Universitat d'Alacant
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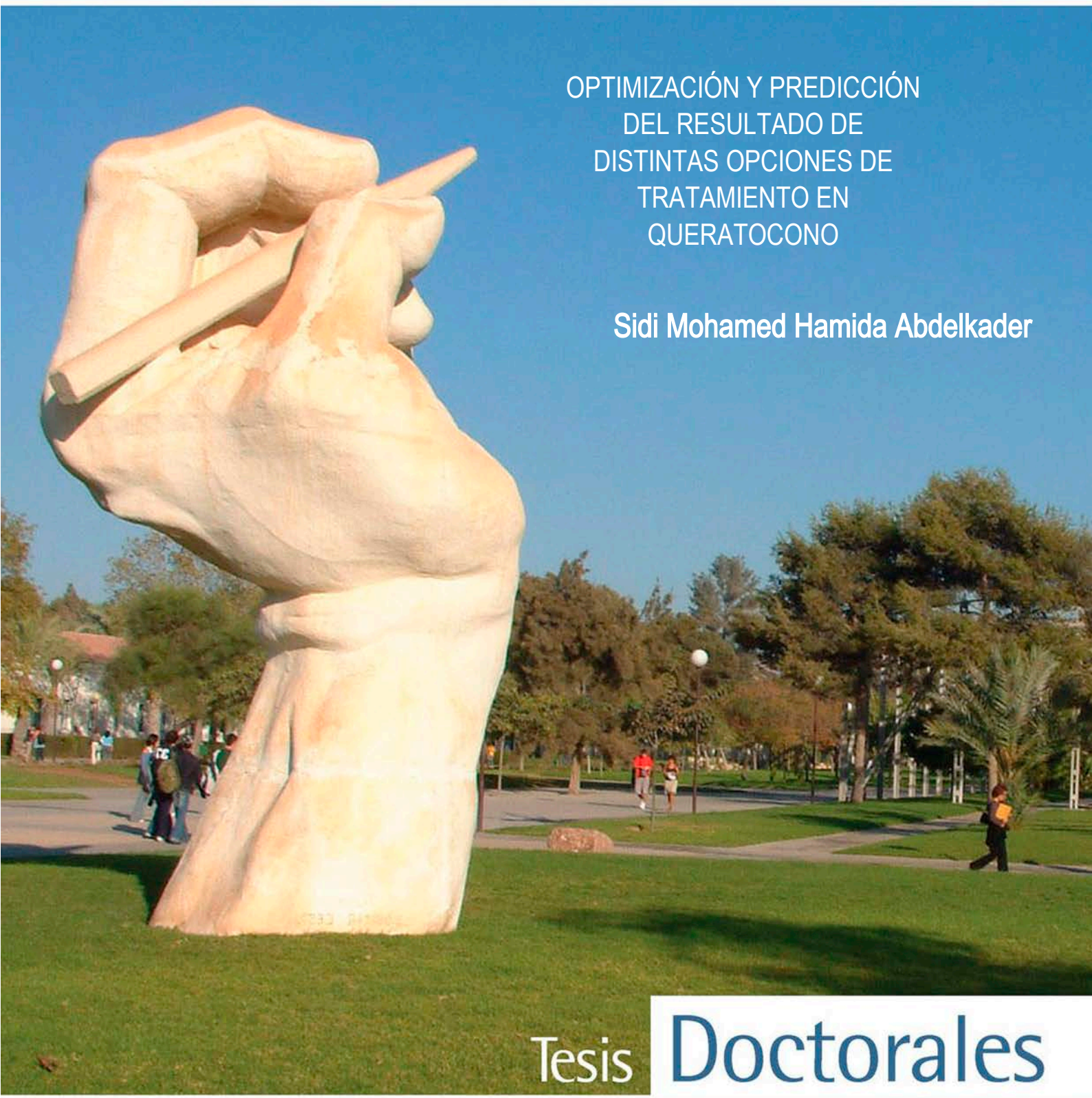
OPTIMIZACIÓN Y PREDICCIÓN DEL RESULTADO DE DISTINTAS OPCIONES DE TRATAMIENTO EN QUERATOCONO

Sidi Mohamed Hamida Abdelkader



Tesis Doctorales
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TESIS DOCTORAL

Optimización y predicción del resultado de distintas opciones de tratamiento en queratocono

Doctorando: **Sidi Mohamed Hamida Abdelkader**

Tesis presentada para aspirar al grado de

DOCTOR POR LA UNIVERSIDAD DE ALICANTE

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Dirigida por:
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“Nuestra recompensa se encuentra en el esfuerzo y no en el resultado”

“Un esfuerzo total es una victoria completa”

Mahatma Gandhi

“Los resultados que consigues serán directamente proporcionales al esfuerzo que aplicas”

Denis Waitley

“Hijo, llegarás lejos si el esfuerzo, la humildad, la honestidad y el respeto, se convierten en tu forma de vida”

Mohamed Hamida Mohamed

ÍNDICE

LISTADO DE ABREVIATURAS

Abreviatura	Inglés	Castellano
QC	Keratoconus	Queratocono
AV	Visual acuity	Agudeza visual
AVLC	Corrected distance visual acuity	Agudeza visual de lejos corregida
AVLSC	Uncorrected distance visual acuity	Agudeza visual de lejos sin corregir
CXL	Cross-linking	Cross-linking
RB	Riboflavin	Riboflavina
LC	Contact lenses	Lentes de contacto
ACI	Intrastromal corneal rings	Anillos corneales intraestromales
QP	Penetrating keratoplasty	Queratoplastia penetrante
QLAP	Deep anterior lamellar keratoplasty	Queratoplastia lamelar anterior profunda
LC RGP	Rigid gas permeable contact lense	Lentes de contacto rígidas gas permeable
LCR	Rigid contact lenses	Lente de contacto rígidas
LCE	Scleral Contact lenses	Lente de contacto escleral
LCC	Corneal Contact Lenses	Lentes de contacto corneal
Epi-on	Epithelium on	Epitelio “encendido” (epitelio no eliminado)

Epi-off	Epithelium off	Epitelio apagado (epitelio eliminado)
Hab	People	Habitantes
LH	Slit Lamp	Lámpara de hendidura
Kmax	Maximum Keratometry	Queratometría máxima
K steep	Steep Keratometry	Queratometria inclinada
UV	Ultraviolet irradiation	Radiación ultravioleta
TCO	Optical Coherence Tomography	Tomografía de Coherencia Óptica
IL	Interleukin	Interleukina
ERO	Reactive Oxygen Species	Especies reactivas de oxígeno
MMP	Matrix Metalloproteinases	Metaloproteinasas de matriz
FNT-a	Tumor Necrosis Factor Alfa	Factor de Necrosis Tumoral Alfa
ARNm	Messenger Ribonucleic Acid	Ácido Ribonucleico mensajero
CXL TE	Transepthitelial CXL	Cross-linking Transepitelial
PiXL	Photorefractive Intrastromal Crosslinking	Cross-linking Intraestromal Fotorrefractivo
CXL-I	Iontophoresis-Assisted CXL	Cross-linking Asistido por Iontoforesis
LO	Wavelenght	Longitud de onda
NM	Nanometers	Nanómetros
F	Ferrara	Ferrara
LA	Arc Length	Longitud de arco
ECA	Randomized Clinical Trials	Ensayos clínicos aleatorizados

PMMA	Polymethyl-methacrylate	Polimetil-metacrilato
EC	Clinical Trials	Ensayo Clínico
RB-H	Hypotonic Riboflavine	Riboflavina Hipotónica
RB-D	Dextrane Riboflavin	Riboflavina Dextrano
RB-HPMC	Hydroxypropyl-methylcellulose Riboflavin	Riboflavina Hidroxipropil-metilcelulosa
CXL-S	Standard Crosslinking	Crosslinking Standard
CXL-A	Accelerated Crosslinking	Crosslinking Acelerado
LDD	Demarcation line	Línea de demarcación
CASPe	Critical Appraisal Skills Program, Spain	Programa de Habilidades de Evaluación Crítica, España
LogMAR	Logarithm of minimal angle of resolution	Logaritmo del ángulo mínimo de resolución
J_{45}	Astigmatism power vectors	Vector de poder astigmático
D	Diopters	Dioptrías
EE	Spherical equivalent	Equivalente esférico
ECC	Central corneal thickness	Espesor corneal central
ECM	Minimal corneal thickness	Espesor corneal mínimo
EAC	Apex corneal thickness	Espesor en el ápex corneal
AAO	Higher order aberrations	Aberraciones de alto orden
ABO	Lower order aberrations	Aberraciones de bajo orden
RMS	Root mean square	Error cuadrático medio
IVS	Index of surface variance	Índice de varianza de la superficie
IAV	Index of vertical asymmetry	Índice de asimetría vertical

OR	Odd Ratio	Odd Ratio
ICD	Irregular Corneal Design	Diseño corneal irregular
AAM	Food and Drugs Administration	Administración de Alimentos y Medicamentos
EEUU	United States	Estados Unidos
VS	Versus	Versus
BAD	Belin/Ambrosio Display	Display Belin/Ambrosio
I	Intacs	Intacs
µm	Microns	Micras
MIN	Minutes	Minutos
MW	Millivats	Milivatios
CM^2	Square Centimeters	Centímetros Cuadrado
O_2	Oxygen	Oxígeno
O_3	Ozone	Ozono

SECCIÓN 1
SÍNTESIS DE LA TESIS

1.1 RESUMEN

El QC es una enfermedad de la córnea caracterizada por adelgazamiento progresivo y ectasia, que conduce secundariamente a un astigmatismo irregular, y que puede causar pérdida de la AV no corregida y AVLC. En los últimos años, se ha producido un incremento de la prevalencia y la incidencia, probablemente por una mejor detección, al disponer de mayor accesibilidad a los aparatos que nos ofrecen análisis avanzados de la estructura corneal. Existen numerosas modalidades de imágenes topográficas y tomográficas e índices de diagnóstico.

Actualmente la literatura científica no presenta una homogeneidad en cuanto a los criterios de diagnóstico de QC progresivo, determinando en el proyecto de investigación que conforma la tesis, que actualmente no existe un método universal para el diagnóstico de QC progresivo, no disponemos de criterios estandarizados para el diagnóstico de este, ni existe un tiempo estándar para definir esa progresión.

Existe varias modalidades de tratamientos para el QC, que incluyen gafas, LC, CXL, ACI y cirugía corneal (QP o QLAP). Sin embargo, el único tratamiento que ha demostrado retrasar la progresión del QC es el CXL, utilizado para fortalecer las propiedades mecánicas de la córnea y, por tanto, detener la progresión del QC.

Se han descrito varias modalidades de CXL, con el objetivo de disminuir las complicaciones relacionados con el CXL-Standard, S (protocolo de Dresden). La tendencia a la afirmación que otras modalidades de CXL, diferentes al CXL-S, considerado el “gold standard”, tengan una eficacia similar a ésta última está cada vez más respaldada

científicamente, tal y como hemos comprobado en la revisión sistemática realizada en la presente tesis. Además, en esta tesis, se ha determinado que la capacidad de la técnica de CXL epi-on de detener la progresión del QC es similar y comparable a la técnica de CXL epi-off, evitando de esta forma las probables complicaciones relacionadas con la técnica epi-off.

La mayoría de las investigaciones y estudios nos muestran de forma comparativa si las diferentes técnicas de CXL son más o menos eficaces o comparables entre ellas. Sin embargo, es muy importante establecer una serie de factores predictivos preoperatorios de los cambios visuales tras el CXL para poder elegir la mejor técnica según el contexto del paciente. En la presente tesis se han podido comprobar qué factores predictivos del cambio visual son importante a tener en cuenta a priori en las córneas sometidas a técnicas de CXL epi-on y epi-off, observándose que dichos factores son diferentes para ambas técnicas, sugiriendo que el mecanismo de acción es distinto en cada una de ellas.

Los ACI reducen el nivel de AAO y, consecuentemente, una mejora en la calidad visual, siempre que se implanten en córneas sin cicatrices y cuando las gafas y LC ya no proporcionan una corrección visual adecuada. Sin embargo, los estudios disponibles presentan una gran variabilidad, que puede ser explicada por los diferentes nomogramas disponibles o los distintos criterios de implantación de los ACI. En la actual tesis se ha podido desarrollar un nomograma optimizado, en el cual se ha considerado las especificidades del patrón topográfico al seleccionar los ACI, incluyendo parámetros como asfericidad o alineación de los ejes comático y astigmático, entre otros factores. El objetivo final ha sido el desarrollo de un nomograma que permita obtener resultados más optimizados y predecibles en las córneas con QC.

Por último, las LCE han adquirido una gran importancia en el manejo del QC estos últimos años, así como en otras patologías donde las córneas son irregulares, siendo una opción imprescindible para la rehabilitación visual. Sin embargo, la mejoría visual lograda varía entre los pacientes, por varios factores, como puede ser la bóveda o vault empleado a la hora de adaptar la lente. En la actual tesis, se ha demostrado buena eficacia en la rehabilitación visual con un modelo especifico de LCE ICD 16.50 y, ésta mejora en la AV, se ha podido predecir a partir de la AVLC con gafas, previa al ajuste de la LCE, y la potencia y la altura sagital de la LCE ajustada.

Los estudios realizados en la presente tesis han sido claves para aclarar las dudas sobre el manejo tanto quirúrgico como no quirúrgico del QC. Se ha comprobado que tanto la técnica epi-on como epi-off son comparables en términos de resultados visuales, refractivos y con una capacidad similar para detener la progresión del QC. Se han demostrado los factores predictivos del efecto del tratamiento del CXL y el uso de las LCE en el QC. Por último, se ha obtenido un nomograma optimizado para la implantación de los ACI.

1.2 ANTECEDENTES Y ESTADO ACTUAL DEL TEMA

1.2.1 DEFINICIÓN

El queratocono (QC) proviene de las palabras griegas keras (córnea) and konos (cono), siendo descrito por primera vez en la literatura en 1854 (Nottingham).[1] Se trata de una enfermedad corneal bilateral y asimétrica, caracterizada por adelgazamiento progresivo, protrusión de la córnea en forma de un cono temporal (ver figura 1), generalmente inferior, cambios en el error de refracción y cambios en el espesor de la córnea.[1-6] Suele aparecer en la adolescencia, progresando hacia la tercera o cuarta década de la vida.[5] Esta enfermedad conduce con frecuencia a una disminución de la calidad visual, secundaria a miopía, astigmatismo irregular o cicatrización corneal.[2,3,5,7] Recientemente, se ha demostrado la existencia de patrones de respuesta inflamatoria en el QC, a diferencia de la definición clásica de QC como una enfermedad no inflamatoria.[4]

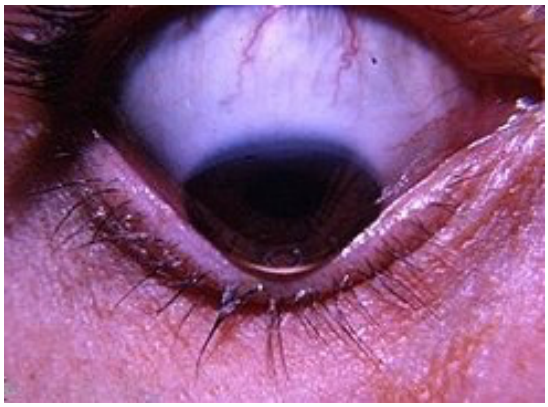


Figura 1.- Córnea cónica característica del QC. Extraída de: https://es.wikipedia.org/wiki/Queratocono

1.2.2 FISIOPATOLOGÍA

Los factores pro-inflamatorios han demostrado jugar un papel importante en la patogénesis del QC.[8-10] Se ha demostrado una sobreexpresión de mediadores inflamatorios, citoquinas e interleukina (IL)-6, en las lágrimas de pacientes con QC y QC subclínico[11,12] y niveles bajos de superóxido dismutasa (capaces de eliminar las especies reactivas de oxígeno (ERO), asociadas con reacciones inflamatorias).[13] Se ha demostrado la existencia en las córneas con QC de una mayor actividad colagenolítica, una actividad alterada en las metaloproteinasas de matriz (MMP), un aumento de los niveles de hidrolasas lisosomales en el epitelio conjuntival, reducción del 75% en el inhibidor de la proteinasa a1, aumento de los niveles de ARNm (ácido ribonucleico mensajero) para la catepsina G y una disminución de los niveles de ARNm para el inhibidor de la proteinasa a1.[14]

En el QC, la degeneración de las células epiteliales conduce a la liberación de enzimas lisosomales, según se ha demostrado en estudios de microscopía electrónica de transmisión.[15] Se ha encontrado en el QC una anomalía en la degradación tisular, debido a una relación alterada entre las MPP y sus inhibidores, afectando sobre todo a los proteoglicanos, e interactuando con las fibrillas de colágeno y, en consecuencia, generando una alteración de las cohesiones interfibrilares y de la disposición fibrilar.[15] Hay que tener en cuenta que un entrecruzamiento anómalo de las fibrillas de colágeno, cambia las propiedades biomecánicas de la córnea y secundariamente podría acelerar la progresión del QC, independientemente de su patogenia primaria.[15]

En el QC, se producen cambios estructurales en el epitelio corneal, membrana basal epitelial, capa de Bowman y el estroma.[16] En el epitelio, se produce un adelgazamiento en el

cono, con engrosamiento en la periferia, con disminución del colágeno I, VI, VII, XII y XIII.[15,17,18] Se ha demostrado una alteración de la expresión del colágeno, fibrina y las lamininas en la membrana basal epitelial.[16] En la capa de Bowman de las córneas con QC, se producen rupturas en las fibras de colágeno en diversos grados, con estroma subyacente distorsionado.[17,19] Las anomalías de la matriz extracelular se ha observado que no son uniformes en una córnea con QC, sugiriendo áreas localizadas de progresión de la enfermedad.[14] A nivel estromal, se ha observado una disminución en el diámetro de las fibrillas de colágeno, menor número de queratocitos, alteraciones en la organización lamelar y alineación lateral de las fibras de colágeno y una disminución del colágeno I, III, IV y V.[16,18] La membrana de Descemet no suele afectarse, pero se han descrito pliegues en la misma, aproximadamente en el 8% de los pacientes con QC.[20]

1.2.3 ETIOLOGÍA

Un **factor ambiental** puede ser fundamental para actuar como desencadenante de la enfermedad en personas predispuestas **genéticamente**.[1] Los factores ambientales son el frotamiento de los ojos, la atopia y la exposición a los rayos UV (radiación ultravioleta), sin conocer actualmente la contribución relativo de cada uno de ellos.[9] Un exceso de cada uno de estos factores ambientales produce un daño oxidativo a las córneas con QC, por la incapacidad de procesar las ERO, generando un proceso de degradación que conduce finalmente al adelgazamiento de la córnea y la discapacidad visual;[21] esto es debido a la falta de enzimas (aldehído deshidrogenasa de clase 3, catalasa o la superóxido dismutasa) corneales para neutralizar las ERO.[22]

Se ha asociado el QC con varias **enfermedades**. Destacamos el síndrome de párpado flácido, con una prevalencia alta en estos pacientes pero sin relación con una mayor gravedad de este síndrome en los pacientes con QC.[23] La obesidad y el síndrome de apnea obstructiva del sueño son condiciones más frecuentes en pacientes con QC, siendo recomendable un screening de rutina a esta población para descartar QC.[24] El síndrome de Gilles de la Tourette, por el frotamiento ocular obsesivo-compulsivo, es otra condición asociada frecuentemente al QC.[25] En pacientes con síndrome de Down, la prevalencia de QC es alrededor del 0,5-15%, sobre todo en pacientes mayores de 18 años, y esta relación se debe probablemente al hábito de frotarse los ojos.[20,26-28]

Frotarse los ojos se ha asociado con el QC, con una odd ratio (OR, por su siglas en inglés) de 3.98 en el trabajo de Bawazeer y cols.[29] Además, una gran parte de los estudios informan que aproximadamente la mitad de los pacientes con QC se frotan los ojos.[29-35] Sin embargo, esta asociación no es necesariamente causal, ya que se sabe que un porcentaje

importante de personas desarrollan QC sin tener antecedentes de frotarse los ojos.[1] La duración de frotarse los ojos en pacientes con QC es mucho más larga (10 a 180 segundos),[1] que la duración típica de menos de 15 segundos de los trastornos alérgicos[36] o infecciosos y menos de 5 segundos de personas sin afección ocular.[30] Frotarse los ojos produce microtrauma epitelial, que genera niveles elevados de MMP-1 y MMP-13[37-38] y mediadores inflamatorios (IL-6 y factor de necrosis tumoral, FNT-a),[12,39] contribuyendo a la aparición del QC y su progresión.[12,37-39]

La mayor prevalencia de QC en países cálidos y soleados respecto a Europa y América del Norte, ha llevado a pensar que la alta **exposición solar** en estos países explica la alta prevalencia de QC.[21-22] La luz es una fuente de ERO y una exposición alta a la luz solar provoca daño oxidativo en las córneas con QC, donde existe un descenso de las enzimas necesarias para la eliminación de las ERO.[21,22,40] Sin embargo, la radiación UV puede aportar beneficios al inducir la reticulación del colágeno corneal, haciendo frente al desarrollo de la enfermedad.[41] Además, la exposición solar no puede explicar la discrepancia encontrada en la prevalencia de QC en Teherán, entre los no persas (árabes, turcos y kurdos) del 7,9% frente al 2,5% de los persas.[42]

La **atopia** es una reacción de hipersensibilidad, que comprende **asma, alergia y eczema**.[1] La asociación entre atopia y QC es contradictoria, ya que hay autores que han observado una relación entre atopia y QC, mientras que otros no encontraron una asociación significativa entre ellas.[29,33,43-47] Esta discrepancia puede ser debida a la diferente gravedad de la enfermedad, los métodos de evaluación (basados en informes de pacientes) y la falta de diferenciación entre autores, de los efectos de la reacción de hipersensibilidad o la evaluación de sólo uno de los síntomas de la atopia.[29-31,43,44,48,49] Bawazeer y cols. no asociaron la atopia con QC, sino con el frotamiento de los ojos, secundario a la atopia.[29] Sin embargo, Kaya y

cols. han observado que los pacientes con QC y atopia tienen una córnea ectásica más curva y delgada que las personas de la misma edad y sexo con QC, pero sin atopia.[47]

A pesar que el tipo más común de QC es el esporádico, se ha informado de la presencia de un gran número de **QC familiar** y se ha observado una fuerte asociación de consanguinidad y endogamia de los padres con QC, sugiriendo un componente genético fuerte en el desarrollo de QC.[1] La tasa oscila entre el 3,34% y 27,9%, de manera que esta gran variación en el porcentaje de familiares con la enfermedad puede indicar una expresión diferente de QC con diferentes formas de herencia.[1] En dos estudios, se ha demostrado un riesgo 4 y 5 veces superior en los hijos de matrimonios consanguíneos en comparación con los hijos de padres no emparentados.[50-51] Esto se traduce en la existencia de un importante componente genético de la enfermedad.[1]

En definitiva, el desarrollo del QC es multifactorial, donde una predisposición genética asociado a factores como dormir sobre el ojo más afectado, podrían ser responsables de su aparición. [5,8,31,52,53]

1.2.4. EPIDEMIOLOGÍA

El QC suele aparecer entre la segunda y tercera década de le vida, con un promedio de edad de 27 años, progresando hacia la tercera o cuarta década de la vida, antes de estabilizarse.[5] Se ha observado que el QC pediátrico es más agresivo, por la alta tasa de progresión en esta población.[6] Afecta tanto a hombres como a mujeres, pero se cree que se desarrolla antes y progresa más rápidamente en los hombres que en las mujeres,[6] pero son las mujeres las que presentan más efectos adversos en su calidad de vida.[6]

La prevalencia del QC es muy variable, desde menos de 1/100.000 habitantes (hab) hasta 229/ 100000 hab,[1] y la incidencia varía entre 1.3-25/100 000 hab/año, siendo en Europa la incidencia y la prevalencia de 5-23/100.000 hab/año y 54/100.000 hab, respectivamente.[5] En el sur de España, se ha demostrado una prevalencia de 30/100.000 hab.[5] El estudio que demostró la prevalencia más baja empleó mediciones de queratometría únicamente para diagnosticar el QC y los estudios que demostraron una prevalencia más alta, combinaron la queratometría con otra evaluación diagnóstica como la retinoscopia o la topografía para el diagnóstico.[1] De manera que la obtención de una menor prevalencia de esta enfermedad puede ser debida a un infra-diagnóstico de la misma por las limitaciones de instrumentos de imagen, de ahí la importancia de una evaluación integral en el diagnóstico de QC.[6] La incidencia entre los diferentes estudios varía entre 1,3 a 25/100 000 hab/año.[6] El aumento de la incidencia en los últimos años se ha relacionado a una mayor sensibilidad en el diagnóstico de la enfermedad por la mejora en las técnicas de detección del QC.[6]

1.2.5. DIAGNÓSTICO

El diagnóstico y la intervención precoces son claves para un pronóstico visual positivo.[6] El diagnóstico de QC en etapas avanzadas es fácil de reconocer e implica la identificación de una serie de signos durante el examen.[43,54-55] Entre estos signos cabe destacar el reflejo de tijera en la retinoscopia, astigmatismo irregular, lecturas queratométricas elevadas, cambios en el mapa topográfico y tomográfico, grosor corneal central reducido en la paquimetría y signos en la lámpara de hendidura, LH (estrías de Vogt, ver figura 2; el anillo de Fleischer, el signo de Rizzuti, el signo de Munson y cicatrización estromal).[1] Sin embargo, puede resultar difícil detectar en etapas tempranas, de forma que los primeros signos de QC incluyen el desplazamiento de la parte más delgada corneal desde la posición central, cambios en la distribución de las células de la capa epitelial corneal, variaciones en la relación astigmatismo corneal anterior/astigmatismo corneal posterior y una variación del espesor corneal desde el centro a la periferia.[6] De esta manera, hay un consenso que la tomografía corneal con tecnología de Scheimpflug, en la que se basa por ejemplo el sistema Pentacam® (Oculus Optikgerate GmbH, Wetzlar, Alemania, ver figura 3) y la tomografía de coherencia óptica (OCT), son de las mejores herramientas para el diagnóstico del QC, especialmente en etapas precoces, permitiendo el estudio de las superficies corneales anteriores, posteriores y paquimétricas.[30,56,57] La combinación de ambas herramientas presentan un área de 1,0 con 100% de sensibilidad y 100% de especificidad en personas con QC en fases precoces y ojos normales, sobre todo aquellos con QC asimétricos.[44] Además si añadimos a estas dos herramientas el análisis de la biomecánica corneal con el dispositivo Corvis ST (Corvis ST® ; Oculus, Wetzlar, Germany, ver figura 4), aumenta aún más la capacidad de diagnóstico, sobre todo en etapas precoces;[58] y la integración de la TCO (tomografía de coherencia óptica) y la

biomecánica corneal podría disminuir la cantidad de falsos negativos.[58] La densitometría corneal es capaz de valorar diferentes etapas de gravedad del QC, de forma que las densidades más brillantes se correlacionan con etapas más avanzadas de la enfermedad.[59] La microscopía de Brillouin es muy sensible en la detección de diferencias mecánicas entre córneas sanas y con QC, demostrando in vitro y en vivo, que tanto el desplazamiento de Brillouin anterior como la pendiente axial, son significativamente diferentes entre las córneas sanas y con QC y entre las regiones del cono y la zona sin cono,[45,,60] como ya se había corroborado previamente, sugiriendo que el inicio del QC podría ser focal, en lugar de generalizado.[61]

Figura 2.- Estrías de Vogt. Extraida de: https://www.atlasophthalmology.net/photo.jsf;jsessionid=741F891181EE4A913E1FEC28C397757B?node=4639&locale=es

A.

