visual y calidad de vida", Subproyecto de Calidad Visual (RD07/0062)

Abstract

PURPOSE: To evaluate the visual, refractive and corneal aberrometric outcomes in keratoconic eyes which underwent intracorneal ring segment (ICRS) reimplantation following a previous segment explantation due to an unsuccessful outcome

SETTING: Vissum Corporation, Alicante, Spain

METHODS: Retrospective non-randomized case series study including a total of 21 consecutive eyes of 21 patients with ages ranging from 18 to 64 years. All cases had the initial diagnosis of keratoconus and were implanted with ICRS in order to manage the corneal irregularity. In all cases the initial ring segments were explanted due to an unsuccessful outcome (extrusion, poor visual outcome or others) and a new ICRS combination was implanted afterwards. A complete ophthalmic examination was performed in all eyes before and 1 month after the initial ICRS implantation, before explantation, and 1 month and 6 months after reimplantation.

RESULTS: A significant improvement in uncorrected visual acuity (UCVA) was observed 1 month after reimplantation ($p=0.03$). Accordingly, a significant improvement in manifest refraction was observed 1 month after reimplantation ($p\leq0.04$). Significant differences were found in the keratometric readings among the preoperative condition and 6 months after reimplantation ($p\leq0.01$). Additionally, a significant corneal aberrometric improvement was also observed after reimplantation ($p\leq0.03$). When comparing eyes with explants due to extrusion and those due to poor visual outcomes, no statistically significant differences were found in any visual, refractive, keratometric or aberrometric parameter ($p\geq0.07$).

CONCLUSIONS: A significant visual and refractive improvement can be achieved with the implantation of a new intracorneal ring segment combination after a previous unsuccessful implantation.

FINANCIAL DISCLOSURE: None of the authors have any financial interest to disclose

Introduction

Intrastromal corneal ring segments (ICRS), which were initially developed for the correction of mild to moderate myopia[1], are now being investigated for the management of keratoconus[2-20] and other ectatic disorders such as the post-laser in situ keratomileusis ectasia[21-29] or the pellucid marginal degeneration.[30-36] The ring segment acts as a passive element that flattens the central cornea due to the "arc-shortening effect" induced on the corneal lamellae structure.[37] Several authors have stated recommendations about its use for the management of keratoconus (for example, the existence of central clear cornea) and have reported favourable outcomes such as decreased corneal surface irregularity, improved spectacle-corrected vision and a delayed need for keratoplasty.[2-20]

Although ICRS implantation is an effective surgical procedure for the management of the corneal ectatic disease, several complications associated to this surgical procedure have been described, such as incomplete tunnel creation, anterior or posterior corneal perforation, epithelial defects, ring segment extrusion and induced astigmatism by central migration of the ICRS along the horizontal corneal diameter.[2,8,9,12,38,39] In most of these cases the explantation of the ring segment is mandatory, with the possibility of a future reimplantation of a more appropriate insert. One of the main postulated advantages for the surgical technique is its potential reversibility because it is a non-tissue-removal procedure. This fact has been previously demonstrated in low and moderate myopic eyes.[40] In addition, the reversibility of the ICRS implantation in keratoconic eyes was also confirmed in 2004[41]. In this case series the authors also support that explantation of the segment was not a contraindication for reimplantation.

The purpose of the present study was to evaluate the visual, refractive and corneal aberrometric outcomes in keratoconic eyes which underwent ICRS reimplantation following a previous segment explantation. To the best of our knowledge, this is the first study that attempts to analyze the corneal aberrometric changes occurring in corneas reimplanted with ICRS.

Patients and methods

Patients

A retrospective chart analysis of outcomes of patients who underwent ICRS explantation followed by the reimplantation of new ring segments from June 2001 to September 2008 in two different centers (Vissum/Instituto Oftalmológico de Alicante, Spain and Kartal Training and Research Hospital, Istanbul, Turkey) was performed. All cases had the initial diagnosis of keratoconus and were implanted with ICRS in order to manage the corneal irregularity. Keratoconus diagnosis was based on corneal topography and slit-lamp observation: asymmetric bowtie pattern with or without skewed axes and the presence of stromal thinning, conical protrusion of the cornea at the apex, Fleischer ring, Vogt striae or anterior stromal scar[42]. A total of 21 consecutive eyes of 21 patients with ages ranging from 18 to 64 years (mean age of 35.95 ± 12.87 years) were included. This study was approved by the local ethical committees of each centre. In addition, during the process of consent for each surgery, patients gave consent to later include clinical information in scientific studies.