B.

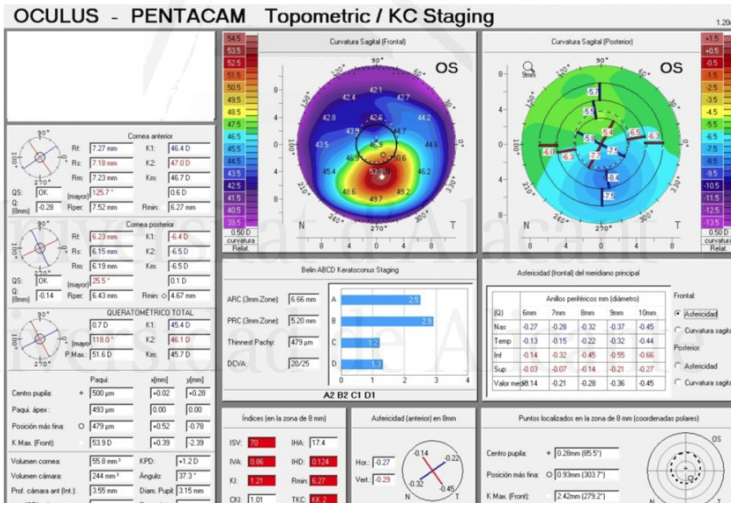
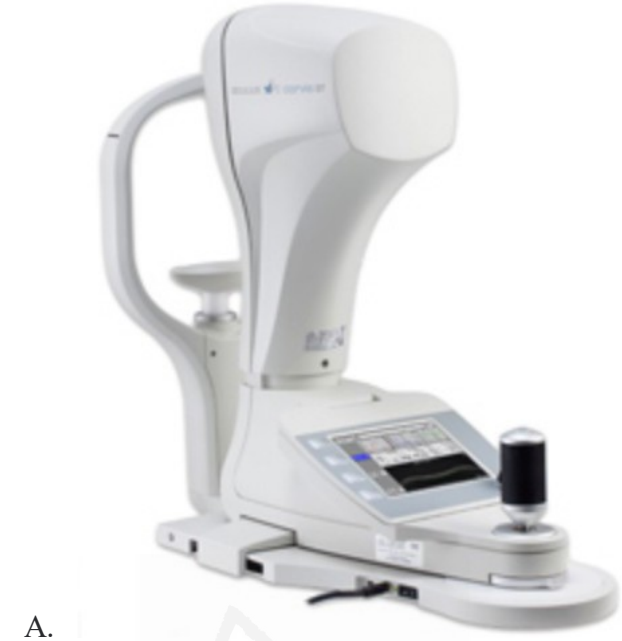


Figura 3.- Imágenes del sistema Pentacam.

A. Sistema Pentacam. Extraída de: https://cyanmedica.com/wp-content/uploads/2020/01/Pentacam-estandar-y-HR-cyan-medica.pdf .

B. QC avanzado. Extraída de: https://www.qvision.es/blogs/javier-martinez/2016/07/24/clasificacion-y-seguimiento-del-queratocono-con-pentacam-2-2/

A.



B.

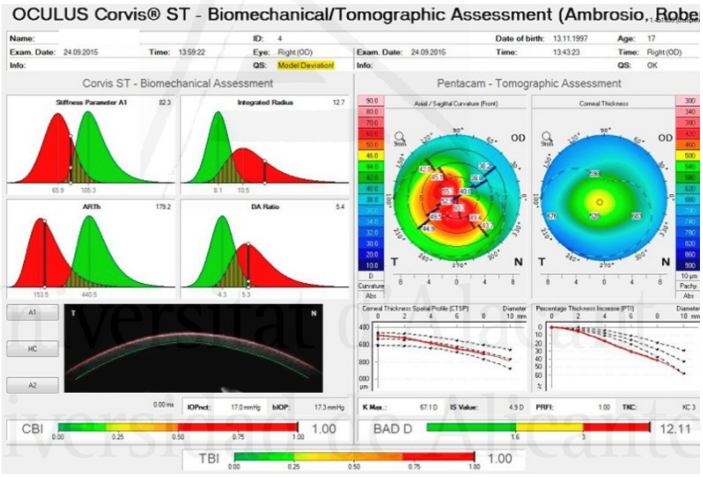


Figura 4.- Imágenes del Sistema CorVis ST.

A. Sistema Corvis ST. Extraída de: https://cyanmedica.com/wp-content/uploads/2020/01/Pentacam-estandar-y-HR-cyan-medica.pdf

B. Display biomecánico/tomográfico. QC avanzado. Extraída de: https://www.mdpi.com/1660-4601/17/6/2113/htm

En resumen, debemos tener presente a la hora del diagnóstico de QC que actualmente no tenemos parámetros que por sí solo sean suficientes para el diagnóstico ni tampoco datos de corte absolutos que nos pongan en alerta sobre la aparición del QC.[54,55,62,63] Además siempre debemos estudiar el ojo adelfo en pacientes con QC unilateral, porque podría ser que esta condición no existiera[54] y, la mayoría de estos pacientes podrían presentar una fase precoz de QC, QC subclínico (ojo adelfo de un ojo con QC con signos sutiles tomográficos sugerentes de QC en el mapa axial, sin alteraciones en la LH ni en la AV, agudeza visual) o frustre (ojo adelfo de un ojo con QC, sin alteraciones tomográficas ni topográficas), aunque se tratan de términos imprecisos y que a veces se superponen.[64,54,55,58,63,65-67]

En definitiva, un diagnóstico precoz de QC tiene el beneficio de un manejo precoz para mejorar los resultados visuales a largo plazo del paciente.[6] De esta manera, el uso de múltiples técnicas de diagnóstico (topografía, sistemas basados en elevación, ultrasonografía de alta resolución, tomografía del segmento anterior y la biomecánica corneal) son importantes para una evaluación corneal detallada y de esta manera, poder diagnosticar pacientes con QC preclínico.[6]

1.2.6. PROGRESIÓN

A lo largo de los años hemos presenciado una mejora significativa en el diagnóstico precoz del QC con la introducción de la tomografía corneal, mapas epiteliales y la biomecánica corneal.[7,64,68-71] Los criterios de definición de la progresión del QC como el tiempo estimado para definir dicha progresión son muy variables en los diferentes estudios, incluso algunos de ellos, no establecen valores de corte de progresión, sino que simplemente hacen mención al parámetro utilizado para definir esa progresión a lo largo del tiempo. El tiempo estimado (ver tabla 1) para definir dicha progresión varía habitualmente de 6 a 12 meses en la mayoría de los artículos publicados.[72-85] La mayoría de los autores establecen como criterios de progresión (ver tabla 1) los siguientes cambios en los parámetros: incremento de queratometría máxima (Kmax, por sus siglas en inglés) de más de 1-1,5 D, de más de 1 D en la queratometría más curva (K steep, por sus siglas en inglés), de 0,5 D o más en el equivalente esférico (EE), de 1 D o más en el cilindro manifiesto o descenso en el punto paquimétrico más delgado de más del 5% y de 0,5 o más líneas de Snellen en la AVLC (agudeza visual de lejos corregida) o AVLSC (agudeza visual de lejos sin corregir).[72-85] La mayoría de los estudios publicados siguen utilizando un cambio de más de 1-1,5 D de Kmax como punto de corte para indicar la progresión del QC.[7] Sin embargo, la Kmax es muy variable y confiar en un solo parámetro podría conducir, tanto a falsos positivos como a falsos negativos.[7]

La pantalla de progresión Belin ABCD se ha introducido en el software nativo de Pentacam (OCULUS Optikgeräte GmbH; Wetzlar, Germany) para evaluar la progresión del QC.[86] Esta pantalla, a diferencia de la pantalla de ectasia mejorada “Display Belin/Ambrosio” (BAD, por sus siglas en inglés), que excluye una zona óptica de 3,0 a 4,0 mm centrada en el

punto más delgado para normalizar la superficie de referencia, tiene la peculiaridad que se basa en esta zona excluida centrada en el punto más delgado, puesto que esta zona representa más globalmente la región ectásica.[86] Esta pantalla ABCD se basa en cuatro variables: curvatura anterior ("A") y posterior ("B") promedio, medidas en una zona óptica de 3 mm centrada en el punto más delgado, paquimetría mínima ("C") y AVLC ("D").[86] La figura 5 demuestra progresión de Kmax, A, B y C, sin embargo, la figura 6 no muestra progresión de Kmax, pero sí de los parámetros B y C.[86]

En definitiva, confiar en la Kmax como el único parámetro para la progresión es considerado una limitación importante en la detección del QC progresivo, por lo que se debe tener en cuenta la correlación demostrada entre Kmax y los cambios en los valores de la pantalla de progresión de Belin ABCD, para manejar de la mejor manera posible los pacientes con QC progresivo.[86]

Estudio	***Criterios de progresión del queratocono***	***Tiempo***
Al Fayez y cols. (2015)	Valores de queratometría > 1 D Cilindro manifiesto > 1 D	12 meses
Rehnman et al (2015)	Incremento en la queratometría más curva y astigmática Descenso de AVLC	
Bikbova y cols. (2016)	Aumento de K max de 1 D o más en el cilindro manifiesto Aumento de 0.5 D o más en el EE de la refracción manifiesta	12 meses
Choi y cols. (2017)	Aumento en la K max de > 1.5 D Disminución de la paquimetría más fina en más de un 5%	
Fry y cols. (2011)	No se han definido criterios de progresión	
Hagem y cols. (2019)	Aumento mínimo de 1 D en la K max o 1 D o más en el cilindro manifiesto Descenso mínimo del EE de 0.5 D	
Hashemi y cols. (2015)	Aumento de 1 D o más en la K max, cilindro manifiesto o EE de la refracción manifiesta Pérdida de al menos 2 líneas de AVLC	12 meses
Mesen y cols. (2018)	Valores de queratometría > 1 D Disminución en > 0.1 mm Incremento > 1 D en el cilindro manifiesto	6 a 12 meses

Nordstrom y cols. (2017)	Aumento de 1 D o más en la K max (1 año) Aumento del astigmatismo queratométrico y la inclinación de la córnea Descenso de la AVLC	
Rosenblat y cols. (2016)	No se han definido criterios de progresión	
Rush y cols. (2017)	Aumento de la K steep > 1 D o más Aumento del astigmatismo o miopía en refracción manifiesta de 1 D o más	12 meses
Sadoughi y cols.(2016)	Aumento de 1 D o más en K max Pérdida de 2 o más líneas de AVLC Aumento de 1 D o más en el cilindro de la refracción manifiesta Aumento de 1 D o más en el EE de la refracción manifiesta	
Sherif y cols. (2014)	Aumento de 1 D o más en la K max Aumento de 1 D o más en el cilindro manifiesto, o 0.5 D o más en el EE de la refracción manifiesta	6 meses
Yildirim y cols.(2017)	Descenso en la AVLSC o AVLC de más de 0.5 líneas de Snellen Aumento de la K max en 1 D	12 meses

	Aumento de la refracción esférica/cilíndrica o índice de simetría (SIA) de más de 0.5 D Descenso de ECC (espesor corneal central) de más de 10 micras (µm)	

Tabla 1.- Definición del tiempo y criterios de progresión del queratocono en diferentes estudios.[87]

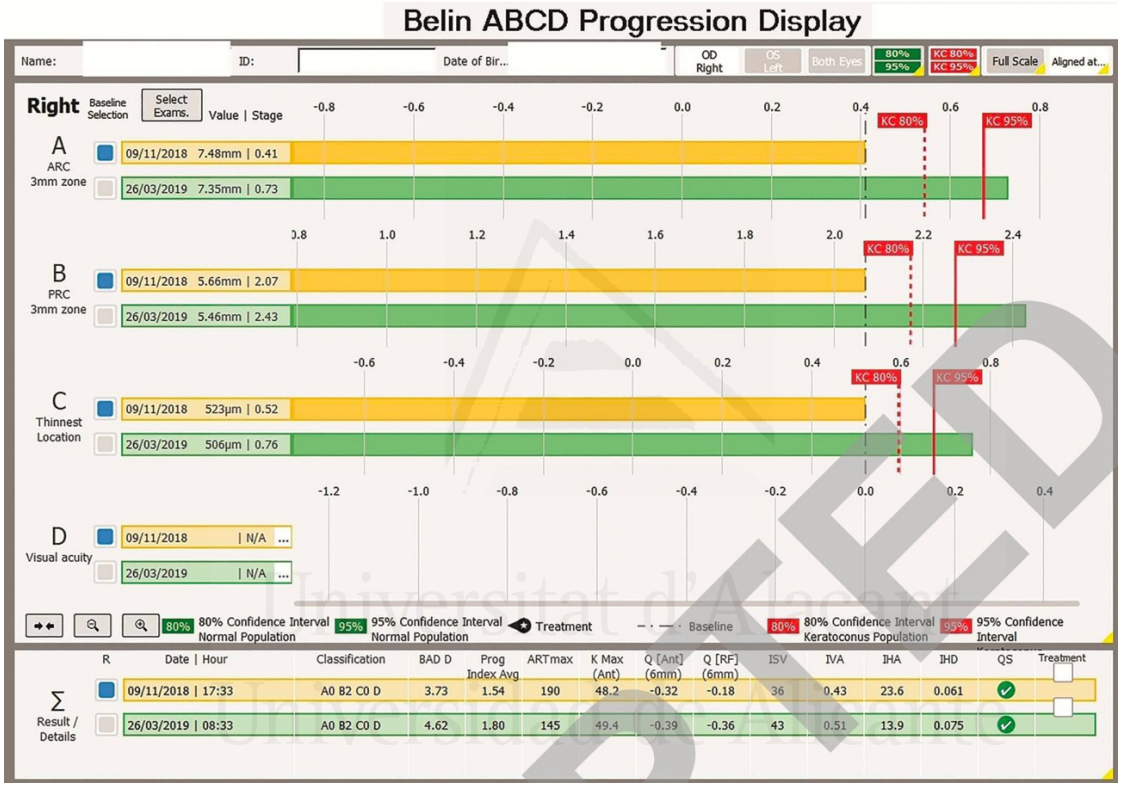


Figura 5.- Queratocono progresivo evaluado con la pantalla de progresión ABCD. La pantalla demuestra progresión en los parámetros K max (aumentó de 48.2 a 49.4 D), A, B y C, por encima de los intervalos de confianza del 95% (línea roja continua). Imagen extraída de la referencia bibliográfica número 86.

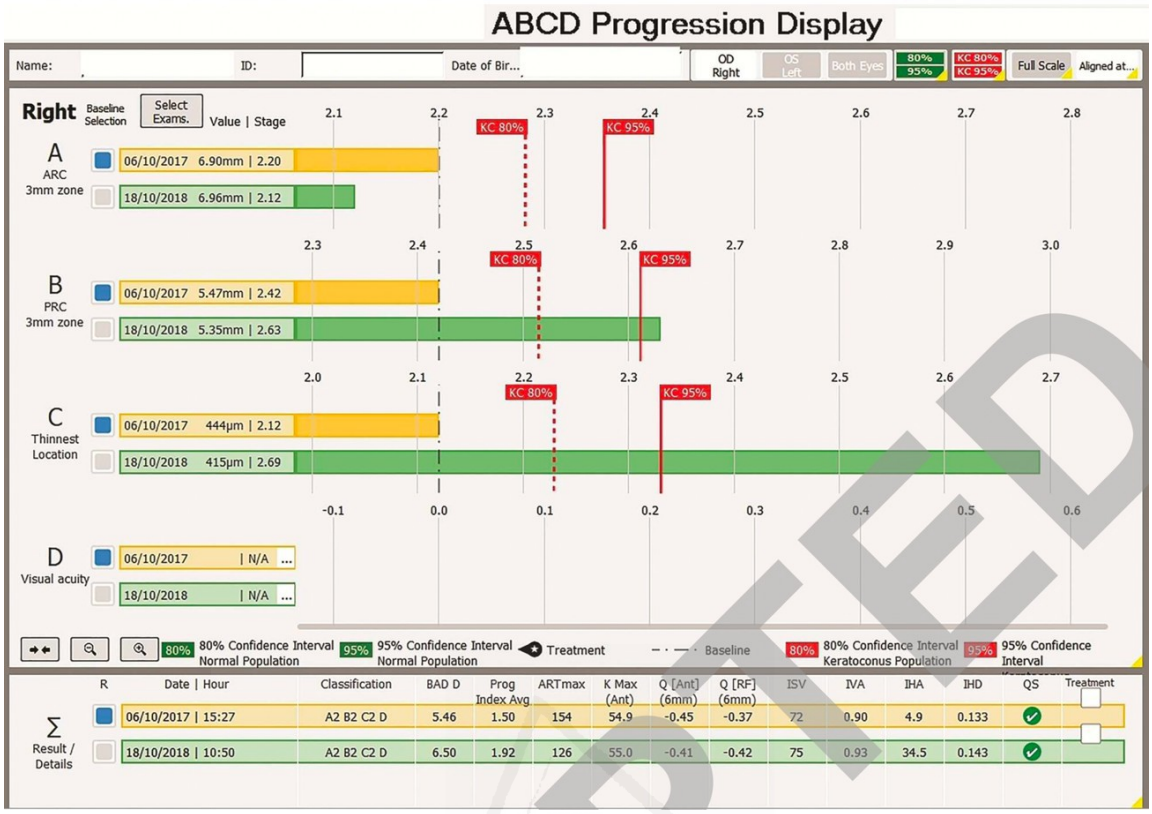


Figura 6.- Queratocono progresivo evaluado con la pantalla de progresión ABCD. No muestra ninguna progresión con respecto a la curvatura anterior (K max y el parámetro A son estables), sin embargo, la curvatura corneal posterior (parámetro B) y el grosor (parámetro C) cambian por encima del intervalo de confianza del 95% (línea roja continua). Imagen extraída de la referencia bibliográfica número 86.

1.2.7. TRATAMIENTO DEL QUERATOCONO

Durante mucho tiempo, el tratamiento tradicional para etapas leves de QC ha consistido en el uso gafas, LCR (lentes de contacto rígidas) para pacientes con QC moderado y trasplante corneal en las etapas avanzadas.[88] Este paradigma ha cambiado por la aparición del CXL (cross-linking), siendo el tratamiento estándar para estabilizar el QC progresivo y la cirugía refractiva (anillos corneales intraestromales (ACI), implante de lentes fáquicos y cirugía láser).[3,88]

Hasta un 25% de los pacientes con QC progresarán a una etapa de la enfermedad en la que no se pueda lograr una buena AV con la corrección de la visión y se requiera cirugía.[3] Actualmente la indicación de CXL se basa principalmente en los cambios en la queratometría a lo largo del tiempo, pero la progresión de la enfermedad es muy variable y otros factores juegan un papel importante, como por ejemplo la edad del paciente.[3]

Un diagnóstico tardío de QC puede suponer que las gafas, LC (lentes de contacto), CXL y los ACI no sean tratamientos viables por un efecto insignificante sobre el retraso de la progresión de la enfermedad.[6] Un QC avanzado a menudo conduce a la cicatrización corneal, haciendo del trasplante, la única opción de tratamiento.[5,89] Sin embargo, se ha publicado que el ajuste de las LCE (lentes de contacto esclerales) puede resultar exitoso en ojos con QC avanzado, concluyendo los autores que el resultado visual para la ectasia en fase cuatro fue mejor y más rápido con la corrección de LCE en comparación con el trasplante corneal.[90]

1.2.7.1 CROSS-LINKING

El primer artículo publicado acerca del CXL (ver figuras 7 y 8) en el manejo del QC fue en el 2003,[91] tratándose de una técnica mínimamente invasiva y segura, que permite la estabilidad de la progresión del QC, con resultados clínicos y topográficos favorables, disminuyendo la irregularidad corneal y mejorando la AV tanto sin corregir como la mejor corregida.[6,7,86,91] La mayoría de los cirujanos de córnea están de acuerdo que, una vez establecida la progresión del QC, se debe indicar el tratamiento con CXL.[86] Es un procedimiento que emplea UV-A y riboflavina (RB) para inducir un incremento de la rigidez corneal secundario al entrecruzamiento entre las fibras de colágeno en el estroma corneal.[86]

Figura 7.- Sistema KXL (CXL) de Avedro. Producto aprobado por la AAM (Administración de Alimentos y Medicamentos) de los EEUU (Estados Unidos) para el tratamiento del QC progresivo. Aparato encargado de la aplicación de radiación UV-A, que junto con la RB (vitamina B2), tienen como objetivo incrementar los enlaces moleculares a nivel de las fibras de colágeno estromales de la córnea, consiguiendo mayor rigidez y estabilización corneal y frenando la evolución del QC.
Extraída de:
https://www.imex.es/aprobacion-fda-kxl-avedro-crosslinking-acelerado/ y
https://www.icoftalmologia.es/es/tecnologias-de-diagnostico-y-tratamiento/el-crosslinking-cxl/

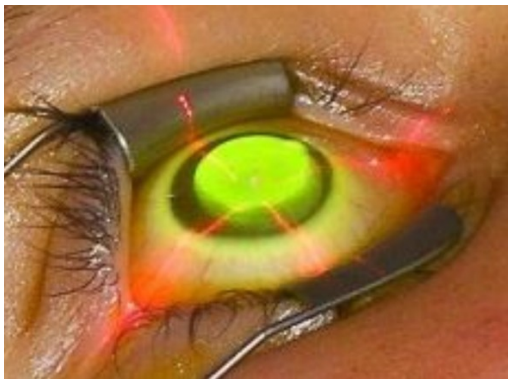


Figura 8.- Córnea durante el proceso de CXL. Extraída de: https://www.centrospalomar.com/index.php?option=com_content&view=article&id=354:tratamiento-cross-linking-corneal-para-el-queratocono&Itemid=&lang=german

La primera técnica de CXL descrita es el método de Dresden (CXL estándar, CXL-S), donde se elimina el epitelio corneal para luego administrar RB al 0.1% y luz UV-A (longitud de onda, LO, de 365 nanómetros, nm) y una intensidad de 3 mW/cm^2 (milivatios/centímetros cuadrado) durante 30 minutos.[74,92] Sin embargo, a lo largo de los años, se han descrito diferentes enfoques, con el objetivo de evitar las complicaciones relacionadas con el desbridamiento epitelial, reducir las molestias postoperatorias y conseguir unos tiempos de recuperación más rápidos.[82] El CXL transepitelial (CXL-TE) es uno de ellos, en el que no se elimina el epitelio corneal, evitando las complicaciones, como las queratitis infecciosas, y supone tiempos de recuperación más rápidos.[82] PiXL (CXL intraestromal fotorrefractivo) es otro enfoque, donde se lleva a cabo un tratamiento de entrecruzamiento individualizado, ejerciendo mayor efecto en la zona más ectásica.[93] El CXL asistido por iontoforesis (CXL-I) ha demostrado su eficacia para la administración transcorneal de fármacos, con las ventajas de reducir el dolor postoperatorio, prevenir el deterioro visual y acortar el tiempo de tratamiento.[74] A pesar que el protocolo de Dresden es el gold standard, cada vez son más los

trabajos publicados en la literatura científica, que demuestran que el CXL-TE tiene una eficacia similar al CXL-S en pacientes con QC, en cuanto a resultados visuales, refractivos y capacidad de detener la progresión del QC.[82,94-96]

El CXL puede detener la progresión del QC, pero también puede producir un empeoramiento de la córnea tratada o simplemente no suscitar ningún efecto en la córnea. En los últimos años, se han investigado los probables factores predictivos para los resultados del CXL en córneas con QC, aunque existe una variabilidad alta en los estudios que evalúan dichos factores.[4] Entre estos factores estudiados, destacan la asfericidad corneal, el índice queratocónico corneal, la AVLC y la excentricidad del cono.[97] Predecir el efecto del CXL sería una herramienta muy útil en la práctica clínica diaria proporcionando a los profesionales información relevante sobre el probable efecto del CXL en la córnea con QC.[97-99]

1.2.7.2 ANILLOS CORNEALES INTRAESTROMALES

Se ha demostrado que los ACI (ver figura 9) reducen el astigmatismo corneal, disminuyen la cantidad de aberraciones corneales y regularizan los mapas topográficos, mejorando el rendimiento visual, la calidad de vida y retrasan o previenen la necesidad de un trasplante corneal.[6,100] Sin embargo, hay una gran variabilidad entre estudios, con discrepancias entre los mismos y uno de los principales factores que explican esta discrepancia es, la gran variabilidad en los nomogramas de implantación de los ACI.

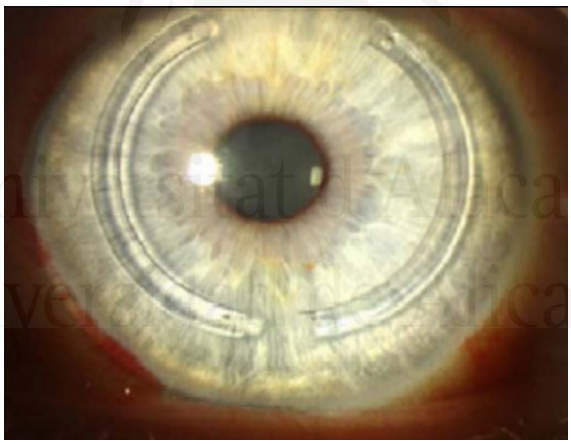


Figura 9.-ACI de Ferrara (F). Extraída de: https://rosinov.com/catalogo/anillos-intracorneales-ferrara-rings/

Existen dos tipos principales de ACI, los F y los Intacs (I), aunque hay otros diseños que resultan ser variaciones de estos.[100] Los ACI de F, fabricados de polimetil-metacrilato

(PMMA), están formados por segmentos semicirculares con un arco de múltiples longitudes (90º, 120º, 140º, 150º, 160º, 180º, 210º y 320º) y una sección triangular fija. Los ACI de F, AFR, tienen una base de 0.60 mm y 5.00 mm de zona óptica y los ACI de F, AFR6, tienen una base de 0.60 mm y una zona óptica de 6.0 mm.[101-104] Hay disponibles varios espesores (0.15, 0.20, 0.25, 0.30 y 0.35 mm) para cada tipo de segmento y cada segmento tiene un orificio de 0.20 mm en cada extremo para facilitar su implantación. [101-104]

Se han informado de buenos resultados, tanto para I como para F, sin embargo, la implantación de los ACI F son superiores a los I, en cuanto a corrección refractiva y resultados visuales.[100] Los ACI F de 320º y 210º de longitud de arco (LA), de elección en pacientes con QC central hiperprolato, inducen mayor reducción de la asfericidad y queratometría media respecto a los ACI F de 160º.[105-107] Los ACI F de 150º implantados inferiormente han demostrado ser de elección en los QC con ejes topográfico y comático no coincidentes.[108] En astigmatismos corneales bajos, la implantación de un ACI F de 150º implantado inferiormente; en astigmatismos moderados, la implantación de un ACI F de 90º superior y un ACI F de 150º inferior; así como el uso de un anillo F de 90º superior y un ACI F de 120º inferior para astigmatismos altos, han demostrado ser los ACI de elección con resultados refractivos y visuales muy buenos; en astigmatismo regular, es recomendado el empleo de dos ACI simétricos.[101,107,109]

1.2.7.3 LENTES DE CONTACTO

El consenso mundial sobre el QC y las enfermedades ectásicas ha destacado la importancia de las LC en la rehabilitación visual de los pacientes con QC.[110] Recomiendan si los pacientes no tienen una visión satisfactoria con gafas, el empleo de LCR gas permeables (LC RPG) o LC blandas.[110] Si los pacientes no tienen una visión satisfactoria con las LC RGP, se podría optar por las LC híbridas (centro rígido, con periferia blanda), bitóricas, tóricas, diseño de LC blandas específicas para el QC, diseño de LC permeables al gas con un diseño específico para el QC, LC corneo-esclerales, miniesclerales y LCE (ver figura 10).[110] La adaptación de las LC, ya sean LC blandas, LCR o híbridas permeables a los gases, para córneas irregulares puede ser difícil en pacientes que no consiguen una buena AVLC con gafas.[111] Hay evidencia que el uso de las LC, sobre todo LCE, podría disminuir la necesidad de trasplante de córnea en pacientes con QC.[88,112] Koppen y cols. informaron que las LCE han reducido la necesidad de trasplante corneal en el 80% de los pacientes con QC avanzado.[99] Las LCE pueden ser necesarias para alcanzar mejor AVLC, a pesar de someter a un paciente con QC avanzado a una QP (queratoplastia penetrante) o DALK (queratoplastia lamelar anterior profunda).[113,114]

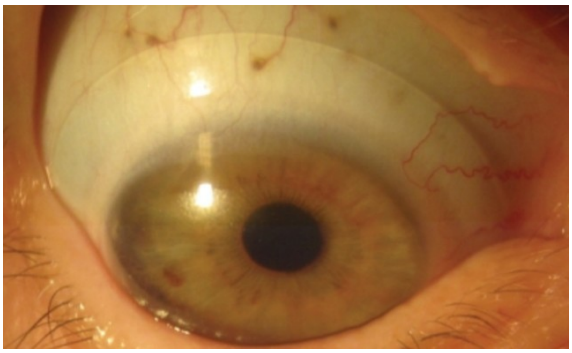


Figura 10.-LCE. Extraída de: https://www.opticapedraza.com/blog/lentes-esclerales-el-presente-y-el-futuro-de-las-lentes-de-contacto/

Las LC han evolucionado en los últimos años, sobre todo las LCE.[115] Las LCE permeables al gas se han introducido hace más de 25 años, y en ese momento su uso estaba limitado a una serie de centros muy especializados por la complejidad de la adaptación de estas lentes.[116-118] En un estudio con usuarios de LCE, se observó que el 80% de los 989 encuestados, indicaban que su primer año de adaptación fue tras el 2005, y el 54% tras el 2010.[119] En los Estados Unidos se ha estimado en 2016 que 70 000 personas eran usuarias de LCE.[120]

Los beneficios de las LCE sobre las LCC (lentes de contacto corneales) son varios, entre ellos cabe mencionar, el hecho de no tocar la córnea, sin exacerbar la formación de cicatrices, son mas cómodos, mejorando la calidad de vida de los pacientes y brindan un ajuste más estable y mejor centrado.[121-122]

Las principales indicaciones de las LCE son la ectasia corneal (27.5-91 %), irregularidad corneal postquirúrgica o postraumática (17.6-40 %), enfermedad de la superficie ocular (3-49 %), afaquia (2-23 %) y los errores refractivos (2.6-10%).[120] El QC es la principal indicación para el uso de las LCE, estimando un manejo exitoso del QC en un 75% de los casos.[120,123]

Las complicaciones más comunes de las LCE son hipoxia que produce edema corneal (7.4 %), neovascularización (1.1-13.3 %), abrasión corneal (3.1 %), irritación mecánica (12.6

%), depósito de proteínas (3.5 %), conjuntivitis papilar gigante (1.7 %), infección, inflamación y mala adaptación de las lentes por la progresión de la enfermedad.[120]

Existen varios factores que podrían explicar la variabilidad de la mejora de la AV lograda con las LCE entre los individuos, como es el caso del "vault" de la LCE.[124,125] De esta manera, predecir el efecto de la LCE en cuanto a la mejora de la AV, resulta interesante en la práctica clínica diaria, ya que proporcionaríamos a los pacientes información acerca del efecto probable conseguido con la adaptación de la LC.

1.2.7.4 TRASPLANTE CORNEAL

Las gafas y LCR son insuficientes para la rehabilitación visual en fases avanzadas del QC y un 10-20% de los pacientes necesitan un trasplante corneal.[126] El trasplante corneal (ver figura 11) sigue siendo el tratamiento principal para los pacientes con intolerancia a las LC y la tasa de supervivencia del injerto es más elevada que los pacientes que se someten al trasplante corneal por otros motivos.[127]

Actualmente la DALK se está imponiendo a la QP, como procedimiento de trasplante corneal de primera línea,[88] pero en una revisión Cochrane no encontraron que una técnica sea mejor que la otra, en cuanto a resultados refractivos o visuales,[127] aunque la tasa de rechazo del injerto corneal fue superior en el caso de QP.[127] La intolerancia a las LC es la principal indicación para la DALK, en pacientes sin hidropesía corneal ni cicatrización corneal y la cicatrización corneal es la primera indicación para la QP.[88,127]

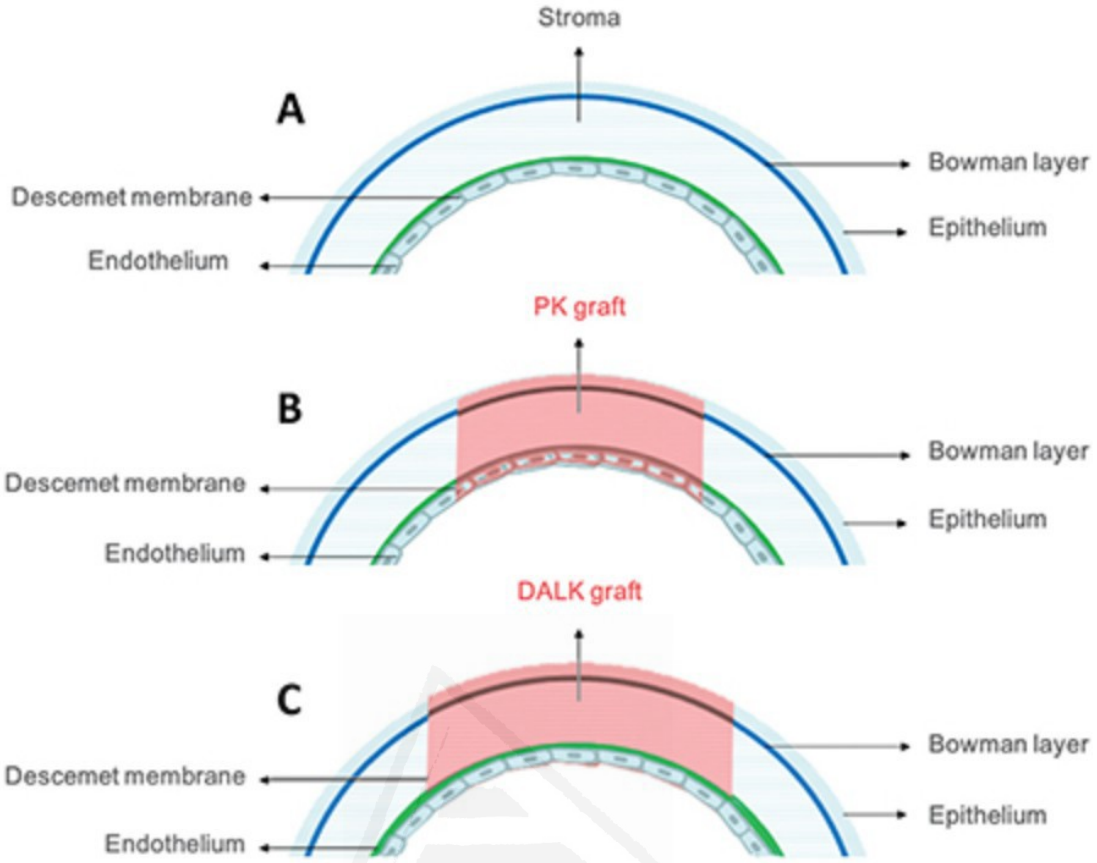


Figura 11.- Esquema para ver la diferencia entre DALK y QP. Extraída de: https://www.clinicbarcelona.org/noticias/el-hospital-clinic-lider-de-trasplantes-de-cornea-en-el-sector-publico-en-catalunya-en-2017.

1.3. JUSTIFICACIÓN DE LA UNIDAD TEMÁTICA

Desde la aparición del primer artículo de CXL publicado en 2003, se han descrito a lo largo de los años múltiples técnicas de CXL para evitar las complicaciones asociadas al desbridamiento epitelial y aportar mayor comodidad a los pacientes durante la técnica. Actualmente el CXL-S continúa siendo la técnica "gold standard", pero los resultados de la técnica epi-off (epitelio eliminado) podrían ser comparable en términos de eficacia a la técnica epi-on (epitelio no eliminado) y con menos riesgo de complicaciones postoperatorias respecto a la técnica epi-off, como se ha demostrado en varios estudios.[83,84] Sin embargo, no se ha analizado la calidad científica, con herramientas validadas, de los trabajos disponibles sobre técnicas de CXL, en el QC progresivo.

Los ACI han sido investigados durante muchos años como opción terapéutica para el manejo del QC,[128,129] y la evidencia disponible ha demostrado la capacidad de estos ACI para reducir el nivel de AAO (aberraciones de alto orden), mejorando la calidad visual de los pacientes con QC.[128,129] Sin embargo, existe una gran variabilidad y discrepancias entre los estudios, ya que se tratan de estudios no controlados e inconsistentes, escasez de ECA (ensayos clínicos aleatorizados) comparativos y fundamentalmente por la gran variabilidad en el nomograma de implantación de los ACI, basados en datos empíricos, aproximaciones o experiencias personales.

Como ya se ha mencionado, Wollensak y cols. en el 2003 introducen el CXL, como un tratamiento estándar, mínimamente invasivo y seguro para los pacientes con QC progresivo,[91] cuyo objetivo principal es la estabilización de la progresión del QC aumentando

la estabilidad mecánica de la córnea. [6,7,86,91] El CXL puede prevenir la progresión del QC y causar la regresión de la córnea ectásica, pero puede producir el efecto contrario, empeorando los parámetros oculares, o simplemente, no generar ningún efecto en la córnea ectásica.[97] En los últimos años, ha aumentando el interés sobre la predicción del efecto de CXL en pacientes con QC progresivo y hasta la fecha se han definido múltiples factores predictivos, pero existe una gran variabilidad entre los pocos estudios que estudian dichos factores y no se han establecido modelos de predicción del efecto de CXL.

Las LCE han alcanzado un gran impacto en la actualidad por su indicación en córneas irregulares, como es el caso del QC, siendo la principal indicación del uso de estas LC.[120,111,130,131] Son varios los autores que han demostrado que el uso de las LCE permite una muy buena rehabilitación visual en pacientes con QC.[115,120,111,132,133] Sin embargo, esta mejoría de la calidad visual varia mucho entre los pacientes por varios factores, algunos de ellos ya descritos, pero no se ha establecido un modelo de predicción del efecto de la LCE, relacionando los factores probables de predicción del efecto de la LCE sobre la mejora de la AV final, tras el ajuste de la LCE.[111,130,132,133]

1.4. HIPÓTESIS DE LA INVESTIGACIÓN

Un mejor conocimiento de la calidad científica de los estudios disponibles sobre CXL en el manejo del QC podría ayudar en el manejo terapéutico, a la indicación de la técnica más viable en función de las características del paciente y, en definitiva, a mejorar el pronóstico de los pacientes con QC progresivo.

Para mejorar la evidencia científica disponible acerca de la implantación de los ACI en los pacientes con QC, consideramos necesario desarrollar un nomograma optimizado para superar las limitaciones con las que nos encontramos a la hora de analizar los nomogramas disponibles y, de esta forma, alcanzar niveles más altos de previsibilidad a la hora de implantar los ACI.

Ante la gran variabilidad en la predicción del efecto del CXL, consideramos muy importante llevar a cabo un estudio exhaustivo para establecer modelos de predicción del efecto del CXL, tanto para epi-on como para epi-off.[97-99] Por lo tanto, disponer de unos modelos de predicción, sería una herramienta muy valiosa para los profesionales con el fin de proporcionar a los pacientes con QC progresivo, información muy útil sobre el curso postoperatorio de su enfermedad.

Se ha demostrado que las LCE consiguen una muy buena rehabilitación visual de los pacientes con QC, tanto por la mejora de la AV como de las aberraciones corneales. Sin embargo, disponer de modelos de predicción del efecto de las LCE en base a una serie de factores predictivos antes del ajuste de las LCE, resultaría en una herramienta muy útil en la práctica clínica diaria de los profesionales y, además, supondría una información muy útil

para los pacientes para estimar a priori, el probable efecto de las LCE en las córneas con QC de los pacientes.

Teniendo en cuenta todo lo mencionado previamente, la hipótesis de la actual tesis doctoral se basa en la posibilidad de definir herramientas, que permitan al profesional predecir el efecto de las distintas opciones de tratamiento del QC. De manera que se podría establecer un nomograma de implantación de ACI más optimizado y modelos de predicción de la mejora visual esperable con el uso de LCE y tras CXL epi-on y epi-off.

1.5. OBJETIVOS DE LA TESIS

A partir de la hipótesis planteada para la presente tesis, se han establecido una serie de objetivos que se detallan a continuación:

1. Analizar la calidad científica de los ECA realizados sobre CXL en el QC e igualmente determinar si las diferentes técnicas de CXL que se han descrito en la literatura actual, son igualmente efectivas.
2. Evaluar los resultados clínicos obtenidos con la implantación de ACI de F utilizando un nomograma optimizado, resultado de varios años de investigación.
3. Investigar los factores predictivos potenciales de los resultados de CXL epi-on y epi-off en pacientes con QC progresivo, considerando una gran variedad de parámetros clínicos y evaluando las diferencias en estos parámetros predictivos, entre las técnicas de CXL.
4. Investigar los factores que se correlacionan con la mejora de la AV lograda con un modelo específico de LCE y definir un modelo para predecir esta mejora, de acuerdo con los datos de ajuste previo.

SECCIÓN 2: TRABAJOS PUBLICADOS

La actual tesis doctoral está conformada por un total de tres artículos científicos publicados en revistas “peer-reviewed”:

- **Artículo 1**: Hamida Abdelkader SM, Férnandez J, Vallejo MR, García AS and Piñero DP. Comparison of Different Methods of Corneal Collagen Crosslinking: A Systematic Review. Semin Ophthalmol 2021; 36 (3):67-74. doi: 10.1080/08820538.2021.1890784. PMID: 33617389.

- **Artículo 2:** Fernández J, Martínez CP, Rueda AP, Hamida Abdelkader SM, Revert MJR and Piñero DP. Evaluation of a new nomogram for Ferrara ring segment implantation in keratoconus. Int J Ophthalmol 2021; 14(9): 1371-1383. DOI: 10.18240/ijo.2021.09.12. PMCID: PMC8403859

- **Artículo 3**: Hamida Abdelkader SM, Férnandez J, Sebastián J, Piñero DP. Preliminary Characterization of Predictive Factors of the Visual Change after Epi-On and Epi-Off Corneal Collagen Crosslinking Techniques. J Ophthalmol 2021; 9680253. DOI: 10.1155/2021/9680253; PMCID: PMC8670975.

A continuación, se incluyen los artículos de forma secuencial, creando un capítulo por cada uno de los artículos.

2.1. CAPÍTULO 1: COMPARISON OF DIFFERENT METHODS OF CORNEAL COLLAGEN CROSSLINKING: A SYSTEMATIC REVIEW

Referencia:

Hamida Abdelkader SM, Férnandez J, Vallejo MR, García AS and Piñero DP. Comparison of Different Methods of Corneal Collagen Crosslinking: A Systematic Review. Semin Ophthalmol 2021; 36 (3):67-74.

COMPARISON OF DIFFERENT METHODS OF CORNEAL COLLAGEN CROSSLINKING: A SYSTEMATIC REVIEW

Short title: Comparison among crosslinking techniques

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Abstract

Purpose: To review the scientific literature on the comparison of the efficacy of different corneal collagen crosslinking (CXL) protocols for the treatment of progressive keratoconus.

Methods: Systematic review of randomized clinical trials (RCTs) on CXL outcomes. A search was carried out using the Cochrane Library, PubMed, EMBASE, Web of Science, Ovid MEDLINE, and Scopus databases. Internal validity was analyzed by applying the filter CASPe (Critical Appraisal Skills Program Spain).

Results: The search yielded 1151 articles, and among these, 14 articles met the inclusion and exclusion criteria defined. Conventional (S) crosslinking (CXL) provided better topographic outcomes than transepithelial (TE) CXL, and S-CXL had a better therapeutic effect of corneal flattening than accelerated (A) CXL. The corneal thinning after CXL was lower with hypotonic riboflavin than with riboflavin-dextran. While one study demonstrated a better therapeutic effect of corneal flattening with S-CXL than with A-CXL, another study showed similar results between both techniques. No correlation was found between the depth of the demarcation line and topographic changes, which was not a direct measure of treatment effectiveness. Quality analysis of the literature reviewed yielded a mean score of 8.64, indicating that the RCTs evaluated had an overall acceptable quality.

Conclusions: Good-quality RCTs comparing CXL techniques have been conducted, and most of them suggest that epi-off CXL can be considered the standard treatment for progressive keratoconus. TE-CXL and iontophoresis-assisted CXL are mainly indicated in patients with a risk of corneal scarring and patients with pain intolerance, respectively.

Keywords: Corneal ectasia; keratoconus; collagen crosslinking; crosslinking assisted by iontophoresis; accelerated crosslinking.

Introduction

Keratoconus is the most frequent ectasia—defined as a progressive non-inflammatory corneal degeneration—that causes corneal thinning, myopia, and irregular astigmatism, as well as corneal scarring in the apical part in some cases, consequently leading to a loss of visual quality.[1-5] A pathophysiologic explanation for primary ectasia is currently lacking, and this suggests the contribution of environmental, biomechanical, genetic, and biochemical disorders; moreover, secondary ectasia may be caused by a purely mechanical process in a predisposed cornea and may be unilateral.[6] Great advances have been made over the last two decades in the diagnosis and management of this pathology.[1-6]

In terms of diagnosis, the advent of corneal topography and corneal tomography has increased the ability to identify corneal ectasia at an earlier stage.[6] In terms of the surgical treatment of keratoconus, intrastromal corneal ring segment implantation, corneal collagen crosslinking (CXL),[7] therapeutic excimer laser treatments, and phakic intraocular lens implantation have been combined in different ways for optical correction and to delay or prevent the need for corneal transplantation. Likewise, new keratoplasty techniques have been developed, including deep anterior lamellar keratoplasty and femtosecond laser-assisted corneal transplantation.[6]

Wollensak et al introduced the CXL treatment in 2003, being considered a standard, minimally invasive, and safe therapeutic option for progressive keratoconus.[8,9] This first treatment was based on the Dresden CXL method in which the corneal epithelium was removed prior to administration of the riboflavin solution and ultraviolet A irradiation.[10] Other approaches were described afterwards to avoid complications

associated with epithelial debridement and to allow for less postoperative discomfort and quicker recovery times:

1. Transepithelial CXL in which the corneal epithelium is left intact,[10] avoiding complications associated with epithelial debridement and promoting less postoperative discomfort and quicker recovery times.[9,10]
2. Transepithelial iontophoresis-assisted CXL (I-CXL) in which the impregnation of the cornea with a hypotonic 0.1% riboflavin solution is performed using an iontophoresis device. A passive electrode (anode) is applied to the inferior part of the cervical vertebrae and the active electrode (cathode), a bath tube made of glass or plastic, is then applied to the open eye.[9]
3. Corneal reshaping and cross-linking (CRXL), which is a CXL procedure combined with mechanical compression of the cornea using a flat rigid contact lens sutured to the cornea during the treatment.[11]
4. PiXL (photorefractive intrastromal crosslinking), technique with an individualized treatment plan, based on the corneal topography, with local augmentation of the treatment effect in the most ectatic zone.[12]

Nevertheless, there is still a need for more randomized clinical trials (RCTs) to determine the effectiveness and visual outcomes of the different CXL techniques. Therefore, this systematic review aimed to analyze the scientific quality of RCTs performed on CXL in keratoconus and to determine whether the different CXL techniques described in the current literature are equally effective.

Methods

The literature search for this systematic review was focused on retrieving comparative studies on the efficacy and safety of different types of CXL for the treatment of progressive keratoconus. This search was performed on the following databases: Cochrane Library, PubMed, EMBASE, Web of Science, Ovid MEDLINE, and Scopus. In the Web of Science and Scopus databases, the option of performing the search in all databases was used to avoid the omission of any potentially relevant article for the current review.

The following search equation was used considering that the terms could appear in the title, summary, or keywords of the article:

((Crosslink*) and (“Corneal ectasia” or “keratoconus”))

Once the relevant articles were identified according to our search equation, their abstracts were carefully analyzed by the same researcher (Sidi Mohamed). The following inclusion criteria were defined for selecting the articles included in the current systematic review: RCTs; articles written in English, French, or Spanish; and comparative articles analyzing at least two different CXL techniques. Therefore, articles not using an intervention group in their methodology; animal, cohort, cross-sectional, and case-control studies; and case series or case reports were excluded from this systematic review. After selecting the relevant articles, manual searches were performed by reviewing the reference list of such articles to identify any additional and potentially relevant articles.

The methodology, results, conclusions, limitations, and biases of each clinical trial were evaluated using the CASPe tool (Critical Appraisal Skills Program Spain), which is a critical reading instrument that allows analysis via questions regarding the

internal validity of the study and its results, as well as whether the results can be extrapolated to the population.[13] The CASPe questionnaire designed for the evaluation of clinical trials was used, and this comprised 11 questions. A result of 7/11 was considered a minimum acceptable quality value for any study evaluated using the CASPe tool.[13] If the quality value of a study was lower, a critical attitude was adopted towards that study.