Follow-up examinations

A complete ophthalmic examination was performed in all eyes before and 1 month after ICRS implantation, before explantation, and 1 month and 6 months after reimplantation including uncorrected visual acuity (Snellen decimal notation), best spectacle corrected visual acuity (Snellen decimal notation), manifest spherical and cylindrical refraction, corneal topographic and aberrometric analysis. Regarding the corneal topographic analysis, two different devices were used: the CSO system (Costruzione Strumenti Oftalmici, Firenze, Italy), which is a placido-based topographer and the Orbscan II system (Bausch & Lomb, Rochester, NY), which is a combined scanning-slit and Placido-disc topography system. The first topographic device was used for monitoring the follow-up in 18 eyes whereas the Orbscan II system in only 3 eyes. The following topographic data were recorded with both corneal topographic devices: the flattest corneal dioptric power for the 3-mm central zone (K1), the steepest corneal dioptric power for the 3-mm central zone (K2), and the mean corneal power in the 3-mm zone (KM).

Corneal aberrometry was also recorded and analyzed only in those patients examined with the CSO topography system (CSO, Firenze, Italy) (18 eyes), because this device has the capability to calculate directly this specific information. The software of this topographic system, the EyeTop 2005, automatically performs the conversion of the corneal elevation profile into corneal wavefront data using the Zernike polynomials with an expansion up to the seventh order. The corneal aberration coefficients and root mean square (RMS) values were calculated for a 6-mm pupil. The following parameters were evaluated and recorded: higher order RMS, RMS for astigmatism, primary coma RMS (computed for the Zernike terms Z3±1), coma-like RMS (computed for third, fifth, and seventh-order Zernike terms), spherical-like RMS (computed for fourth and sixth-order Zernike terms), higher-order residual RMS (computed considering all Zernike terms except those corresponding with primary coma and spherical aberration) and Z40 (corresponding Zernike coefficient for primary spherical aberration).

Surgical procedure

All surgical procedures were performed under topical anesthesia by a total of two experienced surgeons (JLA and AK). The creation of corneal tunnels for the first ICRS insertion was performed by means of a mechanical dissection in 11 eyes (52.3%) and by means of femtosecond technology in 10 eyes (47.6%). The same method for corneal tunnelization was used for reimplantation in 16 eyes: (mechanical; 6 eyes, 28.6%; femtosecond laser; 10 eyes, 47.6%). In 5 eyes (23.8%), ring segments were implanted first using the mechanical technique, whereas reimplantation was performed with the femtosecond laser.

Mechanical tunnel creation

For KeraRing (Mediphacos, Belo Horizonte, Brazil) cases the mechanical surgical procedure was as follows. The Purkinje reflex was chosen and marked as a reference point, corneal thickness was measured by ultrasonic pachymetry at the 5-mm corneal diameter zone, and then ring location area was marked. The entry incision was made on the steepest corneal topographic axis with using a diamond blade. The intrastromal corneal tunnel depth was set at 70% of the thinnest corneal thickness. A suction ring (Moria Inc, USA) was placed to minimise decentration. The corneal tunnel was then created by using a counterclockwise and clockwise spatula.

For Intacs (Addition Technology, Fremont, California, USA), the same surgical procedure was followed but the tunnel was created with an inner and outer diameters of 6.6 and 7.8 mm, respectively.

Femtosecond-assisted tunnel creation

The intrastromal corneal tunnel entry was made on the steepest corneal axis using the 15 kHz femtosecond laser (IntraLase, Advanced Medical Optics Inc., Santa Ana, California, USA). The tunnel depth was set at 70% of the thinnest corneal thickness. The inner to outer diameter of KeraRing tunnels was set from 4.8 mm to 5.6 mm, the ring energy used for channel creation was 1.30 μj, and the entry cut energy was 1.30 μj. For Intacs implantation, the inner to outer diameter was set from 6.8 to 7.8 mm and the energy was set at 6 μj .