Results

The search equation was executed on August 5, 2018, and the literature search was completed on May 5, 2019. The results of the search were as follows: Scopus (449), Web of Science (88), Ovid Medline (320), Cochrane (216), PubMed (29), and EMBASE (49).

All the studies that passed the filter were written in English. According to the inclusion and exclusion criteria, 14 RCTs were selected from all the databases. Of the 14 studies included, 2 compared hypotonic riboflavin (HR) with riboflavin-dextran (DR) [in the 2 studies, S-CXL was used], 5 compared S-CXL with A-CXL, 2 compared TE-CXL with S-CXL, 1 compared S-CXL with CRXL, 1 compared S-CXL with I-CXL, 1 compared different A-CXL techniques, 1 compared PiXL and uniform pulsed CXL, and 1 compared S-CXL, A-CXL and TE-CXL. The analysis included 764 eyes in the epithelial removal group and 227 eyes in the TE group.

All studies fundamentally evaluated the changes in visual, refractive, keratometric, and biomechanical values and corneal densitometry. The different studies used various methodologies to evaluate the following parameters: central corneal thickness, steep and flat keratometry, uncorrected and corrected distance visual acuity (UDVA and CDVA, respectively), refractive error, endothelial cell count (ECC), specular microscopy, corneal hysteresis, corneal resistance factor, area of peak 2, and intraocular pressure.

In general, the evaluated studies used similar criteria for diagnosis and similar study designs. The included articles are listed in alphabetical order of the first author's name in the tables. Table 1 summarizes the main characteristics and results of the study.

Table 1.- Summary of different comparative clinical trials analysed in the current systematic review.

Author, year, journal	CXL technique irradiation intensity (mWcm2) / time (min)	Subjects	Mean age (years)	Time (months)	Summary of the results
Al Fayez et al (2015) ***Cornea***	TE CXL (3/30) vs Standard epi-off CXL (3/30)	34 vs 36	24.8 vs 24.1	36	-Epi-off group was **more effective** in stopping the progression of keratoconus: -Epi-off group: 100% patients -TE group: 45% stabilized or improved and 55% progressed -**K max**: -Decreased in epi-off group -Increased after 3 years in TE group -**UDVA** improved significantly after the first year in Epi-off group. -No differences between groups in **CDVA** -Epi-off was **significantly more effective** than TE CXL, for the visual and corneal results in the medium-term observed
Bikbova et al (2016) ***Acta Ophthalmol***	Standard epi-off (3/30) vs epi-on I-CXL (3/30)	73 vs 76	30 vs 28	24	-**CDVA:** I-CXL produces more increase of CDVA vs S-CXL at 6 months, but no differences at 24 months; maybe because of the greater edema and/or epithelial remodeling in S-CXL -**DD:** -S-CXL 292 +/- 14 microns -TE CXL 172 +/- 16 microns -No DL was detected 1 month and 3 months after CXL in 45% and 100% of the patients.

Table 1. Continued

Author, year, journal	CXL technique irradiation intensity (mWcm2) / time (min)	Subjects	Mean age (years)	Time (months)	Summary of the results
Choi et al (2017) ***Cornea***	Standard epi-off (3/30) vs Accelerated CXL (30 / 3.6)	15 vs 13	25.6 vs 23.7	6	-Improved AV, spherical equivalent increased, Kmax and K m improved (standard CXL) -Both CXL improved the cylindrical refractive error -CCT decreased significantly in standard CXL, without significant change in accelerated CXL -Accelerated CXL presents a smaller topographic flattening compared to standard CXL
Fry et al (2011) ***Invest Opthalmol Vis Sci***	Standard epi-off CXL with DR (3/30) vs Standard epi-off CXL, with HR (3/30)	26 vs 18	29.2 vs 32.5		-The **average corneal thinning** was 95.4 (*HR*) and 126.2 (*RD*) -8 eyes required (3 *HR*, 5 *RD*) HR due to a minimum corneal thickness of 400 µm -After CXL, **average corneal thickness**: *HR* 335.2 µm (baseline 451.6), *RD* 304.4 µm (baseline 433.7) -**Mean corneal thinning** is **less** with **HR** compared to standard *RD*, as the pachymetric changes demonstrated
Hagem et al (2019) ***Cornea***	-Standard epi-off (3/30) vs Accelerated epi-off CXL (9/10) -Solution of 0.1% riboflavin with 1.1% HPMC	17 vs 15	23.4 vs 23	24	-Both groups had statistically significant **improvement in CDVA and K max** (no statistically significant differences in the change between the 2 groups) -Both groups had **not statistically significant changes in ECD** (Endothelial Cell Density) -**Similar topographic flattening** (conventional and accelerated CXL) -**DD:** -Probably the use of riboflavin-methylcellulose produces a **deeper demarcation line**
Hashemi et al (2015) ***J Cataract Refract Surg***	Standard epi-off (3/30) vs Accelerated CXL (18/5)	29 vs 29	25.13	6	-There was **not statistically significant changes between both groups in ECC, CDVA, UDVA, spherical and cylindrical error, MRSE, Kmax and Km** -Changes in **corneal hysteresis, corneal resistance factor and area under peak 2** were similar in both groups -The **mean decrease in the corneal thickness** was: **-16 mm** in the standard group **-13.52** mm in the accelerated group

Table 1. Continued

Author, year, journal	CXL technique irradiation intensity (mWcm2) / time (min)	Subjects	Mean age (years)	Time (months)	Summary of the results
Mesen et al (2018) ***Cornea***	Conventional (3/30), accelerated (18/5) and transepithelial CXL (3/30)	73 vs 39 vs 12	19	24	-**Conventional** CXL: -Statistically significant decrease in **K1, K2, Km, K max** parameters -Significant improvement in BCVA -**Accelerated** CXL: -Statistically significant decrease in **K1** and **K max** -**TE** CXL: **-K1, K2, K mean** and **K max** parameters decreased significantly -There were **no differences** in **K max** between the 3 groups -The use of **riboflavin-dextran or riboflavin with hydroxypropyl methylcellulose**, did **not** produce statistically significant **differences** in the **topographic parameters** -**DD** was **greater** in the **accelerated** and **conventional** CXL.
Nordstrom et al (2017) ***Br J Ophthalmol***	PiXL (7.2 J / cm2, 10 J / cm2, 15 J / cm2) vs uniform pulsed CXL, epi-off (5.4 J / cm2) (8/ 30))	25 vs 23	27.7	12	**PiXL**: 1. Improves the **shape** of the cornea 2. Decrease **spherical refractive error** 3. Improves **visual acuity** 4. Significant decrease in **Kmax**
Rehnman et al (2015) ***JAMA Ophthalmol***	Standard epi-off CXL (3/30) vs CRXL (3/34)	30 vs 30	23.7 / 23.4	6	- Increased **sensitivity**, deeper and more pronounced in the CXL group, with progressive decrease in time and proportional to the reduction of the corneal inclination

Table 1. Continued

Author, year, journal	CXL technique irradiation intensity (mWcm2) / time (min)	Subjects	Mean age (years)	Time (months)	Summary of the results
Rosenblat et al (2016) ***J Cataract Refract Surg***	Standard DR epi-off (3/30) vs HR epi-off CXL (3/30)	26 vs 20	29 vs 28	12	-**Corneal Thickness:** -DR group thinned by 129 microns on average -HR group thinned by 95 microns on average -Corneal thickness is **better maintained** using a **HR** **-Maximum Topographic Keratometry** -There were **no** statistically significant **differences** in the postoperative mean **Kmax** between the 2 groups, although there was an **improvement** in **Kmax** in **each group** **-UDVA** -There was **no** significant **difference** in UDVA outcome between the 2 groups **-CDVA** The **mean change** between the preoperative and 12-months postoperative CDVA was **statistically significant** between the 2 groups -The change in **endothelial cell count (ECC) was:** -**70** cells/mm^2 RD group -**228** cells/mm^2 HR group -There was **no relationship** between the **corneal thickness** and **the change in ECC**
Rush et al (2017) ***Br J Ophthalmol***	Standard epi-off (3/30) vs TE CXL (3/30)	56 vs 75	31.5 vs 29.8	24	-**Epi-off** CXL: -Statistically significant improvement in **K steep, BSCVA** -**Epi-on** CXL: -Statistically significant improvement in **BSCVA** **-Epi-off vs Epi-on**: - Epi-off presented a greater change in **Ksteep** **-Epi-off vs Epi-on**: -There was no difference in **BSCVA**

Table 1. Continued

Author, year, journal	CXL technique irradiation intensity (mWcm2) / time (min)	Subjects	Mean age (years)	Time (months)	Summary of the results
Sadoughi et al (2016) ***Int Ophthalmol***	Standard epi-off (3/30) vs Accelerated CXL (9/10)	15 vs 15	19.40	12	-**Standard** epi-off: -**Spherical equivalent** and **refractive astigmatism** decreased significantly -**Both groups**: -Improvement of **CDVA** was borderline significant -**UDVA** did not change significantly -There was a decrease in **K max** and **K mean** which were not statistically significant -**Topographic astigmatism** decreased, but this was significant only, in standard group -There was not a significant change in **ECD** -There was no significant correlation between change in **ECD** and **CCT**
Sherif et al (2014) ***Clin Ophthalmol***	Standard epi-off (3/30) vs Accelerated CXL (30 / 4.3)	11 vs 14	23.64 vs 21.58	12	-**Accelerated group**: -**Kmin** was reduced, but was not statistically significant -**Kmax** was reduced and this reduction was statistically significant -Mean **CCT** showed a statistically **significant reduction** -Mean **BCVA** improved and the difference was statistically significant -**Conventional group**: -**Kmin** was reduced, but was not statistically significant -**Kmax** was reduced, but was not statistically significant -**BSCVA** improved and the difference was statistically significant -The reduction differences of **K max** between both groups were **no** statistically **significant**
Yildirim et al (2017) ***Curr Eye Res***	Accelerated (5/18) vs Accelerated CXL (4/30)	74 vs 72	22.8 vs 22.4	12	-Mean **UDVA** and **CDVA**: -There was no statistically significant difference between the groups -**K max** was reduced and this reduction was statistically significant -**Mean sphere, cylinder** and **spherical equivalent (SE)**: -There were no statistically significant differences

Abbreviations: CXL, corneal collagen cross-linking; DR, dextran-riboflavin; HR, hypotonic riboflavin; Epi-off, epithelium-off; Epi-on, epithelium-on; S-CXL, standard corneal collagen cross-linking; TE-CXL, transepithelial corneal collagen cross-linking; ACXL, accelerated corneal collagen cross-linking; CRXL, corneal reshaping and cross-linking; I-CXL, corneal collagen cross-linking assisted by epi-on iontophoresis; PiXL, photorefractive intrastromal corneal collagen cross-linking; CDVA, corrected distance visual acuity; UDVA, uncorrected distance visual acuity; DD, depth of the demarcation line; K, keratometry; Kmax, maximum keratometry; Km, average keratometry; MRSE, manifest refraction spherical equivalent; CCT, central corneal thickness; HPMC, hydroxypropyl methylcellulose

Table 2 presents the diagnostic criteria used to define the progression of keratoconus and the results of the CASPe analysis in the different studies. Two trials achieved a minimum CASPe score of 7/11,[14,15] and four achieved a score of 10/11.[10,12,16,17] However, none of the studies achieved the maximum score of 11/11. Most of the trials returned a negative answer to the following three questions in the CASPe tool. Were patients, health workers, and study personnel "blinded" to the treatment? How precise was the estimate of the treatment effect? Were all clinically important outcomes considered? Therefore, the CASPe score decreased in the studies evaluated mainly because of the lack of blinding of the samples and/or the lack of confidence intervals of the results obtained for the different parameters studied.

Table 2.- Results of the quality analysis (CASPe tool) and definition of the keratoconus progression criteria in each study evaluated.

Study	CASPe Score	Keratoconus progression criteria	Time
Al Fayez et al (2015)	10/11	Keratometry values > 1 D Manifest cylinder > 1 D	12 months
Rehnman et al (2015)	9/11	Increase in K steep and astigmatic keratometry Decreasing CDVA	
Bikbova et al (2016)	8/11	Increase K max of 1 D or more in manifest cylinder Increase of 0.5 D or more in manifest spherical equivalent refraction	12 months
Choi et al (2017)	8/11	Increase in K max by > 1.5 D Decrease in the thinnest pachymetry by more than 5%	
Fry et al (2011)	7/11	No progression criteria defined	
Hagem et al (2019)	8/11	Minimal increase of 1 D in K max, 1 D or more in manifest cylinder Minimal decrease in spherical equivalent of 0.5 D	
Hashemi et al (2015)	8/11	Increase of 1 D or more in K max, manifest cylinder or manifest refraction spherical equivalent Loss of at least 2 lines of CDVA	12 months
Mesen et al (2018)	10/11	Keratometry values > 1 D Decrease in > 0.1 mm > 1 D increase in manifest cylinder	6 to 12 months
Nordstrom et al (2017)	10/11	Increase of 1 D or more in K max (1 year) Increase keratometric astigmatism and corneal steepness Decrease in CDVA	
Rosenblat et al (2016)	9/11	No progression criteria defined	
Rush et al (2017)	10/11	Increase of K steep > 1 D or more Increase in astigmatism or myopia by manifest refraction of 1 D or more	12 months
Sadoughi et al (2016)	8/11	Increase 1 D or more in K max Equal or more than 2 lines loss of CDVA Increase 1 D or more in cylinder of manifest refraction Increase 1 D or more in manifest refraction spherical equivalent	
Sherif et al (2014)	9/11	Increase 1 D or more in K max Increase 1 D or more in the manifest cylinder, or 0.5 D or more in the manifest refraction spherical equivalent	6 months
Yildirim et al (2017)	7/11	Reduced UDVA or CDVA of more than 0.5 Snellen lines Increase in the K max by 1 D Increase in the spherical/cylinder refraction or topographic symmetry index (SIA) of more than 0.5 D Decrease in CCT of more than 10 microns	12 months

Abbreviations: CDVA, corrected distance visual acuity; UDVA, uncorrected distance visual acuity; K, keratometry; Kmax, maximum keratometry; CCT, central corneal thickness.

Discussion

As different CXL techniques have been described, comparative studies are crucial to evaluate differences between them. The objective of the current systematic review was to analyze all comparative studies on CXL and to evaluate their quality using a validated methodology. After a careful analysis of the RCTs included in the current systematic review, the main conclusions of these trials have been listed and divided by sections, as described below.

Hypotonic riboflavin vs riboflavin-dextran CXL

Rosenblat et al[18] observed that corneal thinning was reduced by 30% when using HR CXL, albeit without specific differences in terms of clinical efficacy, functionality, or changes in ECC. They showed that if the cornea was thinner than 400 μm, HR could be administered, and ultrasonic pachymetry could be performed to confirm that the cornea was swelled with HR until its thickness was 400 μm or more. Among 48 eyes evaluated in that study, 9 eyes in the standard riboflavin group and 6 in the HR group required hypotonic swelling. The patients were evaluated for maximum keratometry (Kmax), UDVA, CDVA, corneal thickness, and ECC.[18]

In another study conducted by Fry et al,[14] greater corneal thinning was observed with DR than with HR. The use of HR seemed to better maintain a consistent corneal thickness during UV irradiation. In their sample of 44 eyes that underwent CXL, 8 eyes (3 and 5 eyes in HR and DR groups, respectively) required the use of HR to maintain a minimum corneal thickness of 400 μm prior to UV irradiation. The mean corneal thinning with UV irradiation was significantly greater in the no-HR group than in the HR group, with mean thicknesses of 335.2 and 304.4 μm, respectively.[14]

Riboflavin with hydroxypropyl methylcellulose (RHM) CXL

Hagem et al[19] showed an improvement in visual acuity and Kmax after both S-CXL and A-CXL using RHM. The results showed similar topographic flattening between both the techniques and greater topographic flattening after A-CXL with RHM than with DR, which may be due to a potentially higher corneal concentration gradient of methylcellulose-riboflavin, which would facilitate the diffusion of certain molecules into the cornea. Furthermore, the use of RHM could be the reason for the deeper demarcation line found after both CXL modalities, and this may imply that RHM contributes to a deeper and more efficient CXL treatment than does riboflavin-dextran.

Standard epi-on (TE) vs standard epi-off (S) CXL

Al Fayez et al[17] reported than S-CXL was more effective in arresting the progression of keratoconus than was TE-CXL, but the latter was more comfortable for patients. Kmax decreased in the S-CXL group and increased in the TE-CXL group, and UDVA improved significantly in the S-CXL group.

In the study by Rush et al,[10] the results suggested that S-CXL was superior to TE-CXL in improving keratometry measurements, and that ocular surface penetration

of riboflavin into the corneal stroma in the TE-CXL group was inferior to that in the S-CXL group despite the application of a more concentrated riboflavin formulation and the frequent instillation of benzalkonium chloride.

Standard epi-off (S) vs accelerated epi-off (A) CXL

Hashemi et al[20] found that A-CXL and S-CXL arrested the progression of keratoconus similarly defined in terms of changes in visual indices, refraction, topographic and corneal rigidity indices, and ECC. Central corneal thickness was greater in the standard group than in the accelerated group. Nevertheless, no statistically significant differences were found in visual acuity, maximum and mean keratometry, corneal hysteresis, and corneal resistance factor between the two groups.

Choi et al observed that A-CXL induced a smaller topographic flattening effect than did S-CXL, possibly due to a higher oxygen consumption rate with this technique because of the high level of UV-A irradiance. It is probably because if the usage exceeds the amount restored by diffusion, oxygen would be depleted, impeding the CXL process.[21,22] Both CXL techniques were compared in terms of visual acuity, refractive error, keratometry values, corneal thickness, and topometric indexes. The cylindrical refractive error improved in both groups. In the S-CXL group, visual acuity improved significantly, spherical equivalent increased, and Kmax and mean keratometry decreased. In contrast, in the A-CXL group, changes in visual acuity, refractive errors, and keratometric values did not differ significantly.[21]

Sadoughi et al[23] found in another clinical trial that A-CXL provided similar visual, refractive, keratometric, and aberrometric results and had less adverse effects on corneal thickness and endothelial cells than did S-CXL. These authors evaluated changes with both techniques in manifest refraction, UDVA, CDVA, Kmax, mean

keratometry, corneal hysteresis, corneal density factor, endothelial cell density, central corneal thickness, and corneal wavefront aberrations.[23]

Sherif et al[24] found that A-CXL provided comparable results to conventional CXL in arresting the progression of keratoconus. This study included the evaluation of UDVA, CDVA, Kmax, minimum keratometry, and central corneal thickness. It found a significant improvement in manifest refraction spherical equivalent and refractive cylinder in the S-CXL group. However, UDVA, CDVA, and keratometric values did not change significantly in either group.[24]

Comparison of different A-CXL protocols

Yildirim et al[15] demonstrated that the application of the total intended UV-A radiation of 5.4 J/cm^2 or 7.2 J/cm^2 for A-CXL provided similar refractive and topographic outcomes, with no significant differences between techniques in UDVA, preoperative or postoperative corneal topography, keratometric readings, and refractive results.

CXL assisted by epi-on iontophoresis (I-CXL) vs standard epi-off (S) CXL

Bikbova et al[9] showed that I-CXL was effective in arresting keratoconus progression, with a statistically significant improvement in visual and topographic parameters. However, the demarcation line was more superficial and was completely absent in all patients for 3 months, and pachymetry reduction was less than that in patients undergoing S-CXL. Furthermore, the Kmax decrease was more significant (2.15 D) than that in the TE-CXL group. In conclusion, the findings showed that S-CXL was more effective than I-CXI.

PiXL vs uniform pulsed CXL

Nordstrom et al[12] observed that uncorrected visual acuity and best spectacle-corrected visual acuity worsened at 1 month after CXL, but these parameters did improve after PiXL. This could probably be because the central part of the cornea is spared from irradiation in PiXL, and this may lessen the post-treatment haze in the central optical zone.

Although minor improvements in Kmax and refractive errors after PiXL may not be noticed by the individual patient, the impression is that PiXL has a potential for reshaping the keratoconus cornea to a higher degree than does S-CXL.[12]

Comparison of demarcation line depth with different CXL protocols (S-CXL, A-CXL, and TE-CXL)

Mesen et al[16] reported a greater depth of the demarcation line with A-CXL and S-CXL than with TE-CXL, but without any correlation between this demarcation line and the induced topographic changes.

Crosslinking with mechanical compression of the cornea (CRXL) vs standard (S) epi-off CXL

The increase in corneal densitometry is less pronounced in the CRXL group, but the peripheral cornea shows a greater relative increase in densitometry than does the central cornea after CRXL.[11] This could be because the contact lens blocks oxygen from reaching the stroma. Similarly, the potential inferiority of A-CXL observed in some studies may be secondary to oxygen depletion.[11] The increased densitometry becomes more pronounced over the time course in S-CXL than in CRXL, possibly because of higher oxygen tension in the corneal stroma during S-CXL.[11] In summary, differences

in densitometry are more clinically evident in S-CXL than in CRXL.[11]

After summarizing the contents and main conclusions of the included articles, their quality was analyzed using the CASPe tool. According to this analysis, the trials selected were found to have good scientific quality, but none of them reached the highest quality score (11/11) mainly because of the lack of blinding and/or the lack of confidence intervals. In the current systematic review, only comparative RCTs were selected, and all of them achieved a CASPe score of 7/11 or higher.

The limitations of this systematic review are detailed below:

1. The review included a limited number of RCTs comparing CXL techniques.

2. Further studies with larger samples sizes aimed at comparing the complications of TE-CXL vs S-CXL are necessary.

3. Further studies are warranted to determine how to deliver riboflavin to the corneal stroma in a more effective mode during UV-A irradiation.

4. In the study by Rush et al,[10] a change in refraction was used to define disease progression, without considering variables such as changes in pachymetry, keratometry, or ECC.

5. The study by Choi et al[21] presents the limitations of a small sample size (as does the study by Hagem et al[20]) and a short follow-up period.

Our systematic review has important implications for daily clinical practice, focusing the protocol to be used depending on several characteristics of the patient. Randomized controlled trials have demonstrated that riboflavin-UVA S-CXL is successfully able to halt disease progression in keratoconus if keratoconus progression is reliably identified. While the standard Dresden protocol is established as the gold standard treatment for progressive keratoconus, there is also an increasing number of RCTs evaluating other modalities of CXL that can have some specific benefits in some

particular conditions.

Conclusions

The following conclusions can be drawn from this systematic review:

1. Currently, there is a dearth of evidence-based criteria for recommending a specific CXL technique for each type of corneal ectasia. However, CXL (both TE-CXL and S-CXL) seems to provide better results in keratoconus than in pellucid marginal degeneration.

2. S-CXL may be considered a potential gold standard, being more effective than TE-CXL in progressive corneal ectasia.

3. The incidence of complications remains a concern with S-CXL, whereas TE-CXL is well tolerated and has a low risk of complications.

4. CXL decreases corneal thickness generally in the early postoperative course and this finding has been related to the epithelial removal, riboflavin instillation phases and the compression of collagen fibrils or keratocyte apoptosis, which is even maintained at 6 months after surgery.[20,21]

5. The corneal flattening achieved with S-CXL has been shown to be greater than that obtained with A-CXL[21]. However, some authors have found no significant differences in the flattening effect obtaining with both techniques, confirming that there may be factors potentiating the CXL effect achieved with both techniques.[19,20,23,24] Some of these factors, may be the use of methylcellulose-riboflavin, that could facilitate the diffusion of certain molecules into the cornea.[19]

6. TE-CXL may be preferred in patients with diabetes mellitus, a history of herpetic keratitis or other risk factors that can result in delayed corneal epithelium healing.[10]

7. I-CXL may be recommended preferably for use with thin corneas, in pain-intolerant patients, and in older patients with slowly progressing keratoconus.[9]

8. Only one comparative clinical trial evaluating PiXL showed that an increase in irradiation energy (up to 15 J/cm^2) also increased the treatment effect, while being safe for the corneal endothelium. On the basis of this finding, increases in irradiation energy in CXL protocols can be proposed to achieve a greater treatment effect.

9. Corneal thickness is modified less when using a solution of HR during the UV-A irradiation phase in CXL.

10. More controlled studies are required to extract more consistent conclusions about the efficacy and safety of different CXL techniques.

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2.2 CAPÍTULO 2: EVALUATION OF A NEW NOMOGRAM FOR FERRARA RING SEGMENT IMPLANTATION IN KERATOCONUS

Referencia:

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EVALUATION OF A NEW NOMOGRAM FOR FERRARA RING SEGMENT IMPLANTATION IN KERATOCONUS

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Abstract

AIM: To evaluate the short-term clinical outcomes of Ferrara rings in keratoconus using an optimized nomogram developed after several years of research and retrospective analysis of clinical data.

METHODS: This prospective longitudinal non-comparative clinical trial evaluated 88 eyes of 88 patients (age 18-62y) with keratoconus diagnosis from two Spanish centers. Ferrara ring segment (AJL Ophthalmic) implantation was performed in all cases, using the mechanical procedure in 25 eyes (28.4%) and a femtosecond laser-assisted procedure in 63 eyes (71.6%). The ring segments implanted in each case were selected using a new optimized nomogram that considered variables such as anterior corneal asphericity and astigmatism or the discrepancy among astigmatism and coma orientations. Visual, refractive, corneal topographic, aberrometric, and pachymetric changes after surgery were evaluated during a 3-month follow-up.

RESULTS: The implants induced a significant refractive change as well as an improvement in uncorrected (UDVA) and corrected distance visual acuity (CDVA; $P<0.001$). Postoperative CDVA of 0.10 logMAR or better was achieved in 28.4% and 46.5% of eyes, respectively. Two eyes (2.3%) lost two or more lines of CDVA whereas a total of 53.5% of eyes gained lines of CDVA. A significant central anterior and posterior corneal flattening was induced ($P\leq0.003$), with a significant reduction of anterior ($P<0.001$) and posterior corneal astigmatisms ($P=0.048$), and a change in anterior asphericity ($P<0.001$). Total primary coma (6 mm pupil) change was also statistically significant (preoperative 3.66±3.04 μm *vs* postoperative 2.33±2.26 μm, $P<0.001$). No significant differences were found in the effect of ring segments between cases implanted using the mechanical and femtosecond techniques ($P\geq0.101$).

CONCLUSION: The implantation of Ferrara rings based on the nomogram evaluated is safe and effective for promoting a visual rehabilitation in keratoconus, with a relevant control of primary coma aberration.

KEYWORDS: intracorneal ring segment; Ferrara ring segment; femtosecond; keratoconus; coma aberration

INTRODUCTION

Keratoconus is a corneal ectatic disorder that results in progressive thinning of the cornea, increase of corneal irregularity and consequently poor visual quality leading to a reduction of the quality of life[1]. The debut of this condition in pediatric population is usually in a moderate to advanced stage, particularly in female patients[1]. Concerning the management of keratoconus, corneal collagen crosslinking (CXL) is an effective option to control its progression, with an increased risk of evolution of the disease associated to a higher economic burden if this surgical option is delayed when signs of progression are evident[2]. Intracorneal ring segments (ICRS) have been also investigated during many years as a therapeutic option for the management of keratoconus and other corneal ectatic diseases[3-6]. ICRS implantation in keratoconus significantly reduces the level of corneal high order aberrations and irregularity, leading to an improvement in visual quality[3-6]. However, there is also a great variability between studies, with some of them showing discrepant findings[3-6]. One of the main factors accounting for this variability is that most of studies are not controlled or have non-consistent designs, with no randomized comparative clinical trials performed to this date[3]. Another important factor also accounting for the variability among studies, even using the same type of ring segments, is the great variability in the nomogram or implantation criteria used. Many attempts have been done by means of simulation models of predicting the potential effect of ICRS, leading to some trends that have been found to be consistent with clinical data, such as the influence of ring thickness and diameter on the level of central flattening induced as well as the influence of the depth of implantation[7-9]. However, many of the nomograms that are being used in last years are based on empirical data or personal approximations or experiences[10-11]. There is currently a need for the development of new optimized nomograms overcoming the limitation of previous experiences and leading to higher levels of predictability. It should be considered that although ICRS implantation is safe, suboptimal results are still present in some cases, requiring adjustments and even the explantation of the ring segment[12-13].

Ferrara-type ring segments have been investigated during many years and demonstrated to be a safe option to manage corneal irregularities in a great variety of corneal conditions, including keratoconus[14-24]. It has been even confirmed the histological reversibility of the cornea when the ring segments are explanted[25]. Initially, most of case series evaluating the outcomes with this type of implants were empirical, using refraction and keratometry as key factors for the selection of the ring segments to implant in each case[26-28]. These nomograms were significantly optimized considering the peculiarities of the topographic pattern[15,17]. These optimizations were the basis for the development of a highly optimized nomogram in which the topographic pattern is considered when selecting the ring segments to implant, including factors such as asphericity, alignment of astigmatic and comatic axes. The aim of the current study was to evaluate the short-term clinical outcomes obtained with the implantation of Ferrara ring segments using this optimized nomogram which is the result of several years of research.

SUBJECTS AND METHODS

Ethical Approval. The study was evaluated and approved by the Ethics Committee of these two institutions, being performed in accordance with the ethical standards laid down in the Declaration of Helsinki. Before recruitment, the characteristics and risks of the study were carefully explained to each patient. Only those providing written informed consent and accepting the conditions of the study were enrolled.

Subjects A total of 88 eyes with the diagnosis of keratoconus of 88 patients was included in this prospective multicenter longitudinal non-comparative clinical trial (QC-CHT-2017, 46/2017). Implantation of Ferrara ring segments (AJL Ophthalmic, Vitoria-Gasteiz, Spain) was performed in all cases. The recruitment and follow-up of patients was performed in 2 different Spanish ophthalmological centers following the same protocols and guidelines: Hospital Torrecárdenas (Almería) and FISABIO-Oftalmología Médica (FOM) (Valencia).

Inclusion criteria for the study were age of 18y or more and presence of keratoconus according to the standard criteria of diagnosis of this condition consisting of asymmetric topographic

pattern and at least one of the following clinical signs on slit-lamp: stromal thinning, conical protrusion of the cornea at the apex, Fleischer ring or Vogt striae)[29]. Only one eye per patient was selected randomly to avoid the potential bias introduced by the inter-eye correlation that is present when including data from both eyes of each subject. The presence of severe (grade IV, Amsler-Krumeich)[30] or progressive keratoconus (increase of 1.50 D or greater per year)[31], previous ocular surgeries, active systemic or ocular diseases, ocular media opacity, and pregnancy were considered as exclusion criteria for the study. No contact lens fitting was performed in any case during the follow-up of this study.

Clinical Protocol. All eyes underwent a complete eye examination before surgery that included anamnesis, measurement of uncorrected (UDVA) and corrected distance visual acuity (CDVA) using Snellen charts, manifest and cycloplegic refraction, slit-lamp anterior segment examination, infrared pupillometry, corneal topographic, aberrometric and pachymetric analysis with the Pentacam HR system (Oculus Optikgeräte GmbH, Wetzlar, Germany), and fundus evaluation under pupil dilation. An eye examination was performed in all patients the day after surgery, including measurement of UDVA and analysis of the integrity of the cornea by slit lamp. Likewise, patients were revised at 1 and 3 mo after surgery, performing in all cases the following tests: slit lamp biomicroscopy, corneal topography and aberrometry, pachymetry, measurement of UDVA and CDVA, and manifest refraction. Total corneal aberrations considering the contribution of the combination of both anterior and posterior corneal surfaces were considered for the statistical analysis.

Ring Segments and Nomogram. Intracorneal Ferrara rings consists of semicircular segments with an arc of multiple lengths (90º, 120º, 140º, 150º, 160º, 180º, 210º, and 320º) and a fixed triangular section: AFR (0.60 mm base, 5.0 mm optical zone) and AFR6 (0.80 mm base, 6.0 mm optical zone). They are made of polymethyl methacrylate (PMMA) with natural blue light filter. Each segment has an orifice of 0.20 mm at each end to facilitate its implantation. Furthermore, different thicknesses are available (0.15, 0.20, 0.25, 0.30, and 0.35 mm) for each type of segment.

For a more optimized selection of the ring segments to implant in each case, a new nomogram has been developed due to several years of research[15,17]. The research group has conducted some investigations about how to proceed with Ferrara ring segment selection in paracentral keratoconus, confirming the benefit of different combinations of ring segments depending on the differences between the axes of refractive cylinder and the corneal flattest meridian and the comatic aberration map[15,17]. According to all this previous experience, the manufacturer established a new optimized nomogram considering the asphericity of the anterior corneal surface, the magnitude of astigmatism of such surface and the level of discrepancy among astigmatism and coma orientations to define the most adequate combination of ring segments to implant in each case. Specifically, each cornea was classified according to 16 different corneal patterns or phenotypes (Figure 1), which were associated to the recommendation of the implantation of a specific ring segment or combination of segments.

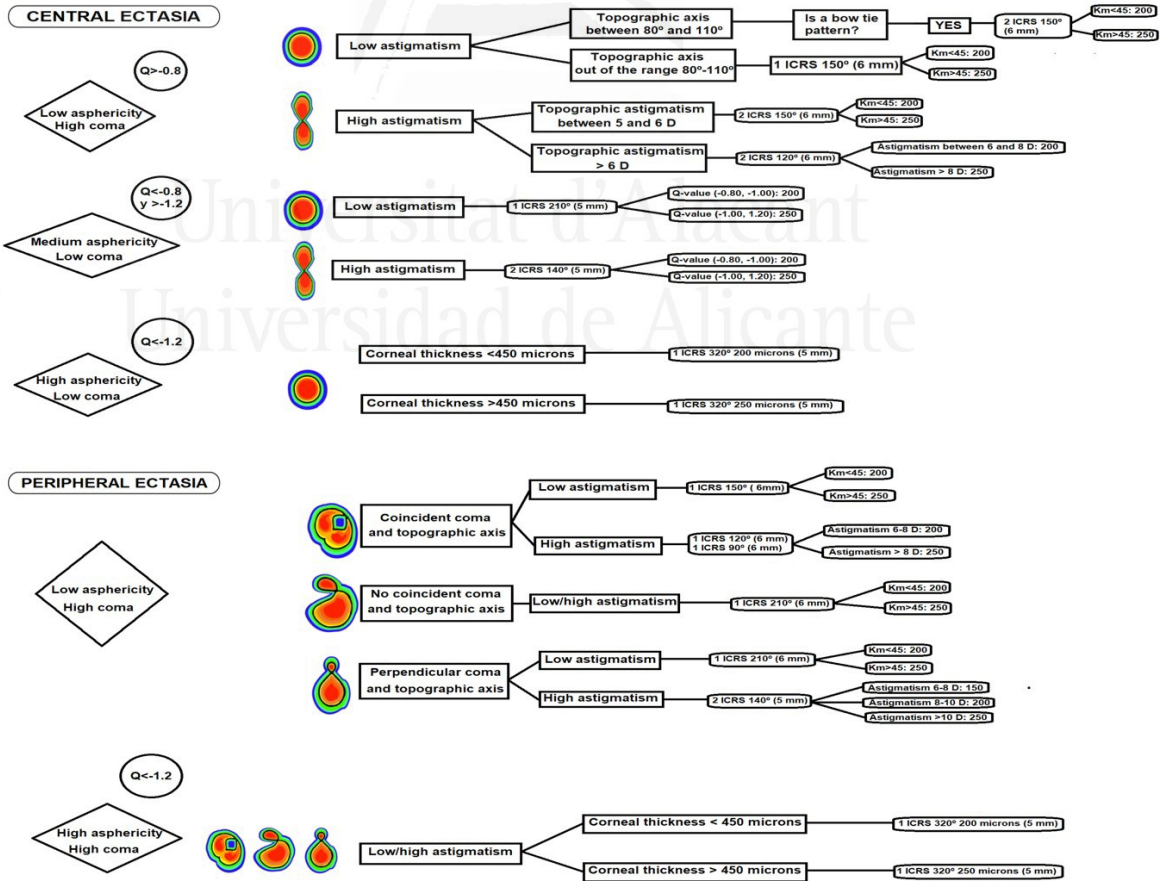

Figure 1.- Personalized nomogram developed for Ferrara ring segments, showing how each case is classified for the selection of the most suitable ring segment to implant. First, corneal asphericity and the primary coma level on the anterior corneal surface (left column) are considered. After this, the relative position of the axes of coma and corneal astigmatism (central column) is evaluated. Finally, the magnitude of astigmatism (right column) is considered, thus defining a total of 16 different phenotypes or corneal topographic patterns.

Surgical Procedures. All surgical procedures were performed by one of two expert surgeons under topical anesthesia (application of 2 drops of Proparacaine 10min before surgery). These procedures were initiated in all cases with the creation of corneal incisions on the steepest meridian according to the topographic map. In FISABIO-Oftalmología Médica Centre, the Intralase® femtosecond laser (Johnson and Johnson Surgical Vision, Groningen, the Netherlands) was used to generate the corneal tunnels for the insertion of ring segments. The first steps for the creation of the tunnels were to mark the center of the pupil reflex on the slit-lamp and afterwards the positioning of the vacuum suction ring onto the eye. Then, the disposable glass lens of the femtosecond laser system was applanated to the cornea to fixate the eye. After this, the femtosecond laser initiated the photodisruption process, creating a continuous circular stromal tunnel at approximately 80% of corneal depth.

In Torrecárdenas Hospital, the technique of mechanical dissection was used for the creation of the tunnels as femtosecond technology was not available in this institution. The creation of a mark to be used as a reference point for centration (pupil reflex) was the first step of the surgical procedure, followed by the generation of a radial incision of approximately 1.8 mm in length. After this, a calibrated diamond knife was set at approximately 80% of the corneal thickness where the initial incision was made. Pocketing hooks (Suarez spreader) were then used to create corneal pockets on each side of the incision, attempting to maintain a constant depth. A semiautomated suction ring (KV-2000 vacuum pump, adapted for Ferrara ICRS by AJL Ophthalmic) was placed around the limbus and two semicircular dissectors were then placed

sequentially into the lamellar pocket created to be steadily advanced by a rotational movement (counterclockwise and clockwise directions).

After the mechanical or femtosecond-guided laser creation of the tunnels, Ferrara rings were inserted throughout the incision into such tunnels, with their corresponding centration afterwards with the help of a Sinskey hook. A postoperative prophylactic treatment was prescribed consisting of the application of tobramycin-dexamethasone eyedrops every 6h for 1wk and the use of a topical lubricant containing polyethylene glycol 0.4% and propylene glycol 0.3% every 6h for 1mo.

Statistical Analysis. Before initiating patient recruitment, sample size estimation was performed using the Dupont-Plummer approach in order to optimize the design of the study[32]. For paired tests, a total of 83 eyes were found to be necessary to detect differences of 0.10 logMAR in visual acuity measurements between consecutive visits, assuming a statistical power of 90%, a standard deviation of differences of 0.25 logMAR according to previous research[6,11], a drop-out rate of 20%, and an alpha error of 0.05.

The commercially available software package SPSS Version 22.0 (IBM Corporation, Armonk, NY, USA) was used for performing the statistical analysis of the data obtained. ~~First,~~ The normality of data samples was evaluated by means of the Kolmogorov-Smirnov test. The paired Student's *t*-test was used to assess the significance of differences between consecutive visits of normally distributed variables, including correction for multiple pairwise comparisons. The Wilcoxon test was used for non-normally distributed data instead. The Pearson or Spearman correlation coefficients were calculated for normally and non-normally distributed data, respectively, to evaluate the relationship between different clinical variables evaluated. Likewise, the comparison between mechanical and femtosecond laser-assisted tunnelization groups was performed using the unpaired Student's *t* and *U* Mann-Whitney tests for normally and non-normally distributed variables, respectively. Regarding the analysis of refractive changes, all spherocylindrical refractions obtained were converted to vectorial notation using the power vector method described by Thibos and Horner[33]. A *P*-value of less than 0.05 was considered as statistically significant for all statistical tests.

RESULTS

The sample included a total of 88 eyes that met the inclusion criteria of a total of 88 patients with a mean age of 36.4y (SD, standard deviation: 12.1; median: 35.5; range: 18 to 62y). Likewise, the sample included a total of 49 men (55.7%) and 39 women (44.3%), as well as a total of 42 right eyes (47.7%) and 46 left eyes (52.2 %). The contribution of each participating center was as follows: Torrecárdenas Hospital Complex (25 eyes, 28.4%) and FISABIO (63 eyes, 71.6%). The average depth of implantation of the segments was 376.5 μm (SD: 49.9; median: 364.0; range: 280 to 495 μm).

The implantation was performed using mechanical tunneling in a total of 25 eyes (28.4%) and femtosecond laser-assisted tunneling in 63 eyes (71.6%). In the current study, a total of 106 ring segments were implanted, with 18 eyes being implanted with two ring segments according to the nomogram recommendations. The most implanted ring segment in the sample was 250 μm thick and 150º arc length (23 eyes, 21.7%), followed by 250 μm thick and 210º arc length (20 eyes, 18.9%). The 5-mm optical zone segments were implanted in a total of 33 eyes (37.5%), while the 6-mm optical zone segments were implanted in 55 eyes (62.5%).

Visual and Refractive Changes. Table 1 summarizes the visual and refractive data obtained in the evaluated sample during the follow-up. One month after surgery, there were statistically significant changes in UDVA, the magnitude of the refractive cylinder, the spherical equivalent, the overall blur strength and CDVA (P<0.001), with no significant additional changes occurring during the rest of the follow-up (P≥0.630). Therefore, the ring segments induced a significant refractive change, with an improvement in UDVA and CDVA associated. The percentage of eyes with UDVA of 0.30 logMAR or better changed from a preoperative value of 12.5% to a 3-month postoperative value of 33.3% (Figure 2). Concerning CDVA, a total of 28.4% and 46.5% of eyes had a preoperative and 3-month postoperative value of 0.10 logMAR or better, respectively (Figure 2). At 3mo after surgery, only 2 eyes (2.3%) lost 2 or more lines of CDVA and a total of 53.5% of eyes gained lines of CDVA (Figure 3).

Table 1. Visual and refractive changes occurring in the sample

Parameters	Preop.	1mo postop.	3mo postop.	*P*
logMAR UDVA	0.80±0.36 0.80 (0.05 to 2.00)	0.64±0.40 0.70 (0.05 to 2.00)	0.59 (0.33) 0.52 (0.05 to 1.30)	<0.001 Preop. 1mo<0.001 1mo-3mo=0.999 Preop. 3mo<0.001
Sphere (D)	-1.46 (3.44) -0.63 (-11.00 to 9.00)	-0.64 (2.77) 0.00 (-10.00 to 8.50)	-0.69 (3.04) 0.00 (-10.00 to 8.50)	0.194
Cylinder (D)	-3.68 (1.78) -3.50 (-9.00 to 0.00)	-2.72 (1.72) -2.50 (-6.00 to 0.00)	-2.86 (1.69) -2.75 (-7.00 to 0.00)	<0.001 Preop. 1mo<0.001 1mo-3mo=0.630 Preop. 3mo<0.001
Spherical equivalent (D)	-3.24 (3.51) -2.75 (-15.50 to 7.75)	-2.00 (2.96) -1.13 (-12.25 to 7.25)	-2.12 (3.11) -1.50 (-12.25 to 7.25)	<0.001 Preop. 1mo<0.001 1mo-3mo=0.999 Preop. 3mo<0.001
J_0 (D)	-0.45 (1.32) -0.63 (-2.82 to 3.90)	-0.46 (1.03) -0.38 (-2.95 to 2.11)	-0.53 (1.00) -0.50 (-3.29 to 1.61)	0.593
J_{45} (D)	-0.06 (1.51) 0.00 (-3.05 to 3.03)	0.04 (1.16) 0.00 (-2.50 to 2.60)	0.05 (1.22) 0.00 (-2.50 to 2.60)	0.258
B (D)	4.30 (2.91) 3.62 (0 to 16.14)	2.94 (2.58) 2.00 (0 to 12.45)	3.23 (2.53) 2.69 (0 to 12.45)	<0.001 Preop. 1mo<0.001 1mo-3mo=0.999 Preop. 3mo<0.001
logMAR CDVA	0.36 (0.24) 0.30 (0 to 1.00)	0.26 (0.18) 0.22 (0 to 0.82)	0.25 (0.20) 0.20 (-0.08 to 0.82)	<0.001 Preop. 1mo<0.001 1mo-3mo=0.768 Preop. 3mo<0.001

D: Diopters; UDVA: Uncorrected distance visual acuity; CDVA: Corrected distance visual acuity; J_0, J_{45}: Power vector components of astigmatism; B: Overall blur strength.

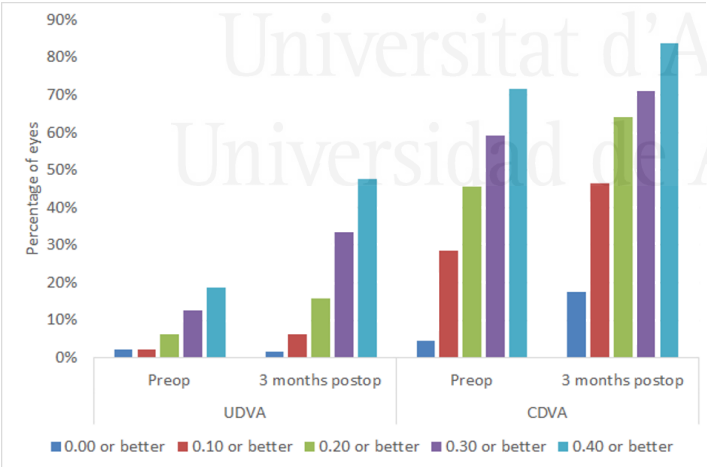

Figure 2.- Distribution of preoperative and postoperative UDVA and CDVA in the sample evaluated.

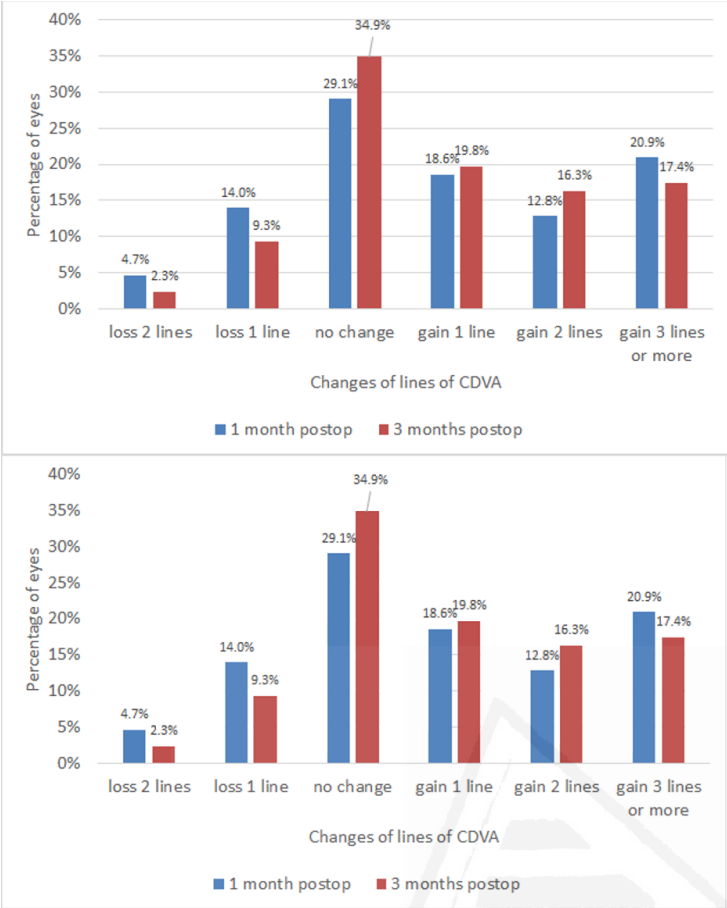

Figure 3.- Distribution of changes in lines of CDVA at the end of the follow-up in the sample evaluated.

Corneal Topographic Changes. Table 2 summarizes the corneal topographic data obtained in the evaluated sample during the follow-up. Significant decreases in the corneal power corresponding to the flattest (K1) and steepest (K2) meridians of the anterior and posterior surfaces as well as in the mean corneal power (KM) values were detected at 1mo after surgery ($P \leq 0.003$), with no additional significant changes occurring during the rest of the follow-up ($P=0.999$). Likewise, a significant reduction of the magnitude of anterior corneal astigmatism (ACA) was observed at 1mo postoperatively ($P<0.001$), without no additional significant changes afterwards ($P=0.999$). Furthermore, a significant reduction of the magnitude of posterior corneal astigmatism (PCA) was found at 3mo after surgery ($P=0.048$). Finally, only

the asphericity of the anterior corneal surface (Qant) showed a significant change at 1mo postoperatively (P<0.001), with no significant changes afterwards (P=0.999). This change consisted of a decrease in prolaticity, which is consistent with the central corneal flattening observed. Indeed, a statistically significant correlation of the change in anterior KM was found with the change with surgery in Qant (r=-0.819, P<0.001) as well as with the change in posterior KM (r=-0.702, P<0.001). Likewise, a poorer but statistically significant correlation was found between the change in ACA and PCA (r=-0.476, P<0.001). Furthermore, the correlation between the change with surgery in the magnitude of ACA and the change in manifest cylinder was limited although statistically significant (r=-0.389, P<0.001).