Segment explantation

In cases of poor visual outcome, corneal neovascularization and night vision disturbances, not progressive corneal steepening, aberrometric increase or corneal thinning was observed after the first implantation. The period of time between the initial implantation and the explantation varied from 1 to 84 months (Median: 6 months). Specifically, in 11 eyes (52.38%) ring segment explantation was performed 6 months after the initial explantation or sooner, and in 7 eyes (33.33%) explantation were performed during the first 3 months after the initial implantation. Only in 2 cases (9.52%) explantation was done 24 months after the initial surgery.

In those cases suffering ring segment extrusion, the extruded side of the segment was pulled out with forceps and then a Sinskey hook was introduced to grab the segment at its distal end near the wound. After grabbing the segment, it was easily pulled out of the corneal tunnel. In the remaining cases (poor visual outcome, corneal neovascularization and night vision disturbances), ring segment explantation was also easily performed by grabbing one segment edge through the incision entry and pulling out the segment. No sutures were needed afterwards in any case. The interval between ring segment explantation and reimplantation varied depending on the case. There were cases where the reimplantation was performed immediately after the previous ring segment explantation and cases where the reimplantation was performed at a specific point of time after the explantation (from 1 to 12 months afterwards). In cases of night vision disturbances or poor visual outcome, a 3-month follow-up was always completed before explantation in order to assess the evolution of the case and the patient's visual adaptation.

After all procedures, lomefloxacine and dexametasone eye drops were prescribed four times a day postoperatively as a prophylactic treatment as well as artificial tears six times a day for three weeks.

Ring segment selection

The selection of the number (1 or 2) and thickness of the initial implantation of Intacs segments was performed following the criteria defined and reported by our research group[43]. Regarding KeraRing, arc-length, thickness and number of segments were selected considering the nomogram defined by the manufacturer.

In those cases explanted due to a poor postoperative visual outcome, different criteria were followed for the selection of the reimplanted ring segment combination: change from Intacs to KeraRing (3 eyes, 27.27%), insertion of new inferior ring segment with larger arc-length (change from 160º to 210º) (2 eyes, 18.18%), elimination of the superior ring segment and introduction of a new inferior ring segment (3 eyes, 27.27%), insertion of a thicker inferior segment (2 eyes, 18.18%), and rotation of the ring segment (2 eyes, 18.18%). In the rest of cases, the same criteria used for the initial implantation was followed (our Intacs nomogram or KeraRing manufacturer nomogram).

Statistical analysis

SPSS statistics software package version 15.0 for Windows (SPSS, Chicago, Illinois, USA) was used for statistical analysis. Normality of all data samples was firstly checked by means of Kolmogorov-Smirnov test. When parametric analysis was possible, the Student t test for paired data was performed for all parameters comparisons between preoperative and postoperative examinations or consecutive postoperative visits (preoperative, 1 month postoperative, before explantation, 1 and 6 months after reimplantation) whereas the Student t test for unpaired data was performed to compare the outcomes obtained after reimplantation in two groups of eyes, those explanted due to ring segment extrusion and those explanted due to a poor visual outcome with the initial implants. When parametric analysis was not possible, the Wilcoxon Rank Sum test was applied to assess the significance of differences between preoperative and postoperative data and the Mann-Whitney test was performed for the comparison of outcomes between independent groups, using in all cases the same level of significance ($p<0.05$).

Results

The contribution of the two participating centres to the current study was as follows: 18 eyes from Vissum Alicante and 3 eyes from Kartal Training and Research Hospital, Istanbul. All cases included in the current study were unilateral. There was a balanced distribution of right and left eyes (9 eyes vs. 12 eyes). Cone opacity was observed only in 2 cases (9.5%). According to the Amsler-Krumeich grading system, 6 eyes had a cone grade I (28.6%), 5 eyes a cone grade II (23.8%), 4 eyes a cone grade III (19.0%) and 6 eyes a cone grade IV (28.6%). Considering the corneal aberrations and according to the Alió-Shabayek grading system, 3 eyes had a cone grade I (14.3%), 3 eyes a cone grade II (14.3%), 3 eyes a cone grade III (14.3%) and 7 eyes a cone grade IV (33.3%).