Table 2.- Corneal topographic changes in the sample evaluated

Parameters	Preop.	1mo postop.	3mo postop.	*P*
Anterior surface				
K1 (D)	46.08±3.79 46.25 (35.90 to 56.20)	44.26±3.21 44.15 (33.60 to 51.70)	44.19±3.10 44.20 (33.80 to 52.10)	<0.001 Preop. 1mo<0.001 1mo-3mo=0.999 Preop. 3mo<0.001
K2 (D)	50.44±4.12 50.40 (42.30 to 59.80)	47.27±3.41 46.75 (38.90 to 55.20)	47.31±3.61 46.80 (38.80 to 59.50)	<0.001 Preop. 1mo<0.001 1mo-3mo=0.999 Preop. 3mo<0.001
KM (D)	48.23±3.80 48.45 (39.10 to 58.00)	45.74±3.15 45.40 (36.25 to 53.45)	45.71±3.20 45.25 (36.30 to 53.85)	<0.001 Preop. 1mo<0.001 1mo-3mo=0.999 Preop. 3mo<0.001
Astigmatism (D)	4.36±2.25 4.25 (0.00 to 12.10)	3.08±1.93 2.85 (0.20 to 8.90)	3.13±2.06 2.95 (0.00 to 11.30)	<0.001 Preop. 1mo<0.001 1mo-3mo=0.999 Preop. 3mo<0.001
Kmax (D)	57.26±5.63 56.70 (46.60 to 73.90)	54.22±5.11 53.85 (45.80 to 77.60)	54.07±5.39 53.00 (45.70 to 81.50)	<0.001 Preop. 1mo<0.001 1mo-3mo=0.171 Preop. 3mo<0.001
Q	-0.79±0.49 -0.79 (-2.46 to 0.57)	-0.38±0.50 -0.39 (-1.50 to 1.31)	-0.40±0.50 -0.41 (-1.40 to 1.44)	<0.001 Preop. 1mo<0.001 1mo-3mo=0.999 Preop. 3mo<0.001
Posterior surface				
K1 (D)	-6.80±0.79 -6.80 (-8.90 to -4.40)	-6.69±0.71 -6.70 (-9.40 to -5.00)	-6.69±0.66 -6.70 (-8.20 to -4.90)	0.003 Preop. 1mo=0.006 1mo-3mo=0.999 Preop. 3mo=0.018
K2 (D)	-7.64±0.77 -7.65 (-9.80 to -5.90)	-7.42±0.76 -7.40 (-10.00 to -5.70)	-7.42±0.74 -7.40 (-9.40 to -5.70)	<0.001 Preop. 1mo <0.001 1mo-3mo=0.999 Preop. 3mo<0.001
KM (D)	-7.21±0.75 -7.28 (-9.25 to -5.15)	-7.05±0.71 -7.03 (-9.70 to -5.50)	-7.05±0.67 -6.98 (-8.80 to -5.70)	<0.001 Preop.1mo <0.001 1mo-3mo=0.999

				Preop.3mo<0.001
Astigmatism (D)	0.84±0.47 0.80 (0.00 to 2.20)	0.73±0.42 0.70 (0 to 2.00)	0.73±0.45 0.60 (0 to 2.00)	0.004 Preop. 1mo=0.189 1mo-3mo=0.999 Preop. 3mo=0.048
Q	-0.87±0.55) -0.92 (-1.94 to 0.86)	-0.86±0.53) -0.89 (-2.38 to 0.92)	-0.87±0.53) -0.89 (-2.41 to 0.43)	0.441

D: Diopters; K1: Corneal power in the flattest meridian; K2: Corneal power in the steepest meridian; KM: Mean corneal power; Kmax: Maximum corneal power; Q: Asphericity.

Corneal Aberrometric Changes. Table 3 summarizes the corneal aberrometric data obtained in the evaluated sample during the follow-up. A large and statistically significant reduction in primary coma RMS was observed at 1mo after surgery (P<0.001), with a non-significant reduction during the remaining follow-up (P=0.432). No significant changes with surgery were detected in the rest of corneal aberrometric data evaluated (P≥0.432).

Table 3.- Total corneal aberrometric changes in the sample evaluated

Parameters	Preop.	1mo postop.	3mo postop.	*P*
High order RMS (μm)	6.68±5.89 4.43 (0.57 to 25.22)	6.01±7.36 3.84 (1.29 to 35.32)	6.67±5.39 4.86 (1.10 to 20.04)	0.846
Primary coma RMS (μm)	3.66±3.04 2.81 (0.00 to 17.90)	2.42±2.38 1.76 (0.03 to 12.18)	2.33±2.26 1.74 (0.24 to 12.79)	<0.001 Preop. 1mo<0.001 1mo-3mo=0.183 Preop. 3mo<0.001
Zernike coefficient for primary spherical aberration (μm)	-0.39±0.69 -0.34 (-2.01 to 0.83)	-0.07±0.71 -0.11 (-1.41 to 1.76)	0.06±0.64 0 (-1.06 to 1.64)	0.595
Trefoil RMS (μm)	0.39±0.34 0.27 (0.03 to 1.41)	0.46±0.34 0.50 (0.03 to 1.41)	0.51±0.42 0.37 (0 to 1.76)	0.432

RMS: Root mean square.

Pachymetric Changes. Figure 4 shows changes in central (CCT) and minimum corneal thickness (MCT) occurring during the follow-up in the sample evaluated. Statistically significant changes were found in both pachymetric parameters (P<0.001), with a significant increase at 1mo postoperatively (P<0.001) and no significant changes during the rest of follow-up (P≥0.699). Additionally, there was a trend to a minimal change in the position of the corneal point corresponding to the MCT, but the modifications of the X (P=0.621) and Y coordinates

(*P*=0.295) of such position after surgery did not reach statistical significance (Figure 5).

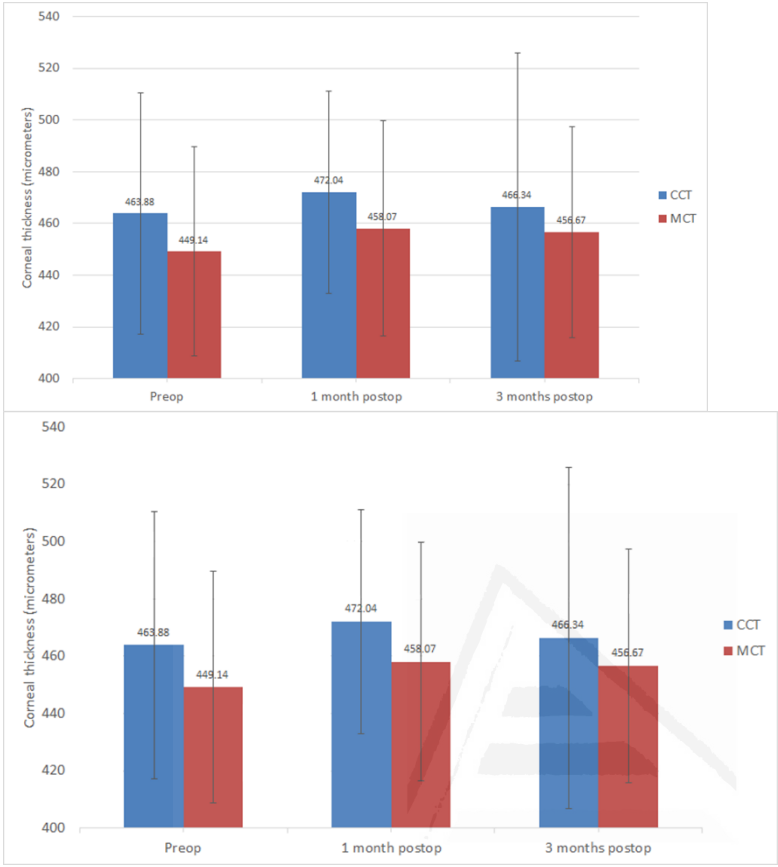

Figure 4.- Pachymetric changes in the sample evaluated during the follow-up
MCT: Minimum corneal thickness; CCT: Central corneal thickness.

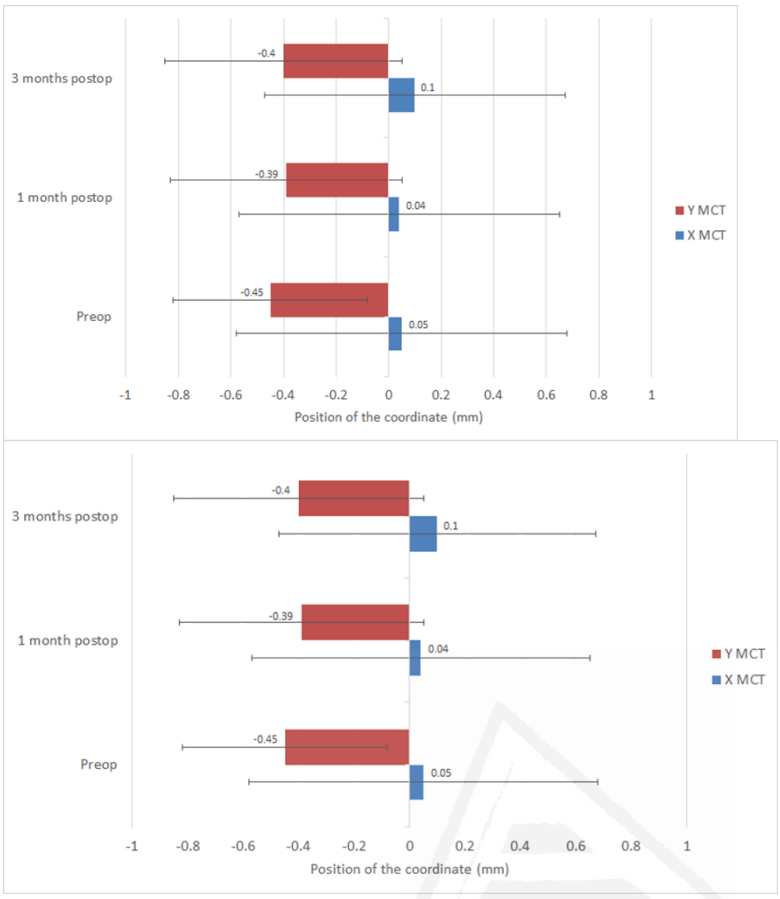

Figure 5.- Changes in the X and Y coordinates of the position of the point of minimum corneal thickness (MCT) in the sample evaluated during the follow-up.

Complications. No serious complications occurred in the sample evaluated during the follow-up.

DISCUSSION

The implantation of Ferrara rings has been significantly optimized from the development and use of empirical nomograms several years ago to select the ring segment to implant in each specific case[26-28] to more complex nomograms considering the topographic pattern, corneal aberrations and tomographic data[15,17,34]. The aim of the current study was to evaluate the results obtained with the implantation of Ferrara rings using a new nomogram which is the result of several years of research and clinical experience of different authors.[15,17,19-22,35-38] This optimized nomogram considers the level of anterior corneal astigmatism, primary coma and asphericity as well as the level of misalignment between topographic and coma axes for the

selection of the ring segment thickness and arc length to implant. It has been demonstrated that the 320º and 210º ring segments induce more reduction in mean keratometry and asphericity than 160º rings, being a more adequate option in patients with central hyperprolate keratoconus[36-38]. Likewise, one Ferrara-type ICRS of 150º of arc length with a thickness of 150, 200 or 250 μm implanted inferiorly has been shown to be the most adequate option to reduce both astigmatism and corneal coma-like aberrations in keratoconus eyes with no coincident topographic and comatic axes[35]. In the case of keratoconus cases with coincident topographic and coma axis, the use of one Ferrara-type segment with 150º of arc implanted inferiorly for low corneal astigmatism, the use of 1 segment with 90º of arc superiorly and 1 with 150º of arc inferiorly for moderate astigmatism, and the use of 1 with 90º of arc superiorly and 1 with 120º of arc inferiorly for high astigmatism were found to provide good visual and refractive outcomes[17]. Furthermore, the use of two symmetrical segments have been recommended in the presence of regular astigmatism[38-39]. For this reason, the optimized nomogram evaluated considers the level of anterior corneal astigmatism, primary coma and asphericity as well as the level of misalignment between topographic and coma axes. The study was conducted in two different centers using a different method of creation of tunnels for the insertion of the ring segments to evaluate all potential factors that may influence on the outcome achievable with this new nomogram. Table 4 summarizes the main clinical outcomes obtained with Ferrara ring segments by previous authors using different types of nomograms and the outcomes of the current series.

In our sample, the implantation of Ferrara rings based on the optimized nomogram led to a significant improvement in UDVA (mean improvement of 2 lines logMAR) and CDVA (mean improvement of 1 line logMAR), which is consistent with previous series evaluating the effect of Ferrara ring implantation in keratoconus based on the use of previous nomograms and also observing a visual improvement after surgery[19-20,23,26-28,40-44]. Hamdi[19] reported in a sample of moderate to severe keratoconus cases treated with Ferrara rings using a previous nomogram of implantation an improvement of CDVA in 64% of eyes. In our series, the percentage of eyes improving CDVA at 3mo postoperatively was 53.5%, but it should be considered that cases of

all types of topographic patterns were included, combining corneas with aligned and misaligned topographic and comatic axes. In any case, in our sample, a total of 88.4% of eyes improved or maintained the CDVA after surgery. It has been demonstrated that Ferrara rings provide a more efficient effect in eyes with moderately advanced asymmetric keratoconus with an initial visual acuity worse than 0.4 logMAR[41]. Alfonso *et al*[35] found that a total of 48.78% of cases from a sample of paracentral keratoconus eyes with no coincident topographic and coma axes improved CDVA after Ferrara-type ring segment implantation. The same research group reported in another study evaluating the effect of Ferrara-type ring segments in keratoconus eyes with coincident corneal keratometric, comatic and refractive axes that 84.5% of cases maintained or improved their CDVA at 5y after surgery[45]. One additional remarkable finding in our series is that 33.7% of cases gained 2 lines of CDVA or even more, which is a better result than those reported by previous authors using previous nomogram approaches for Ferrara-type ring segment implantation (26.83% keratoconus with no coincident topographic and coma axis, Alfonso *et al*[35], 25.7% keratoconus with coincident topographic and coma axis of more than 30 years old, Fernández-Vega *et al*[45]). For this reason, a safety index (ratio of postoperative CDVA to preoperative CDVA) of 1.36 was obtained in the current series, which reflects the positive overall trend to gain of lines of CDVA. Slight lower safety indices have been reported by other authors using other nomograms (Piñero *et al*[11], 1.29; Abu Ameerth *et al*[43], 1.22). However, other authors have reported higher values of safety index using other nomograms (around 1.6)[28,40], but not indicating the percentage of the sample with cases with significant discrepancies between comatic and topographic axes and high levels of primary coma. In our sample, almost all cases presented a relevant level of discrepancy between these two axes. Regarding the comparison in terms of the efficacy index (ratio of postoperative UDVA to preoperative CDVA, a variability between 0.42 and 0.86 have been reported in previous studies using a great variety of nomograms[11,23,28,40,43]. A value of 0.52 was obtained in the current study. Future randomized comparative studies between this optimized nomogram and previous nomograms should confirm the real benefit in terms of spherocylindrical correction of the nomogram preliminarily evaluated in the current study.

Table 4.- Summary of the main clinical outcomes of Ferrara ring segment implantation in keratoconus reported by other authors using other types of nomograms

Author (y)	N (age range)	Ring segments (surgical technique)	Nomogram	Change in logMAR CDVA	Change in SE (D)	Change in refractive cylinder (D)	Follow-up (mo)
Siganos *et al* (2002)[28]	26 KC	Ferrara (mechanical)	2 segments 160º 150 µm SE<-4 D 200 µm -4.25 to -6 D 250 µm -6.25 to -8 D 300 µm -8.25 to -10 D 350 µm SE>-10 D	Preop. 0.37±0.25 Postop. 0.60±0.17 (decimal) Efficacy index 0.81 Safety index 1.62	Reduced SE in most of cases	---	6
Miranda *et al* (2003)[27]	36 severe KC	Ferrara (mechanical)	2 segments 160º 200 µm cone stage I 250 µm cone stage II 300 µm cone stage III 350 µm cone stage IV	CDVA improved in 80.56%	Preop. -7.29±3.12 Postop. -4.80±3.04	---	12
Kwitko & Severo (2004)[26]	51 KC	Ferrara (mechanical)	2 segments 160º 200 µm cone stage I 250 µm cone stage II 300 µm cone stage III 350 µm cone stage IV	CDVA improved in 86.4% did not change 1.9% worsened 11.7%	Preop. -6.08±5.01 Postop. -4.55±5.71	Preop. -3.82±2.13 Postop. -2.16±2.07	13.0±8.7
Torquetti *et al* (2009)[23]	28 KC	Ferrara (mechanical)	Nomogram based on position of the conus on the cornea, topographic astigmatism and pachymetric map	Preop.0.41±0.25 Postop.0.59±0.19 (decimal) Efficacy index 0.76 Safety index 1.44	---	---	5-12y
Ferrara & Torquetti (2009)[22]	80 KC and post-LASIK ectasia	Ferrara (mechanical)	210º arc length ring segment up to 2 D: 150 µm 2.25 to 4 D: 200 µm 4.25 to 6 D: 250 µm >6.25 D: 300 µm	Preop.20/125 to postop. 20/55	Preop. -5.22 to postop. -2.26 D	Preop. 3.65 to postop. 2.69 D (keratom astig)	6.65±7.73
Piñero *et al* (2010)[11]	72 KC (15-68y)	KeraRing (fs)	Manufacturer's nomogram	Preop.0.36±0.27 Postop.0.27±0.23 Efficacy index 0.42 Safety index 1.29	Preop. -5.64±5.00 Postop. -3.99±4.50	Preop. -4.07±2.40 Postop. -2.86±1.91	3
Hamdi (2011)[19]	100 KC (16-39y)	Ferrara (mechanical)	Manufacturer's nomogram	CDVA improved 1-6 lines in 64% Unchanged 27% lost 1-2 lines 9%	Preop. -3.60±3.10 Postop. -2.52±3.10	Preop. -5.18±2.10 Postop. -2.90±2.50	6
Ferrara *et al* (2012)[39]	972 KC (oval or bow tie) (17-59y) 101 KC (nipple-type) (14-64y)	Ferrara (mechanical)	160º arc length: oval bow tie 210º arc length: nipple-type	Preop.20/100 to postop.20/40 Preop. 20/110 to postop. 20/60	Preop. -3.99±4.22 Postop. -2.26±3.09 Preop. -8.52±5.63 Postop. -4.14±4.37	--- ---	23.8±12.2 22.9±15.1
Abu Ameerh *et al* (2012)[43]	79 KC (13-44y)	Ferrara (mechanical)	Manufacturer's nomogram	Preop. 0.51±0.17 Postop. 0.62±0.20 (decimal) Efficacy index 0.86 Safety index 1.22	Preop. -2.32±2.75 Postop. -2.04±1.92	Preop. -3.05±1.70 Postop. -2.87±1.67	6
Torquetti *et al* (2018)[37]	138 KC (10-63y)	Ferrara (mechanical/fs)	320º arc length Manufacturer's nomogram	Preop. 20/100 to postop. 20/40	Preop. -7.02±4.80 Postop. -3.29±3.80	Preop. 4.62±2.87 Postop. 2.74±2.07 (topo astig)	6.2±3.3
Sanders *et al* (2018)[40]	58 KC (33.3±13.2y)	Ferrara (fs)	140º arc length Asymmetric KC <4 D: 1 seg 150 µm >4 D and <8 D: 1 seg 200 µm >8 D: 1 seg 250 µm symmetric KC <6 D: 2 seg 150 µm >6 D and <10D: 2 seg 200 µm >10 D: 2 seg 250 µm	Preop. 0.50±0.20 Postop. 0.30±0.21 Safety index 1.67	---	Preop. -8.00±3.45 Postop. -4.53±2.52 (topo astig)	16.81±10.8
Fernández *et al* (2021)	88 KC (18-62y)	Ferrara (mechanical/fs)	Optimized nomogram considering variables such as anterior corneal asphericity and astigmatism or the discrepancy among astigmatism and coma orientations	Preop. 0.36±0.24 Postop. 0.25±0.20 Efficacy index 0.52 Safety index 1.36	Preop. -3.24±3.51 Postop. -2.12±3.11	Preop. -3.68±1.78 Postop. -2.86±1.69	3

N: Number of eyes; KC: Keratoconus; CDVA: Corrected distance visual acuity; SE: Spherical equivalent; D: Diopters.

Concerning refraction, a significant change in the magnitude of manifest cylinder and spherical equivalent was found after Ferrara ring segment implantation based on the optimized nomogram evaluated. This is the main factor contributing to the significant improvement in UDVA observed after surgery. Previous series have also reported significant changes in refraction after Ferrara ring segment implantation using different type of nomograms and for different types of topographic patterns[15,17,35-36,38,40-41,43], with poorer results especially with the first developed nomograms[26-28]. In our series, a reduction of the spherical equivalent by more than 50% was observed in 41.5% of eyes, changing from a mean preoperative value of -3.24±3.51 D to a mean 3-month postoperative value of -2.12±3.11 D. Hamdi[19] reported a reduction in spherical equivalent after Ferrara ring implantation in keratoconus eyes based on a not fully optimized nomogram from a mean preoperative value of -3.60±3.10 D to a mean 3-month postoperative value of -2.52±3.10 D, not reaching statistical significance (*P*=0.209).

The myopic correction induced with the implantation of the Ferrara ring segments in the current study could be consistently explained by the significant reduction generated in the central curvature of the anterior corneal surface. This central corneal flattening is consistent with the results of all previous series evaluating the outcomes of Ferrara rings in keratoconus[15-17,19-20,23,26-28,35-38,41,43-45]. This significant flattening of the anterior corneal surface was observed in the steepest and flattest meridians, with an additional reduction of the magnitude of anterior corneal astigmatism and maximum keratometric reading associated. The change in manifest cylinder was explained in part by this reduction of anterior corneal astigmatism, but it was not the only factor. Indeed, a poor although statistically significant correlation was found between changes in manifest cylinder and anterior corneal astigmatism (ACA). Additionally, no significant changes with surgery were found in the power vector components of manifest astigmatism. The relevant contribution of PCA to refractive cylinder in keratoconus[46] as well as changes in specific types of high order aberrations with the potential of interfering with astigmatism may have accounted for this. It should be considered that the implantation of Ferrara rings also induced significant changes in the magnitude of PCA. Likewise, significant changes were observed in posterior central curvature, confirming that Ferrara rings induce a modeling of the global corneal

structure, not only of the anterior corneal shape. This is consistent with the results of previous series showing the induction of significant modifications of the shape of the posterior corneal surface after the implantation of Ferrara rings[47-48]. The impact of these changes in the predictability of astigmatic correction should be investigated further. This may be an area for future optimizations of next nomograms of implantation of ring segment.

Besides curvature changes, a significant modification was also observed after Ferrara ring implantation in the asphericity of the anterior corneal surface, changing to a less prolate value. This modification was consistent with the significant central flattening induced, with a strong and statistically significant correlation between changes in mean keratometry and anterior corneal asphericity. However, no significant changes were detected with the implantation of the ring segments in the asphericity of the posterior corneal surface. This is consistent with previous studies reporting significant changes in anterior and posterior central corneal curvature as well as in anterior asphericity after the implantation of Ferrara rings[37,39-40,47]. This significant change of anterior asphericity with Ferrara rings was found to be especially large in magnitude when 320º arc length segments are used[37].

The significant change in anterior shape was associated with a change towards less negative value of total corneal spherical aberration, although this trend did not reach statistical significance in our series. In contrast, the change in total primary coma was statistically significant and with a mean magnitude of 1.33 µm (preoperative 3.66±3.04 µm *vs* postoperative 2.33±2.26 µm, 6-mm pupil). Previous series on Ferrara rings outcomes using other nomograms have also reported significant changes in primary coma and coma-like aberrations, but of less magnitude[15,35-36,45,49]. Alfonso *et al*[35] reported a change in corneal coma-like RMS from 0.80±0.53 µm before surgery to 0.61±0.59 µm (4.5 mm pupil) in a sample of keratoconus eyes with no coincident topographic and coma axis implanted with Ferrara-type ring segments. The same research group reported a change after Ferrara-type ring segment implantation in another sample of 409 paracentral keratoconic eyes a significant change in coma-like RMS (4.5 mm pupil) from a mean preoperative value of 1.32±1.01 µm to a mean postoperative value of 1.06±0.85 µm[15]. Therefore, the control of corneal primary coma seems to be one of the most

relevant benefits of the use of this optimized nomogram. This is consistent with the significant improvement in CDVA observed in our series, with 37.4% of eyes gaining 2 logMAR lines of CDVA or more. It should be considered that the primary coma aberration is the high order aberration degrading most the visual quality in keratoconus[29-30]. Esaka *et al*[50] found by means of stepwise multiple regression analysis that CDVA in keratoconus could be predicted considering the RMS of anterior corneal elevation and total coma aberration (adjusted R=0.546).

No severe adverse events occurred during the follow-up in the current study, confirming the safety of the implant. Likewise, no corneal structural alterations were detected, although significant changes in minimum and central corneal thicknesses were found during the follow-up. Specifically, a significant increase of around 10 μm of the pachymetric parameters were found during the 3mo of follow-up postoperatively. This contrasts with previous series reporting decreases of pachymetry after Ferrara ring implantation but in a longer term[42]. Several factors may account for the pachymetric increase found in our series including a potential redistribution of corneal tissue due to the ring implantation or the level of intrasession repeatability of Pentacam pachymetric measurements. Indeed, de Luis Eguileor *et al*[51] have recently confirmed that the repeatability limits for the thinnest corneal thickness measurements obtained with the Pentacam system is 10 μm.

Finally, we have analyzed the potential effect on the outcomes of the use of the mechanical or femtosecond-laser assisted technique for the implantation of the ring segments as a more precise dissection plane depth has been demonstrated to be achieved using the femtosecond technology[52]. Although some differences were found between eyes implanted with both techniques in terms of the corneal flattening and aberrometric change induced as well as in some postoperative data, the magnitude of such differences did not reach statistically significance at 3 mo after surgery. This is consistent with the results of Monteiro *et al*[49] that also found comparable visual, refractive and aberrometric outcomes when comparing the results of Ferrara-type ring segments implanted mechanically or with femtosecond laser. Future studies should be conducted to analyze the impact of inter-surgeon variability using the mechanical

implantation method on the incidence of complications, considering that previous series have reported more complications with the mechanical dissection[49] and even poorer aberrometric correction[49,53]. Likewise, differences in the initial postoperative period between mechanical and femtosecond laser assisted-assisted procedures should be investigated further as they may be the consequence of the less precise dissection plane achieved with the mechanical procedure or even of a more relevant structural or inflammatory modifications with such procedure.