A total of 16 eyes (76.19%) were implanted with ICRS and reimplanted again with ring segments after the explantation of the initial insert by using the same surgical technique for corneal tunnelization, mechanical (6 eyes, 28.6%) or femtosecond-guided procedure (10 eyes, 47.6%). Only in 5 eyes (23.8%) ring segments were implanted initially using the mechanical dissection, whereas reimplantation were performed by means of the femtosecond laser technology. Regarding the ring segment type, 9 eyes (42.86%) were implanted and reimplanted after explantation with the same ring segment type (KeraRing, 6 eyes, 28.6%; Intacs, 3 eyes, 14.3%), whereas in the remaining cases the ring segment profile was changed (Intacs to KeraRing, 7 eyes, 33.3%; KeraRing to Intacs, 23.8%).

Regarding the cause of explantation and posterior reimplantation, four different factors were reported: ring segment extrusion (7 eyes, 33.3%), very poor visual outcome (11 eyes, 52.4%), corneal neovascularization (2 eyes, 9.5%), and significant night visual disturbances as glare or halos (1 eyes, 4.8%).

Visual and refractive outcomes

No significant changes were observed in any visual and refractive parameters after the first implantation of ring segments (Wilcoxon and paired Student t tests; UCVA, p=0.26; Sphere, p=0.33; Cylinder, p=0.81; BSCVA, p=0.55) (Table 1). However, a significant reduction in sphere and cylinder was observed at 1 month after explantation and ring segment reimplantation (Wilcoxon test; Sphere, p=0.04; Cylinder, p=0.01). In addition, a significant uncorrected visual improvement could also be observed 1 month after reimplantation (Paired Student t tests, p=0.03). No significant changes were observed in BSCVA after reimplantation (Wilcoxon test, p=0.03). During the rest of follow-up, no statistically significant changes were observed in any visual and refractive parameter (Wilcoxon and paired Student t tests; UCVA, p=0.47; Sphere, p=0.08; Cylinder, p=0.69; BSCVA, p=0.06), although a trend to an improved BSCVA at 6 months after reimplantation was observed (Table 1).

In addition, the visual and refractive outcomes were analyzed separately in groups according to the reason for explantation. As only 2 cases were explanted due to corneal neovascularization and 1 case due to night disturbances, the comparative analysis was solely performed for the cases of extrusion and poor visual outcome. Before explantation, no statistically significant differences were found in any visual and refractive parameter (Mann-Whitney test, p≥0.15). This trend was mantained during the follow-up after reimplantation (Mann-Whitney test, 1 month, p≥0.51; 6 months, p≥0.53).

Keratometric outcomes

Mean and flattest keratometric readings were significantly reduced 1 month after the first implantation procedure (Paired Student t test, p<0.01) (Figure 1). However, the steepest keratometric reading did not experienced a significant change (Paired Student t test, p=0.16). 1 month after explantation and the posterior reimplantation of ring segments, keratometric readings were not modified significantly (Paired Student t test, p≥0.71). At 6 months after the second implantation, keratometric readings slightly decreased although changes did not reach statistical significance (Paired Student t test, p≥0.07). When the keratometric reading 6 months after reimplantation were compared with the preoperative condition (before all surgical procedures), significant differences were found (Paired Student t test, p≤0.01)

After explantation and before ring segment reimplantation, statistically significant differences were found in the steepest keratometric reading between explanted cases due to ring segment extrusion and explanted cases due to a poor visual outcome which showed the lowest values (Mann-Whitney test, p=0.04) (Figure 2). After ring segment reimplantation, no statistically significant differences in any keratometric reading was found between explantation groups (Mann-Whitney test, p≥0.07), although a non-significant trend to higher values of K2 was observed post-reimplantation in those cases explanted due to ring extrusion (Figure 2).

Corneal aberrometric outcomes

Regarding corneal aberrations (Table 2), no significant changes were detected in any corneal aberrometric parameter after the first surgery (Wilcoxon and paired Student t test, p≥0.11) in spite of existing a slight reduction of the comatic component. After ring segment explantation and the reimplantation of a new ring segment combination, significant changes were detected in the RMS values corresponding to the primary coma (Wilcoxon test, p=0.01), higher order residual (Wilcoxon test, p=0.01), spherical-like (Wilcoxon test, p=0.02) and coma-like aberrations (Wilcoxon test, p=0.03) (Table 2). Specifically, primary coma and coma-like aberrations were reduced and the spherical-like and higher order residual aberrations were increased. Between month 1 and month 6, RMS values for spherical-like (Paired Student t test, $p<0.01$) and higher order residual aberrations (Wilcoxon test, $p=0.01$) decreased significantly. In addition, a change of the primary spherical aberration in the limit of statistical significance towards less negative values was also observed (Wilcoxon test, $p=0.05$).

When comparing the aberrometric outcomes between explanted cases due to ring segment extrusion and explanted cases due to a poor visual outcome, no statistically significant differences could be observed (Wilcoxon test, $p\geq0.07$). In any case, a trend to a higher magnitud of coma-like and higher order residual aberrations (Wilcoxon test, $p=0.20$) was observed after explantation and before reimplaintation in those cases explanted due to ring segment extrusion, but it did not reach statistical significance. In addition, primary spherical aberration was less negative on average in cases of extrusion, but changes did not reach statistical significance (Wilcoxon test, $p=0.07$). It should be considered that not in all cases aberrometric examination was performed. Specifically, it was only done in 7 eyes of each group. This aberrometric trend after explantation was also observed during the follow-up after ring segment reimplantation.

Complications

No ring extrusion or migrations were observed after ring segment reimplantation during the follow-up. In 4 cases (19.05%) a residual haze in the area where the explanted rings were placed remained 6 months after surgery in spite of corticosteroid therapy.

Discussion

The safety and efficacy of ICRS implantation for the management of keratoconus has been previously demonstrated in several clinical trials.[2-20] These implants placed circumferentially into two-thirds depth of the peripheral corneal stroma are able to correct the ectatic corneal protrusion by flattening the center of the cornea through an arc-shortening effect. ICRS do not involve direct manipulation of the central cornea or tissue removal and therefore the outcome of the procedure seems to be not so dependent on the individual wound-healing characteristics. The outcome of this corneal remodelling should be mainly dependent on the biomechanical properties of the corneal tissue. The human cornea is a viscoelastic tissue[44] due to its structural properties and then it has a response in the presence of a force. This corneal response depends on this force magnitude and also on the velocity of the force application (biomechanical behaviour). A specific ring segment inducing a specific force to the cornea will generate different changes in the ectatic corneal profile, depending on the underlying corneal biomechanical status. Theoretically, the cornea should have the ability of returning to its original state after stopping the force application (explantation of the ring segment). In addition, it should be able to be remodelled again with other combination of forces (new ring segments implanted). The main objective of this study was to demonstrate if a cornea implanted with ICRS and with a poor or inappropriate outcome can be reimplanted again (after initial ICRS explantation) with a new combination of ring segments. For this reason, we have evaluated the visual, refractive and corneal aberrometric outcomes in case series of keratoconic eyes which underwent ICRS reimplantation following a previous segment explantation.

It has been demonstrated in previous studies that the refractive and topographic changes induced by ICRS are reversible after explantation of the segments[41]. Alió and colleagues safely and effectively extracted the segments from 5 eyes due to problems of corneal melting and segment extrusion[41]. In two of these cases new ring segments were implanted 6 months after the explantation procedure, with visual improvement and reduction of the refractive component. In concordance with these findings and supporting the idea of the reversibility, Samimi et al[45] demonstrated that the histological effects of ICRS implantation were also reversible after segment removal. Regarding the initial use of Intacs for myopia correction, the U.S. clinical trials reported promising results from a few patients who had an Intacs exchange procedure.[46,47] Furthermore, successful Intacs exchanges in 2 myopic patients because of undercorrection and patient dissatisfaction were reported in another study[48]. In these both cases, an improvement in UCVA (3 to 5 lines) and decreased residual myopia was observed after the exchange procedure. In our cases series, a statistically significant reduction was also found in spherical and cylindrical refraction after reimplantation. This refractive improvement was concordant with the significant improvement in UCVA also observed. Regarding the BSCVA, there was a trend to an improved BSCVA at 6 months after reimplantation, but this change did not reach statistical significance.