There are several limitations that should be acknowledged. The main limitation was the non-comparative nature of the study, not including a control group operated on using a classical nomogram to evaluate the real improvement of our nomogram over previous approaches. Once demonstrated the safety and efficacy of the implantation of Ferrara rings with this nomogram, future comparative clinical trials should be conducted to analyze the real benefit of this new proposal of nomogram over conventional or previously developed nomograms. In any case, some discussions comparing with the results of previous nomograms have been included in the current article but taking care of extracting definitive conclusions as a direct clinical comparison (with or without randomized assignment) has not been done. Another limitation was not including the analysis of ocular wavefront aberrations as with this information a more exhaustive analysis of astigmatism could have been performed, including the analysis of discrepant astigmatism (DA), which is the discrepancy between refractive astigmatism and the sum of total corneal astigmatism and lenticular astigmatism (derived from ocular wavefront aberrometric analysis)[51]. It should be considered that DA is normally negligible in eyes with normal optics but can become significant when coma-like high order aberrations refract as astigmatism[54]. The effect of considering DA in this nomogram should be investigated further. In addition, the inclusion of eyes implanted with Ferrara rings using two different types of corneal dissection may be considered as a limitation and a potential source of bias. However, this potential bias introduced by this factor seems to be limited. No significant differences were found in the changes occurring in a great variety of parameters at 3mo postoperatively between eyes operated on using the mechanical and femtosecond-guided procedures in the current series.

In conclusion, the implantation of Ferrara rings based on a new optimized nomogram considering the level of anterior corneal asphericity, astigmatism and primary coma aberration as well as the level of misalignment between topographic and coma axes is safe and effective for promoting a visual rehabilitation in keratoconus. Using these ring segments, a significant central anterior and posterior corneal flattening is induced, leading to a refractive change and a significant reduction of the prolate shape and irregularity, and consequently to a corrected-distance visual improvement. The main advantage of this new nomogram seems to a better aberrometric control, although this should be investigated in future comparative clinical trials.

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2.3 CAPÍTULO 3: PRELIMINARY CHARACTERIZATION OF PREDICTIVE FACTORS OF THE VISUAL CHANGE AFTER EPI-ON AND EPI-OFF CORNEAL COLLAGEN CROSSLINKING TECHNIQUES

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PRELIMINARY CHARACTERIZATION OF PREDICTIVE FACTORS OF THE VISUAL CHANGE AFTER EPI-ON AND EPI-OFF CORNEAL COLLAGEN CROSSLINKING TECHNIQUES

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Abstract

Purpose: To investigate potential predictive factors of the visual change achieved with accelerated epi-on and epi-off corneal collagen crosslinking (CXL) in keratoconus.

Methods: This retrospective comparative study analyzed 67 eyes who were treated with accelerated epithelium-on (epi-on group) and epithelium-off (epi-off group) CXL. Clinical outcomes were evaluated and compared during a 1-year follow-up. Likewise, the relationship of the change achieved with both CXL techniques in corrected distance visual acuity (CDVA) with different preoperative data was investigated.

Results: Mean CDVA change at 3 months postoperatively was -0.04±0.19 and -0.07±0.25 in the epi-on and epi-off groups, respectively (p=0.809). In the epi-on group, this change was significantly correlated with preoperative apical (r=-0.375, p=0.045) and central corneal thickness (r=-0.402, p=0.031). In the epi-off group, the CDVA change was also significantly correlated with preoperative apical (r=0.402, p=0.028) and central corneal thickness (r=0.367, p=0.046), but also with some topometric and aberrometric indices ($r \leq -0.374$, $p \leq 0.042$). Furthermore, the change in CDVA in the epi-on group could be predicted from age, preoperative refractive astigmatism J_{45} component, anterior corneal asphericity and posterior corneal high order aberration root mean square (p=0.002, R^2=0.503). In the epi-off group, the CDVA change could be predicted from preoperative minimum corneal thickness and magnitude of vertical anterior corneal primary coma component (p=0.001, R^2=0.446).

Conclusions: Clearly different predictive factors of the visual change induced with accelerated epi-on and epi-off CXL techniques are present, suggesting a different mechanism of action for stiffening the cornea and inducing changes in this structure.

Keywords: Corneal thickness, corneal collagen cross-linking, cornea, corneal topography, treatment outcome, keratoconus, epithelium on accelerated cross-linking, epithelium off accelerated cross-linking, predictive factors.

Introduction

Keratoconus (KC) is a progressive disease, in which the cornea becomes thinner, inducing irregular astigmatism and reduced quality of vision.[1,2,3] The exact mechanism of KC development is not well understood, but it is commonly accepted that both genetic susceptibility and environmental factors are necessary.[2] In addition, secondary ectasia may be caused by a purely mechanical process in a predisposed cornea and may be unilateral.[4] Factors associated with KC include a positive family history, atopic constitution, eye rubbing, sleep apnea, place of living, blood group, genetic syndromes such as Down, chromosome translocation and chromosome ring abnormality.[1,2]

Conservative treatment modalities, such as spectacles and gas permeable rigid contact lenses, become insufficient for visual rehabilitation in advanced stages of KC and 10–20% of patients need corneal transplantation.[3] Wollensak et al[5] introduced the CXL treatment in 2003, being considered a standard, minimally invasive, and safe therapeutic option for progressive KC.[5-18] The principle goal of CXL is to stabilize the progression of KC by increasing the mechanical stability of the cornea.[4-18] Likewise, a successful CXL can prevent the progression of KC and can even cause the ectatic cornea to regress, but also a non-effect or even worsening of the ocular parameters can occur.[2] For this reason, CXL research in recent years has attempted to define predictive factors for the outcomes achieved with this technique with the aim of helping clinicians to manage patients' expectations and to minimize the exposure to potential side effects. To date, multiple factors have been defined, including preoperative visual acuity, eccentricity of the cone, pretreatment K_{max}, age, and gender.[2]

There is a significant variability between the few previous studies evaluating predictive factors of CXL outcome in KC.[1,2,6] This situation has increased the interest in recent years on this issue.[6] Peyman et al[2] demonstrated that lower pretreatment corneal asphericity and corneal keratoconus index (CKI) was associated to a higher K_{max} reduction after CXL.[2] Badawi et al[6] observed that preoperative best corrected visual acuity (BCVA) of more than 0.3 logMAR and K_{max} higher than 54 D were good predictors for post-CXL improvement in BCVA. Likewise,

Wisse et al[1] demonstrated that the eccentricity of the cone was the only predictor of keratometric changes during a 1-year follow-up after CXL.[1]

For clinicians, the prediction of the effect of CXL treatment is a valuable tool to provide patients useful information about the postoperative course. The aim of the current study was to investigate the potential predictive factors of epi-on and epi-off CXL outcomes in KC eyes considering a great variety of clinical parameters, evaluating the differences in these predictive factors between CXL techniques.

Methods

Study population

The study was designed as a retrospective comparative study in which the medical records of 69 eyes of adult patients with progressive KC grades 1-4 (based on Amsler-Krumeich grading system) were revised. All of them had undergone accelerated epithelial-on or accelerated epithelial-off CXL in the Torrecardenas University Hospital (Almeria, Spain) from May 2017 to January 2020. The classification of KC severity into four stages was performed in accordance with the Amsler-Krumeich grading criteria which is based on the mean corneal power, transparency, astigmatism, and the thinnest point of corneal thickness.[19] The research was carried out in accordance with the principles of the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of Torrecárdenas Hospital (study code: FACCROSS-2021). Written informed consent was obtained from all patients before revising their medical records.

KC progression was defined as more than 1 D of steepening of maximum keratometry in the 6-month period before the surgery, an increase of more than 1.00 D in manifest cylinder or an increase of more than 0.50 D in manifest refraction spherical equivalent in the previous twelve months, and a decrease of corneal thickness of 30 μm or more in the 6-month period before CXL surgery. Inclusion criteria were biomicroscopic examination and corneal topography consistent with KC, at least 18 years of age, inferior-superior ratio on topographic

map of more than 1.5 D, highest keratometric reading of 70 D or below, minimum corneal thickness (MCT) of 400 μm or higher, clear cornea without scarring and a minimum follow-up period of 12 months. Regarding exclusion criteria, the following conditions were considered: corneal scarring, eyes with prior corneal surgery, other corneal diseases (e.g., herpetic keratitis and corneal opacities), serious medical conditions, malignancy, rheumatologic diseases, collagen vascular disease, hereditary connective tissue disorder (e.g., Marfan disease), severe dry eye, and pregnancy or lactation.

Clinical examinations

The data collection of the study was divided into two parts. The first part included the collection of demographic data, such as age, gender, place of birth and residence, atopic constitution, family history (positive family history is defined as the existence of documented KC in first-degree and second-degree relatives), and eye rubbing history (was evaluated using a 4-point Likert scale).[20] The second part of the data collection consisted of extracting the information recorded in the ophthalmologic examinations performed during the follow-up in each patient, such as the grade of KC, preoperative uncorrected distance visual acuity (logMAR UDVA) and corrected distance visual acuity (logMAR CDVA) measured with a Snellen chart, slit-lamp biomicroscopy findings, tonometry, manifest refraction, dilated fundoscopic examination findings, keratometry, and topometric parameters. Topometric parameters included keratoconus index (KI), index of surface variance (ISV), index of height decentration (IHD), index of vertical asymmetry (IVA), minimum sagittal curvature (Rmin), anterior average radius of curvature taken from the 3.0 mm optical zone centered on the thinnest point (ARC), and posterior average radius of curvature taken from the 3.0 mm optical zone centered on the thinnest point (PRC). All this topographic information was obtained using Scheimpflug imaging-based topography device (Pentacam HR; Oculus GmbH, Wetzlar, Germany) that provides anterior and posterior elevation data, as well as pachymetric, topometric and keratometric data.[8]

In all patients, follow-up examinations were performed the next day, on the third day and 1 week after surgery to evaluate possible complications, epithelial scarring and absence of postoperative infection and at 1, 3 and 12 months after CXL surgery. On each examination, manifest refraction, UDVA, CDVA, slit lamp biomicroscopic findings, corneal topography and corneal thickness were recorded, except for visits up to one week after surgery, the assessment was with a slit lamp to assess complications and epithelial scarring. For statistical analyses, visual acuity data measured with a Snellen chart were converted to logMAR (logarithm of minimal angle of resolution) units.

Surgical procedures

In all cases revised in this retrospective analysis, the CXL procedure had been performed under sterile conditions in an operating room and under local anesthesia with 5% proparacaine HCl (Alcaine, Alcon). A speculum was placed on the eyelids after draping and the following steps were followed according to the technique used:

a) Epithelium-off accelerated CXL:
    1. Placement of the patient in a supine position and removal of corneal epithelium over the desired area
    2. Application of the solution Vibex Rapid (VibeX, Avedro Inc., Waltham, MA, USA; composition: 0.1% riboflavin, saline solution, and Hydroxypropyl-methyl cellulose, HPMC) to completely wet and cover the exposed stroma. This combination diffuses twice as fast as dextran and minimizes corneal thinning, allowing a safer procedure.
    3. Reapplication of this solution at least once every 2 minutes for a total of up 10 minutes depending on the desired depth of cross-linking
    4. Rinsing of the eye with balanced saline solution (BSS) prior to irradiation
    5. Initiation of pulsed ultraviolet-A (UVA) treatment at 30 mW/cm^2 for 8 minutes (1 second on, 1 second off) for a dose of 7.2 J/cm^2
    6. Wetting of the cornea with BSS during UVA treatment as needed
b) Trans-epithelial (epithelium-on) accelerated CXL:

1. Placement of the patient in a supine position, not removal of corneal epithelium
2. Application of Paracel Part One (VibeX, Avedro Inc., Waltham, MA, USA; composition: 0.25% riboflavin, Benzalkonium Chloride (BAC), Ethylenediaminetetraacetic acid (EDTA) and HPMC) to completely cover the cornea and repetition of this procedure every 90 seconds for 3.5 to 4 minutes. This solution loosens the epithelial junctions before the stroma is loaded with Paracel Part Two.
3. Rinsing of the cornea completely with Paracel Part Two (VibeX, Avedro Inc., Waltham, MA, USA; composition: 0.22% Riboflavin, Saline, Isotonic).
4. Application of sufficient Paracel Part Two to completely cover the cornea and repetition of this procedure every 90 seconds for 6 to 6.5 minutes (for a total riboflavin soaking time of 10 minutes).
5. Rinsing of the cornea completely with BSS
6. Initiation of pulsed UVA at 45 mW/cm^2 (higher irradiance needed due to UVA attenuation by the epithelium barrier) for 5 minutes and 20 seconds (1 second on, 1 second off) for a dose of 7.2 J/cm^2.
7. Rinsing of the cornea completely with BSS. Patients were instructed not to rub the eye

After the surgery, all the patients were examined with a slit-lamp on the 3rd day, and 1 week after surgery to evaluate possible complications, epithelial healing, and absence of postoperative infection. Topical moxifloxacin eye drops (Vigamox, Alcon, Fort Worth, Texas, USA) were prescribed to be applied 4 times daily for a period of one week as well as artificial tears to be applied 4 times daily for a period of one month. Fluorometholone 0.1% drop treatment (FML, Allergan, Dublin, Ireland) was initiated after epithelial healing in epithelium-off patients, with the application of drops 4 times daily for two weeks and then the dose frequency was tapering gradually. Soft contact lenses were fitted on the corneas postoperatively

and removed after the corneal epithelium was fully cured, typically at 3 to 5 days postoperatively.

Statistical analysis

Statistical analysis was performed with SPSS program version 20 (SPSS, Chicago, IL). Descriptive statistical data were displayed as mean ± standard deviation (SD) for continuous data and as a number with a percentage for categorical data. The Kolmogorov-Smirnov test was used to check if data distributions followed a normal distribution. The Chi-square test was utilized for the analysis of categorical variables. The Student t test for unpaired data and the Mann-Whitney tests were used to analyze the differences between epi-on and epi-off groups if data variables compared were normally distributed or not, respectively. A p-value of less than 0.05 was considered as statistically significant. The Spearman correlation coefficient was used to analyze the strength of the relationship between different variables within each group.

Besides these analyses, multiple linear regression analysis (backward elimination method) was used to obtain a mathematical expression relating the change in CDVA after CXL surgery with preoperative variables for each technique, epi-on and epi-off CXL. Analyses of residuals, homoscedasticity (normality of unstandardized residuals), and influential points or outliers (Cook's distance) were performed to confirm the assumptions of the model obtained. Likewise, the Durbin–Watson test and the calculation of the variance inflation factor (VIF) were performed to assess the absence of correlation between errors and multicollinearity.

Results

Demographic characteristics

This study included 69 patients (69 eyes) with KC who underwent CXL from May 2017 to January 2020. Of those, two patients did not have a complete follow-up and were excluded from the analysis (both undergoing epi-off CXL). Therefore, data from 67 patients (67 eyes) with a complete follow-up of 12 months after CXL were analyzed. The sample included a total

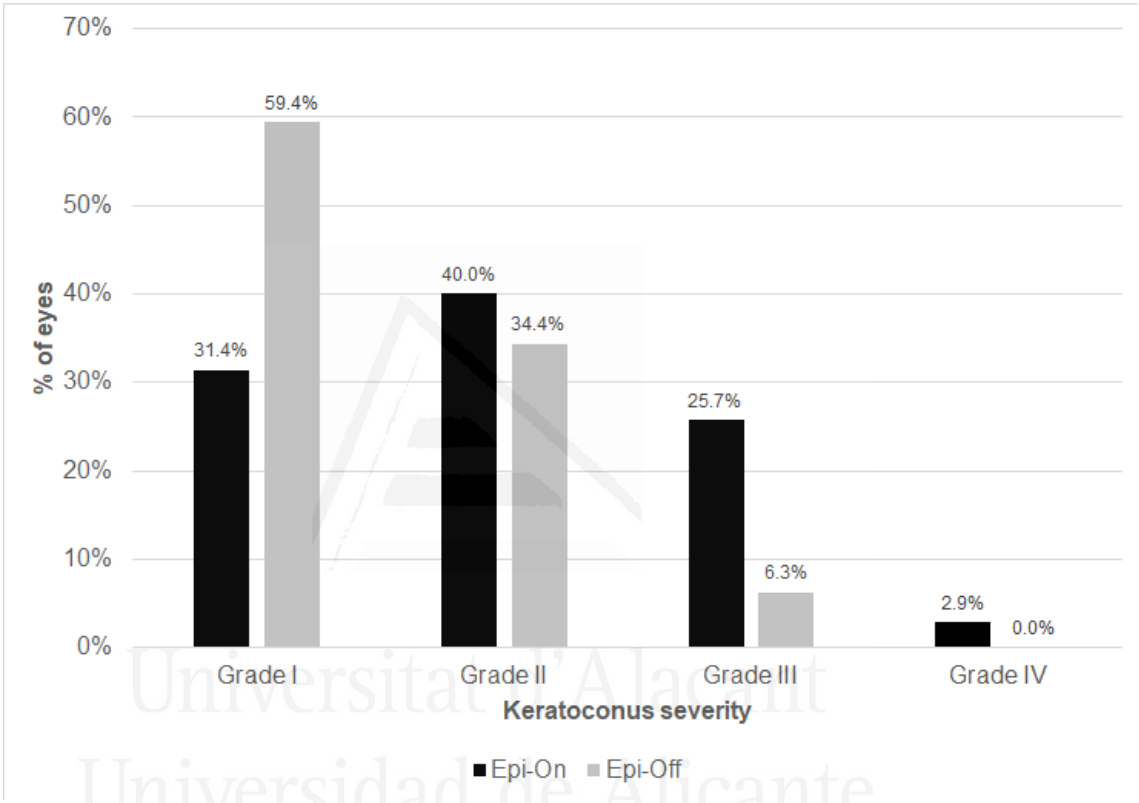
of 71.0% of males and 29.0% of females. The epi-on group consisted of a total of 35 eyes of 35 patients (50.7%), while the epi-off group comprised a total of 32 eyes of 32 patients (46.4%). Mean ages of the epi-on and epi-off groups were 26.5 ± 1.0 and 23.5 ± 1.0 years (p=0.130) (Table 1). According to the Amsler-Krumeich grading system, a total of 30 KC eyes grade I (43.5%), 26 eyes grade II (37.7%), 12 eyes grade III (17.4%) and 1 eye grade IV (1.4%) were included. No significant differences between epi-on and epi-off groups were found in terms of keratoconus severity (p=0.060) (Figure 1). A total of 23 patients (34.3%) were contact lens wearers during the follow-up period of this study. Specifically, 9 (25.7%) and 14 patients (43.8%) from the epi-on and epi-off groups were contact lens wearers (p=0.173).

Table 1.- Demographic data of the patients enrolled in study

CXL type	Epi on 35 (50.7%)
	Epi off 34 (49.3%)
Sex	49 males (71.0%)
	20 females (29.0%)
Age (years)	24.9 ± 1.0
	Epi-on 26.5 ± 1.0
	Epi-off 23.5 ± 1.0
Laterality	36 right eyes (52.2%)
	33 left eyes (47.8%)
Contact lenses	No 46 (66.7%)

Yes 23 (33.3%)

Figure 1.- Distribution of keratoconus severity according to the Amsler-Krumeich grading system in epi-on and epi-off groups.



Visual and refractive changes

Table 2 shows the UDVA, CDVA, and manifest refraction data at the preoperative, 3-month postoperative and 12-month postoperative visits. As shown, no significant differences between epi-on and epi-off groups were found preoperatively in any visual and refractive parameter ($p \geq 0.166$). Postoperatively, no significant differences were found between epi-on and epi-off groups in UDVA, CDVA, sphere, cylinder, spherical equivalent, and astigmatism power vectors ($p \geq 0.072$).

Table 2.- Differences between epi-on and epi-off groups in visual and refractive parameters in the different visits of the follow-up.

Mean (SD) Median (Range)	***Preoperative***		***P-value***	***Postoperative 3 months***		***P-value***	***Postoperative 12 months***		***P-value***
	Epi-on	***Epi-off***		***Epi-on***	***Epi-off***		***Epi-on***	***Epi-off***	
UDVA	0.75 (0.44)	0.75 (0.38)	0.741	0.67 (0.42)	0.73 (0.40)	0.620	0.65 (0.36)	0.66 (0.42)	0.993
(logMAR)	0.7 (1.90)	0.82 (1.25)		0.82 (1.25)	0.70 (1.25)		0.70 (1.25)	0.61 (1.30)	
Sphere (D)	-0.75	-1.58 (3.14)	0.166	-0.67 (2.11)	-1.53 (3.36)	0.396	-0.73 (1.78)	-1.57 (2.94)	0.366
	(1.70)	-0.75		0.00 (0.75)	-0.50 (17.00)		-0.13 (9.00)	-0.68	
	0.00 (8.00)	(16.00)						(14.00)	
Cylinder (D)	-3.35	-3.01 (1.50)	0.584	-2.61 (2.08)	-2.35 (1.75)	0.983	-2.74 (1.96)	-2.39 (1.59)	0.542
	(1.75)	-3.00 (5.50)		-2.00 (8.00)	-2.50 (6.00)		-2.50 (9.25)	-2.37 (7.00)	
	-3.00								
	(8.00)								
SE (D)	-2.42	-3.09 (3.13)	0.384	-1.98 (2.41)	-2.71 (3.57)	0.335	-2.11 (2.11)	-2.77 (3.22)	0.170
	(1.95)	-2.37		-1.25	-1.63 (18.50)		-1.62	-1.70	
	-2.00	(15.63)		(10.75)			(11.13)	(17.00)	
	(9.50)								
J_0 (D)	-0.02	-0.21 (1.26)	0.485	-0.39 (1.24)	-0.31 (1.08)	0.917	-0.25 (1.30)	-0.21 (0.95)	0.998
	(1.34)	-0.23 (4.52)		-0.62 (6.35)	-0.21 (4.95)		-0.50 (6.35)	-0.21 (3.87)	
	0.00 (5.45)								
J_{45} (D)	0.17 (1.35)	0.17 (1.11)	0.772	0.05 (1.06)	0.10 (0.95)	0.706	0.19 (1.12)	0.33 (1.02)	0.505
	0.00 (5.93)	-0.16 (3.80)		0.00 (4.50)	0.00 (3.96)		0.04 (4.74)	0.16 (4.97)	
CDVA	0.36 (0.23)	0.33 (0.28)	0.322	0.31 (0.23)	0.27 (0.15)	0.630	0.28 (0.23)	0.16 (0.14)	0.072
(logMAR)	0.30 (1.00)	0.30 (1.30)		0.30 (0.70)	0.30 (0.70)		0.26 (0.82)	0.15 (0.52)	

Abbreviations: UDVA, uncorrected distance visual acuity; logMAR, logarithm of minimal angle of resolution; SD, standard deviation; SE, spherical equivalent; CDVA, corrected distance visual acuity; J_0 and J_{45}, astigmatism power vectors; D, diopters.

Corneal tomographic changes

Table 3 shows the corneal tomographic data at the preoperative, 3-month postoperative and 12-month postoperative visits. Significant differences between epi-on and epi-off groups were found in different tomographic parameters: anterior flattest keratometry (K1) (p=0.038), anterior steepest keratometry (K2) (p=0.035), posterior K1 (p=0.048), anterior maximum keratometry (K-max) (p=0.020), total deviation value (D index) (p=0.002), central corneal thickness (CCT) (p=0.004), minimal corneal thickness (MCT) (p<0.001) and apex corneal thickness (ACT) (p=0.001). Specifically, eyes included in the epi-on group had corneas with more curvature and lower corneal thickness compared to eyes from the epi-off group (Table 3). These significant differences found preoperatively in anterior K1, anterior K2, anterior K-max, D index, CCT, MCT and ACT were also found at 3 months (p≤0.028) and 12 months postoperatively (p≥0.027). However, the difference between epi-on and epi-off groups did not reach statistical significance for posterior K1 at 3 (p=0.137) and 12 months after surgery (p=0.129). Furthermore, at 12 months postoperatively, a significantly lower corneal volume was found in the epi-on group compared to the epi-off group (p=0.044).

Table 3.- Differences between epi-on and epi-off groups in corneal tomographic parameters in the different visits of the follow-up.