As expected considering previous evidence[2-12,43], a significant flattening was observed after the first implantation procedure. Specifically, a significant change was only found for the flattest keratometric reading. This implied a negative effect on astigmatism. Indeed, if the flattest keratometric reading decreased and the steepest value did not change, the astigmatism was expected to increase. Therefore, the refractive results were poor, with no significant change in sphere, cylinder and visual acuity. After reimplantation, no significant keratometric changes were observed, although post-reimplantation keratometric readings were significantly flatter than the preoperative. One reason for this fact could be the differences in the interval between ring segment explantation and reimplantation for each case (from 1 to 12 months). Probably, there were cases where the cornea did not return completely to its original state when the new ring segments were implanted. In any case, a significant refractive change on average was observed.

An interesting report of this series was the evaluation of the corneal aberrometric change after ICRS reimplantation. To the best of our knowledge, this is the first study providing such analysis. It should be remembered that the anterior corneal aberrometric analysis is a very important tool in the clinical practice for evaluating the ocular optical quality because the first refractive interface (air-cornea) is the most important contributor to the total power of the eye because of the large difference in refractive index existing at this point. In highly aberrated corneas, the corneal aberrations of the anterior corneal surface are the most important sources of optical errors in the eye. In the current study, after ring segment explantation and the reimplantation of a new ring segment combination, significant reduction were detected in the primary coma and coma-like aberrations during the 6-month follow-up. In addition, the primary spherical aberration showed a change toward less negative values. Therefore, although no significant changes occurred in keratometry, corneal irregularity was reduced significantly with the reimplantation. It seems that one reason for the bad visual outcome with the first implant was the presence of a significant corneal irregularity which induced a relevant retinal blur. It should be considered that a ring segment extrusion was previously demonstrated to be a significant source of corneal aberrations[2].

In this study, a comparative analysis of the outcomes considering the cause of explantation was also performed. As only 2 cases were explanted due to corneal neovascularization and 1 case due to night vision disturbances, the comparative analysis was only performed for two groups: reimplanted cases after ring segment extrusion and reimplanted cases with a poor visual outcome with the first implant. No significant differences between groups were found in any visual and refractive parameter after explantation and also after reimplantation. However, after explantation, ring segment extrusion cases showed significantly higher steepest keratometric readings than poor visual outcome cases. After reimplantation a similar trend was observed although the difference did not reach statistical significance. Regarding corneal aberrations, a trend to higher amounts of corneal higher order aberrations was observed in the ring segment extrusion cases, as expected, but the difference did not reach statistical significance.

The explantation was feasible in all cases and no intraoperative complications occurred. The ring segments were extracted safely and easily from the keratoconic corneas. A faint channel haze persisted after removal in some cases several months after the explantation. However, this haze did not affect the visual function and it seemed to decrease over time.

In conclusion, a significant visual and refractive improvement can be achieved with the implantation of a new ring segment combination after a previous unsuccessful implantation. Part of this improvement is due to the more efficacious control of corneal irregularity achieved with the new implant. Therefore, ICRS explantation does not seem to be a contraindication for reimplantation in cases with no pathological sequelae. Indeed, in this study similar visual, refractive and aberrometric evolution was observed in cases with ICRS explantation due to ring segment extrusion and due to poor visual outcomes. In future studies, new implantation criteria with a scientific basis should be developed for those cases with a poor visual outcome and significant irregularity using the manufacturer’s nomogram. Probably these corneas failing with the nomogram present a significantly different corneal biomechanical behaviour and then new implant requirements are needed.

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Figure legends

Figure 1.- Changes in keratometric parameters during the follow-up: corneal dioptric power in the flattest meridian for the 3-mm central zone (K1) (grey line), corneal dioptric power in the steepest meridian for the 3-mm central zone (K2) (white line), and mean corneal power in the 3-mm zone (KM) (dotted line).

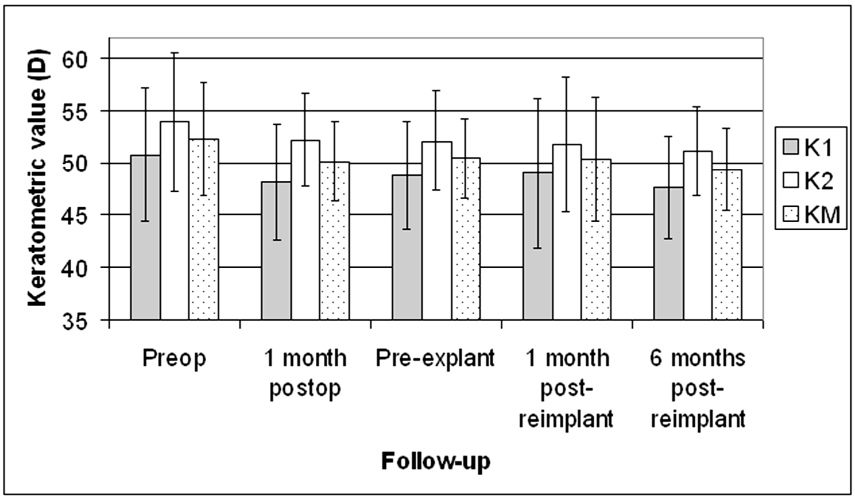

Figure 2.- Differences in the keratometric readings during the follow-up between explanted cases due to ring segment extrusion and explanted cases due to a poor visual outcome. Notations: corneal dioptric power in the flattest meridian for the 3-mm central zone (K1) (grey line), corneal dioptric power in the steepest meridian for the 3-mm central zone (K2) (white line), and mean corneal power in the 3-mm zone (KM) (dotted line).

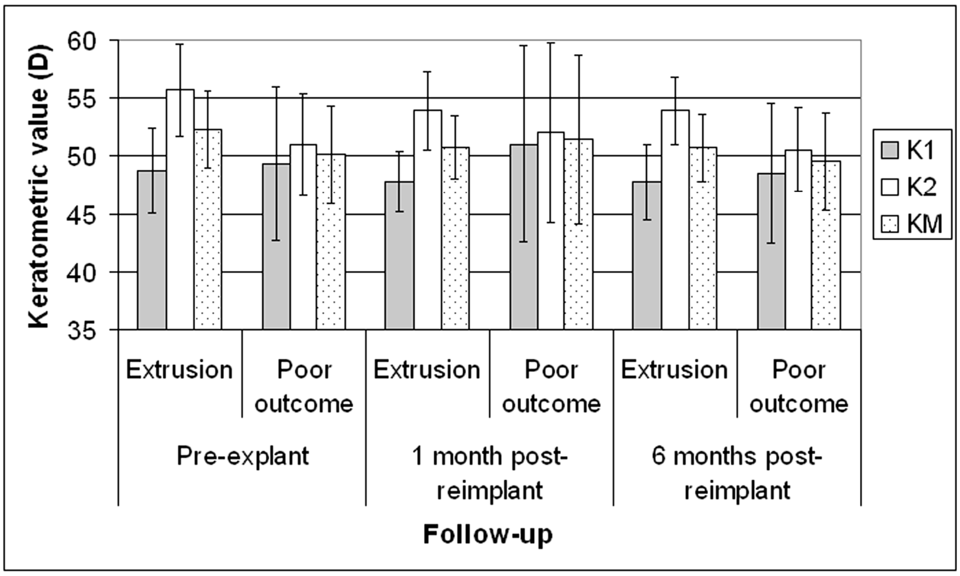

Table 1.- Summary of the refractive outcomes during the follow-up.

Parameter (range)	Preop	1 month postop	Pre-explant	1 month post-reimplant	6 months post-reimplant
UCVA	0.97 ± 0.58 (0.30, 2.00)	0.83 ± 0.42 (0.10, 1.70)	0.90 ± 0.34 (0.47, 1.48)	0.61 ± 0.39 (-0.02, 1.30)	0.58 ± 0.30 (0.05, 1.30)
Sphere (D)	-3.53 ± 4.10 (-12.00, +2.50)	-2.41 ± 3.94 (-14.00, +1.50)	-1.93 ± 3.37 (-9.00, +3.00)	+0.25 ± 1.73 (-4.00, +3.00)	-1.08 ± 3.04 (-7.00, +5.25)
Cylinder (D)	-3.88 ± 1.96 (-7.00, 0.00)	-3.42 ± 2.39 (-9.00, 0.00)	-4.56 ± 2.33 (-9.00, 0.00)	-3.52 ± 2.40 (-10.00, -1.00)	-3.55 ± 1.44 (-6.00, -1.50)
BSCVA	0.49 ± 0.41 (0.00, 1.78)	0.42 ± 0.22 (0.00, 0.82)	0.41 ± 0.28 (0.05, 1.30)	0.34 ± 0.19 (0.00, 0.70)	0.26 ± 0.16 (0.00, 0.52)

* Ranges are shown in brackets below each mean value.

* Abbreviations: D, diopters; UCVA, uncorrected visual acuity; BSCVA, best spectacle-corrected visual acuity.

Table 2.- Summary of the corneal aberrometric outcomes during the follow-up.

Parameter (range)	Preop	1 month postop	Pre-explant	1 month post-reimplant	6 months post-reimplant
Higher order RMS (μm)	4.22 ± 1.21 (2.25,5.91)	3.81 ± 1.27 (1.76,5.97)	4.28 ± 1.68 (1.55,7.26)	3.85 ± 1.52 (1.06,6.09)	3.63 ± 1.28 (1.90,5.30)
RMS for astigmatism (μm)	3.95 ± 2.11 (0.48,7.35)	3.43 ± 1.68 (0.44,5.81)	3.50 ± 2.08 (0.51,7.86)	3.14 ± 1.92 (0.51,8.15)	3.41 ± 1.73 (1.83,7.32)
Z_4^0 (μm)	-0.52 ± 0.84 (-2.74,0.57)	0.10 ± 0.95 (-1.62,2.03)	-0.64 ± 0.84 (-2.91,0.23)	-0.66 ± 1.42 (-4.34,1.02)	-0.30 ± 0.87 (-1.71,1.26)
Primary coma RMS (μm)	3.76 ± 1.19 (1.71,5.29)	3.19 ± 1.27 (1.53,5.27)	3.54 ± 1.77 (0.48,6.68)	2.77 ± 1.16 (0.64,4.80)	3.00 ± 1.29 (1.06,4.84)
Residual RMS (μm)	1.60 ± 0.51 (0.97,2.71)	1.73 ± 0.75 (0.76,3.20)	1.92 ± 0.88 (0.72,3.89)	2.17 ± 1.02 (0.62,4.65)	1.75 ± 0.74 (0.96,3.61)
Spherical-like RMS (μm)	1.19 ± 0.65 (0.40,2.46)	1.33 ± 0.64 (0.42, 2.52)	1.45 ± 0.89 (0.33,3.27)	1.81 ± 1.24 (0.38,4.89)	1.25 ± 0.68 (0.04,2.57)
Coma-like RMS (μm)	4.01 ± 1.18 (2.20,5.60)	3.52 ± 1.26 (1.68,5.62)	3.98 ± 1.54 (1.51,6.82)	3.31 ± 1.20 (0.89,5.27)	3.37 ± 1.21 (1.90,5.08)

* Ranges are given in brackets below each mean value.

* Definitions of each kind of corneal aberration: primary coma, Zernike terms $Z_3^{\pm 1}$; primary spherical aberration, Zernike term Z_4^0; residual aberrations, all Zernike terms except $Z_3^{\pm 1}$ and Z_4^0; spherical-like aberrations, Zernike terms fourth and sixth order; coma-like aberrations, Zernike terms third and fifth order.

* Abbreviations: RMS, root mean square.

Reunido el Tribunal que suscribe en el día de la fecha acordó otorgar, por a la Tesis Doctoral de Don/Dña. la calificación de .

Alicante de de

El Secretario,

El Presidente,

UNIVERSIDAD DE ALICANTE
CEDIP

La presente Tesis de D. ____ ha sido registrada con el nº ____________ del registro de entrada correspondiente.

Alicante ___ de __________ de _____

El Encargado del Registro,