Mean (SD) Median Range)	*Preoperative Epi on off*	*Epi*	*P-value*	*Postoperative 3 months Epi on off*	*Epi*	*P-value*	*Postoperative 12 months Epi on*	*Epi off*	*P-value*
Anterior K1 (D)	46.90 (3.93) 47.50 (14.70)	45.02 (3.22) 44.40 (12.80)	0.038	47.20 (3.81) 47.70 (13.50)	45.05 (3.34) 44.60 (12.10)	0.021	47.07 (4.20) 47.55 (16.60)	44.75 (3.52) 44.20 (12.40)	0.027
Anterior K2 (D)	51.93 (4.87) 52.25 (19.80)	49.52 (4.18) 49.25 (18.30)	0.035	51.71 (4.68) 52.70 (19.30)	49.15 (4.07) 49.25 (17.30)	0.024	51.88 (5.36) 52.01 (20.10)	48.89 (4.34) 48.60 (17.80)	0.021
Posterior K1 (D)	-6.94 (0.83) -6.85 (3.30)	-6.55 (0.72) -6.50 (2.70)	0.048	-6.90 (0.77) -7.00 (2.60)	-6.61 (0.73) -6.55 (2.90)	0.137	-6.91 (0.83) -7.00 (3.60)	-6.60 (0.71) -6.50 (2.90)	0.129
Posterior K2 (D)	-7.92 (1.00) -7.90 (3.80)	-7.53 (0.84) -7.55 (3.60)	0.092	-7.95 (0.98) -8.00 (3.90)	-7.50 (0.84) -7.45 (3.60)	0.054	-7.86 (1.02) -7.95 (3.90)	-6.75 (3.14) -7.50 (17.20)	0.085
K-max (D)	60.31 (6.47) 59.50 (26.50)	56.54 (6.35) 55.60 (23.40)	0.020	59.90 (6.24) 60.35 (25.70)	56.15 (6.27) 55.75 (23.30)	0.028	59.88 (7.19) 59.85 (28.50)	55.49 (6.62) 54.30 (25.30)	0.018
D index	11.26 (4.09) 11.49 (16.53)	8.31 (3.36) 7.82 (13.52)	0.002	11.54 (4.09) 11.81 (15.67)	8.38 (3.18) 8.53 (14.35)	0.001	10.96 (4.55) 11.44 (16.85)	8.23 (3.32) 8.39 (13.97)	0.011

CCT	455.64	484.34	0.004	460.58	485.09	0.015	458.78	488.54	0.004
(µm)	(36.47)	(42.16)		(38.34)	(41.67)		(35.88)	(40.02)	
	454.38	476.0		447.00	476.00		460.00	477.00	
	(135.00)	(157.00)		(142.00)	(155.00)		(140.00)	(149.00)	
ACT	442.47	477.03	0.001	446.00	478.59	0.002	447.00	480.64	0.003
(µm)	(38.91)	(41.89)		(39.79)	(42.17)		(36.59)	(42.05)	
	436.00	468.00		435.00	469.00		443.50	469.00	
	(135.00)	(158.00)		(129.00)	(167.00)		(132.00)	(145.00)	
MCT	428.70	467.09	<0.00	430.61(37.	468.75(42.58	0.001	433.07	470.19	0.001
(µm)	(35.36)	(41.08)	1	08)	)		(35.02)	(42.46)	
	419.50	461.0		425.0(158)	461.0(170)		428.50	463.0	
	(141.0)	(157.0)					(126.0)	(145.0)	
Corneal	55.62	57.21	0.094	56.14	57.70 (4.09)	0.114	56.01	58.16	0.044
volume	(3.47)	(4.11)		(3.63)	59.00		(3.75)	(4.23)	
(mm³)	55.65	57.90		56.40	(16.00)		56.30	59.10	
	(16.40)	(16.60)		(17.40)			(16.60)	(16.70)	
Q-val	-0.94 (0.53)	-0.78 (0.43)	0.187	-0.94 (0.55)	-0.77 (0.46)	0.192	-0.91 (0.51)	-0.69 (0.41)	0.064
	-0.85 (2.52)	-0.80 (1.62)		-0.99 (2.26)	-0.73 (2.02)		-0.97 (1.98)	-0.68 (1.47)	

Abbreviations: K1, flattest keratometry; K2, steepest keratometry; K-max, maximum keratometry; K-max: maximum keratometry; D, total deviation value; CCT, central corneal thickness; ACT, apex corneal thickness; Q-val, asphericity of the anterior corneal surface; MCT: minimal corneal thickness

Changes in topometric indices

Table 4 shows the topometric indices measured at the preoperative, 3-month postoperative and 12-month postoperative visits. Significant differences between epi-on and epi-off groups were found in all preoperative parameters: IHD (p=0.005), ISV (p=0.012), IVA (p=0.029), KI (p=0.037), ARC (p=0.018), and PRC (p=0.010). At 3 months postoperatively, significant differences between groups were found in IHD (p=0.031), ISV (p=0.015), KI (p=0.035), and Rmin (p=0.020). Likewise, statistically significant differences between epi-on and epi-off groups were at 12 months after surgery in ISV (p=0.035), Rmin (p=0.020), ARC (p=0.012), and PRC (p=0.020).

Table 4.- Differences between epi-on and epi-off groups in corneal topometric parameters in the different visits of the follow-up.

Mean (SD) ***Median*** ***Range)***	***Preoperative*** ***Epi on***	***Epi off***	***P-value***	***Postoperative 3 months*** ***Epi on***	***Epi off***	***P-value***	***Postoperative 12 months*** ***Epi on***	***Epi off***	***P-value***
IHD	0.20 (0.14)	0.13 (0.07)	0.005	0.19 (0.12)	0.13 (0.07)	0.031	0.21 (0.16)	0.17 (0.15)	0.191
	0.18 (0.88)	0.12 (0.35)		0.18 (0.67)	0.13 (0.32)		0.18 (0.67)	0.13 (0.71)	
ISV	114.11	89.78	0.012	113.55	91.81	0.015	110.25	88.61	0.035
	(34.63)	(41.90)		(36.10)	(36.63)		(40.96)	(39.80)	
	110.00	84.50		110.00	91.00		106.50	86.00	
	(149.00)	(193.00)		(144.00)	(180.00)		(147.00)	(191.00)	
IVA	1.23 (0.47)	0.94 (0.59)	0.029	1.21 (0.49)	0.98 (0.53)	0.087	1.17 (0.52)	0.96 (0.56)	0.161
	1.23 (1.72)	0.87 (2.76)		1.14 (1.72)	0.98 (2.52)		1.15 (1.64)	0.95 (2.65)	
KI	1.32 (0.14)	1.24 (0.15)	0.037	1.31 (0.14)	1.24 (0.14)	0.035	1.31 (0.16)	1.23 (0.14)	0.058
	1.33 (0.64)	1.22 (0.75)		1.33 (0.65)	1.23 (0.69)		1.29 (0.61)	1.24 (0.74)	
Rmin *(mm)*	5.66 (0.62)	6.03 (0.66)	0.021	5.67 (0.61)	6.05 (0.63)	0.020	5.71 (0.69)	6.15 (0.70)	0.020
	5.67 (2.70)	6.07 (2.46)		5.58 (2.67)	6.06 (2.34)		5.64 (2.85)	6.22 (2.67)	
ARC *(mm)*	6.32 (0.63)	6.68 (0.55)	0.018	6.25 (0.59)	6.74 (0.53)	0.108	6.36 (0.65)	6.80 (0.61)	0.012
	6.09 (2.40)	6.60 (2.04)		6.08 (2.42)	6.68 (2.04)		6.09 (2.37)	6.71 (2.34)	
PRC *(mm)*	4.65 (0.58)	5.02 (0.56)	0.010	4.56 (0.52)	5.03 (0.50)	0.095	4.69 (0.63)	5.05 (0.52)	0.020
	4.52 (2.44)	4.98 (2.17)		4.53 (2.19)	4.98 (1.91)		4.59 (2.52)	5.01 (2.09)	

Abbreviations: IHD, index of height decentration; ISV, index of surface variance; IVA, index of vertical asymmetry; KI, keratoconus index; Rmin, minimum radii of curvature; ARC, anterior average radius of curvature taken from the 3.0 mm optical zone centered on the thinnest point; PRC, posterior average radius of curvature taken from the 3.0 mm optical zone centered on the thinnest point.

Corneal aberrometric changes

Table 5 shows the corneal aberrometric data measured at the preoperative, 3-month postoperative and 12-month postoperative visits. Statistically significant differences were found between epi-on and epi-off groups in the preoperative aberrometric variables: anterior (p=0.013) and posterior (p=0.010) total RMS, anterior HOA RMS (p=0.042), and anterior (p=0.014) and posterior (p=0.013) LOA RMS. At 3 months after surgery, significant differences between epi-on and epi-off groups were found in these same variables as preoperatively (p≤0.044) as well as in posterior HOA RMS (p=0.005). At 12 months postoperatively, these significant differences were only maintained in anterior total RMS (p=0.045), anterior (p=0.048) and posterior (p=0.048) HOA RMS, and anterior LOA RMS (p=0.048).

Table 5.- Differences between epi-on and epi-off groups in corneal topometric parameters in the different visits of the follow-up.

Mean (SD) Median (Range)	***Preoperative Epi on Epi off***		***P-value***	***Postoperative 3 months Epi on Epi off***		***P-value***	***Postoperative 12 months Epi on Epi off***		***P-value***
Anterior total RMS	15.84 (5.35) 15.14	12.93 (6.10) 12.33	0.013	15.63 (5.38) 15.01	12.30 (5.73) 12.09	0.018	15.00 (6.19) 13.71	11.71 (6.14) 11.44	0.045

(μm)	(22.97)	(28.58)		(22.33)	(26.45)		(23.21)	(28.01)	
Anterior	4.06	3.32	0.042	4.04	3.14	0.022	3.84	3.01	0.048
HOA	(1.43)	(1.68)		(1.50)	(1.45)		(1.63)	(1.52)	
RMS	4.03	3.09		4.12	3.05		3.40	3.00	
(μm)	(6.14)	(8.39)		(5.99)	(7.17)		(5.75)	(7.64)	
Anterior	15.30	12.49	0.014	15.09	11.88	0.019	14.49	11.34	0.048
LOA	(5.19)	(5.89)		(5.19)	(5.57)		(5.99)	(5.98)	
RMS	14.84	11.91		14.50	11.72		13.36	11.01	
(μm)	(22.26)	(27.33)		(21.64)	(25.47)		(22.82)	(27.02)	
Anterior	-3.14	-2.51	0.075	-3.08	-2.48	0.125	-2.93	-2.36	0.239
Z_3^{-1}*(μm)*	(1.68)	(1.75)		(1.67)	(1.63)		(1.78)	(1.67)	
	-3.38	-2.55		-3.16	-2.62		-2.63	-2.60	
	(7.03)	(8.82)		(7.03)	(8.31)		(6.14)	(8.60)	
Anterior	-0.07	0.08	0.397	-0.13	0.04	0.398	0.00	0.02	0.861
Z_3^{1}*(μm)*	(1.49)	(0.87)		(1.57)	(0.82)		(1.51)	(0.83)	
	-0.36	0.13		-0.42	0.13		-0.30	0.08	
	(5.38)	(3.96)		(7.08)	(3.49)		(5.32)	(3.36)	
Anterior	-0.86	-0.47	0.116	-0.88	-0.56	0.189	-0.85	-0.45	0.131
Z_4^{0} *(μm)*	(0.99)	(0.92)		(0.95)	(0.84)		(1.00)	(0.87)	
	-0.79	-0.28		-0.97	-0.49		-0.81	-0.16	
	(4.34)	(3.33)		(3.74)	(2.95)		(3.94)	(3.29)	
Posterior	3.66	2.87	0.010	3.61	2.86	0.024	3.45	3.17	0.816
total	(1.19)	(1.32)		(1.33)	(1.16)		(1.52)	(2.75)	
RMS	3.48	2.83		3.09	2.79		2.94	2.60	
(μm)	(4.70)	(5.94)		(4.75)	(5.54)		(6.34)	(15.40)	
Posterior	0.77	0.64	0.162	1.08	0.81	0.005	1.04	0.88	0.048
HOA	(0.48)	(0.34)		(0.37)	(0.32)		(0.45)	(0.67)	

RMS	0.76	0.47		0.94	0.79		0.89	0.73	
(μm)	(0.83)	(1.11)		(1.54)	(1.62)		(1.70)	(3.70)	
Posterior	3.49	2.74	0.013	3.44	2.74	0.044	3.28	3.05	0.860
LOA	(1.15)	(1.27)		(1.28)	(1.12)		(1.46)	(2.67)	
RMS	3.38	2.66		2.97	2.68		2.83	2.47	
(μm)	(4.49)	(5.69)		(4.58)	(5.36)		(6.15)	(15.01)	
Posterior	0.76	0.58	0.081	0.77	0.59	0.072	0.72	0.58	0.309
Z_3^{-1}*(μm)*	(0.41)	(0.37)		(0.43)	(0.37)		(0.46)	(0.37)	
	0.74	0.57		0.71	0.61		0.64	0.65	
	(1.68)	(1.74)		(1.78)	(1.73)		(1.72)	(1.70)	
Posterior	0.02	-0.02	0.667	0.02	-0.01	0.554	-0.01	0.00	0.891
Z_3^{1}*(μm)*	(0.41)	(0.24)		(0.44)	(0.23)		(0.40)	(0.23)	
	0.09	0.00		0.05	-0.03		-0.01	-0.01	
	(1.48)	(1.04)		(1.98)	(0.95)		(1.53)	(1.00)	
Posterior	0.11	0.07	0.386	0.10	0.07	0.462	0.10	0.04	0.298
Z_4^{0} *(μm)*	(0.22)	(0.23)		(0.20)	(0.19)		(0.23)	(0.17)	
	0.11	0.03		0.12	0.07		0.11	0.04	
	(0.92)	(1.06)		(0.76)	(0.80)		(1.13)	(0.82)	

Abbreviations: RMS: root mean square, HOA: higher order aberrations, LOA: lower order aberrations; Z_3^{-1}: vertical coma; Z_3^{1}: horizontal coma; Z_4^{0}: spherical aberration.

Correlation of visual changes with preoperative variables

Mean change at 3 months after surgery in logMAR CDVA was -0.04 ± 0.19 and -0.07 ± 0.25 in the epi-on and epi-off groups, respectively (p=0.809). At 12 months postoperatively, mean change in logMAR CDVA was -0.07 ± 0.19 and -0.16 ± 0.23 in the epi-on and epi-off

groups, respectively (p=0.087). In the epi-on group, mean 3-month change in CDVA was significantly correlated with preoperative apical corneal thickness (r=-0.375, p=0.045), central corneal thickness (r=-0.402, p=0.031) and anterior corneal asphericity (r=-0.363, p=0.050). In the epi-off group, mean 3-month change in CDVA was significantly correlated with preoperative apical corneal thickness (r=0.402, p=0.028), central corneal thickness (r=0.367, p=0.046), ISV (r=-0.405, p=0.027), IVA (r=-0.394, p=0.031), anterior total RMS (r=-0.374, p=0.042) and anterior LOA RMS (r=-0.374, p=0.042).

In the epi-on group, no correlation of the visual change at 3 (r=-0.084, p=0.664) and 12 months (r=-0.043, p=0.835) after surgery with age was found. Likewise, no significant differences in the visual change at 3 (-0.03 ± 0.15 vs. -0.06 ± 0.26, p=0.649) and 6 months (-0.06 ± 0.16 vs. -0.09 ± 0.25, p=0.874) were found between patients not wearing contact lenses and those wearing them. Similarly, in the epi-off group, no correlations of age with 3-month (r=-0.146, p=0.426) and 12-month (r=-0.059, p=0.749) visual changes were found. Furthermore, in this same group, no significant differences in the 3-month (-0.04 ± 0.18 vs. -0.16 ± 0.34, p=0.343) and 12-month (-0.10 ± 0.14 vs. -0.28 ± 0.30, p=0.116) visual changes were found either between not contact lens users and those using them.

Multiple linear regression analysis

In the epi-on group, a statistically significant linear relationship between 3-month changes in CDVA *(f..CDVA*) was obtained according to the following expression (p=0.002, R^2=0.503, adjusted R^2: 0:420, Durbin-Watson: 2.207):

$$f..CDVA = 0.063 - 0.006 \times Age - 0.075 \times J_{45} - 0.203 \times Q\text{-}val - 0.140 \times HOA_{post}\ RMS$$

where J_{45} is one of the refractive astigmatism power vectors, Q-val is the anterior corneal asphericity, and HOA_{post} RMS is the posterior higher order aberration root mean square.

The normality of the unstandardized residuals distribution (p=0.200) and the absence of influential points or outliers (mean Cook's distance=0.045 ± 0.076) confirmed the

homoscedasticity of this model. Likewise, no multicollinearity was detected in the model (variance inflation factor between 1.068 and 1.283).

In the epi-off group, a statistically significant linear relationship between 3-month changes in CDVA *(!'lCDVA*) was obtained according to the following expression (p=0.001, R^2=0.446, adjusted R^2: 0:398, Durbin-Watson: 2.200):

$$!'lCDVA=-1.551 + 0.003 \times MCT + 0.171 \times Z_3^{-1}$$

where MCT is minimal corneal thickness and Z_3^{-1} is the Zernike term corresponding to the anterior vertical primary coma.

The normality of the unstandardized residuals distribution (p=0.200) and the absence of influential points or outliers (mean Cook's distance=0.044 ± 0.080) confirmed the homoscedasticity of this model. Likewise, no multicollinearity was detected in the model (variance inflation factors 1.073).

Discussion

Corneal CXL, as a photo-oxidative procedure, enhances the mechanical stability of the cornea because of synthesis of well-structured collagen and new lamellar interconnections in the cornea.[5,21-23] The promising results of CXL in the management of either KC or corneal ectasia have encouraged the researchers to consider it as one of the substantial initial treatment procedures for these conditions.[24,25] Few studies with variable results have been conducted to date to define potential predictive factors for the clinical outcome obtained with this surgical procedure in terms of visual or corneal tomographic changes or even in terms of progression of KC.[26-29] There are clinical studies proving additional insights into factors associated with CXL outcomes in KC patients.[1,2,3,6] However, preoperative predictors of visual changes after CXL were not entirely illustrated and there is still a necessity for further research on this issue. In this

study, the predictive factors for the visual change induced after two different techniques of CXL, accelerated epi-on and epi-off, have been investigated.

In the present study, the visual and refractive results obtained with the two CXL techniques did not differ significantly at preoperative and postoperative visits, suggesting that both techniques were comparable in terms of visual and refractive outcomes and potentially in the ability of halting the progression of keratoconus during a 1-year follow-up. Likewise, the visual acuity outcomes of our study are consistent and comparable to other CXL reports for the treatment of progressive corneal ectasia.[9,30-36,37-39] Shalchi et al[40] revised the clinical outcomes of 45 articles that evaluated the CXL epithelium-off technique and six articles that evaluated the transepithelial CXL technique. These authors could not perform a meta-analysis with all these data because there was only one randomized, controlled clinical trial comparing the two CXL techniques, and this particular trial evaluated only corneal morphological changes on confocal microscopy and optical coherence tomography and did not report corneal topography or visual outcomes.[40] Using the published data in the review article of Shalchi et al,[40] a mean change in CDVA of −0.08 ± 0.07 logMAR (range, −0.23 to +0.06) was calculated for the 45 articles evaluating the epi-off CXL technique. For the six articles evaluating the transepithelial technique, a mean change in CDVA of −0.08 ± 0.04 logMAR (range, −0.12 to −0.04) was calculated. It is important to note that in our study, data of epi-on accelerated CXL have been analyzed in comparison to the review of Shalchi et al[40] that analyze articles reporting the outcomes of epi-on standard CXL surgery. In the current sample, mean changes in CDVA of -0.06 ± 0.19 (range, -0.14 to 0.01) and -0.16 ± 0.23 (range, -0.24 to -0.07) were found at 1 year after accelerated epi-on and epi-off CXL, respectively.

In our study, we observed in the two groups that anterior K2, K-max, CCT, MCT and ACT showed improvement at one year of follow-up, although the magnitude of the change achieved was relatively small (Table 3). Rossi et al. showed that both treatments epi-on and epi-off stopped the progression of keratoconus in all eyes from their comparative study over a 12-month period.[41] Magli et al. compared epi-on vs epi-off and they observed similar results in a study with pediatric patients under 18 years of age.[42] In contrast, some studies have found that

patients treated with epi-on CXL had a greater KC progression than those treated with epi-off CXL.[43] Kocak et al.[44] reported a stabilization of the corneal ectasia in 89% of eyes treated with epi-off CXL, whereas only in 35% of eyes treated with Epi-on CXL. Cerman et al.[45] found that 97% of Epi-off eyes achieved stabilization in a comparative study and 80% of Epi-on eyes, although these authors associated the greater ectasia progression in Epi-on eyes to the presence of more cases of advanced and progressive KC disease in such group. Despite the differences in the results, the four studies found a faster visual recovery and a reduction of pain and infections related to epithelial defects in the epithelium-on groups. Mean preoperative and postoperative Kmax (D) values in the epi-on group in different comparative studies were 52.41 ± 5.39 and 50.5 ± 5.37 D,[41] 49.27 ± 4.1 and 48.13 ± 5.4 D,[42] 48.75 ± 6.82 and 50.57 ± 6.82 D,[44] 60.12 ± 6.17 and 60.0 ± 6.31 D,[45] and 54.7 ± 4.0 and 53.7 ± 3.7 D,[46] respectively. Caruso et al[47] observed a reduction in mean Kmax value of -1.10 ± 1.22 D at the end of the follow-up after Epi-on CXL. In our study, mean preoperative and postoperative Kmax values in the Epi-on group were 60.31 ± 6.47 and 59.88 ± 7.19 D, respectively. Concerning, mean values of CCT (microns) in the Epi-on group in different comparative studies, preoperative and postoperative values of 451 ± 39.51 and 448.4 ± 37.32 μm,[41] 490.2 ± 22.3 and 488.0 ± 19.3 μm,[42] 470 ± 38 and 446 ± 59 μm,[44] and 484 ± 37 and 491 ± 27 μm[46] have been reported, respectively. Cerman et al[45] analyzed MCT changes in a study with 18 months of follow-up, finding mean values of 425.3 ± 22.4 and 419.4 ± 24.3 μm before and at the end of the follow-up, respectively. Caruso et al[47]observed a mean increase in MCT of 6.6 ± 24.0 μm at the end of the follow-up. In our study, mean CCT and MCT values in the Epi-on group were 455.64 ± 36.47 and 458.78 ± 35.88 μm preoperatively and 428.70 ± 35.36 and 433.07 ± 35.02 μm at the end of the follow-up.

Besides these investigations, other CXL protocols have been evaluated that are based on the epi-on concept, such as the CXLO protocol that uses a new sodium iodide riboflavin formulation that theoretically allows a greater level of penetration.[48,49,50,51,52] These investigations have shown that the use of the CXLO protocol can halt the progression of ectasia and result in better visual acuity without the risk associated to epi-off CXL.[48,49,50,51,52] Three of

these studies shows the results of this type of CXL applied one day after conductive keratoplasty (CK).[48,49,50] Sinjab et al[50] observed at the end of follow-up a mean reduction of Kmax with the combination of CK and CXLO of 3.8 D, being the mean baseline Kmax value 65.1 ± 11 D. Rechichi et al[53] evaluated changes in refraction and corneal aberrations in keratoconus after selective transepithelial topography-guided photorefractive keratectomy combined with accelerated corneal crosslinking (STARE-X), and demonstrated effective results to stop the progression of keratoconus. Specifically, there was an improvement of both visual acuity and corneal aberration, and a statistically significant reduction in Kmax at 2 years after surgery.

In the current sample, mean changes in Kmax were -0.45 ± 1.96 D and -1.05 ± 1.56 D at 1 year after surgery in the Epi-on and Epi-off CXL groups, respectively. Likewise, mean changes in MCT were 3.75 ± 1.56 μm and 2.41 ± 1.69 μm at 1 year after surgery in Epi-on and Epi-off groups, respectively. These results should be analyzed considering that the percentage of moderate and advanced keratoconus (grade III and IV) was 28.6% and 6.3% in Epi-on and Epi-off groups, respectively. Thus, in our study, patients included in the accelerated epi-on group tended to have a more severe keratoconus than in the accelerated epi-off group, presenting higher baseline K-max and K2 and lower ACT, CCT and MCT values. This can be explained by the fact that in our hospital epi-on techniques are preferred in thinner corneas that are normally present in more severe keratoconus for protecting the corneal endothelium from excessive riboflavin penetration and UV radiation. Considering this situation (worse baseline conditions in the epi-on group), better results were expected at the end of the follow-up in the epi-off group, but differences in the visual results did not reach statistical significance, while discrepancies between groups in terms of corneal tomographic and topographic data were maintained. Sloot et al[54] demonstrated that the amount of flattening by CXL was directly proportional to the steepness of the cornea. However, in our series, the results of epi-on CXL were not inferior to those obtained with epi-off CXL technique at 1 year after the surgical procedure was done despite the significantly worse baseline conditions of patients in the epi-on group.

Concerning corneal volume, statistically significant (p=0.044) differences between epi-on and epi-off groups were only found at 12 months after surgery (epi-on 56.01 ± 3.75 mm^3 vs. epi-off 58.16 ± 4.23 mm^3). However, corneal volume also tended to be lower in the epi-on group preoperatively and at 3 months after surgery, which is consistent with the more reduced measures of corneal thickness (ACT, CCT and MCT) obtained in this group at all visits. This lower corneal volume in the epi-on group compared to the epi-off is due to the inclusion of more cases of moderate to advanced keratoconus in such group, as a greater reduction in corneal volume is present in eyes with more advanced keratoconus.[55] In the current study, an analysis of corneal biomechanical variables was not performed, but in another study the parameters of corneal hysteresis (CH) and corneal resistance factor (CRF) were found to be correlated with morphogeometric and volumetric parameters in corneas with keratoconus, but this correlation was highly influenced by the thickness of the cornea.[56]

As in the epi-on group more patients with moderate to advanced keratoconus were included, the presence of high order aberrations was higher, as they had a more altered and irregular cornea. Indeed, significant differences between groups were found preoperatively and postoperatively in other indices characterizing the level of corneal irregularity, such as IHD, ISV, or KI. It should be considered that Kanellopoulos et al[57] concluded that ISV and IHD may be the most sensitive and specific criteria in the diagnosis and progression of keratoconus. The anterior corneal HOAs and LOAs showed a trend toward improvement in both groups, as in other previous studies.[8,58] However, the difference between groups was maintained during the follow-up in most of aberrometric parameters. It should be considered that this aberrometric change was associated to a visual improvement in both groups, as in previous series evaluating the outcomes of different CXL techniques.[8,24,25,59] Ghanem et al[60] concluded that the improvement in high order aberrations in keratoconus patients was attributed to the flattening of the corneal apex caused by the CXL effect. In contrast to what happens in the anterior corneal surface after CXL, a trend towards worsening of posterior high order aberrations RMS was found after both techniques, epi-on and epi-off, maintaining the differences between groups during the follow-up. This could be explained by the significant changes that occur in the

mechanical resistance of the anterior cornea as a consequence of the CXL procedure and this probably produces changes in the geometry of the posterior corneal surface. A similar finding was reported in a previous study evaluating the posterior aberrometric impact of accelerated epi-on CXL surgery.[61] In this same study, significant steepening and change to significant prolateness was observed in these patients undergoing epi-on CXL.[61]

Regarding the safety of CXL, we observed in the epi-off group one case of sterile infiltrates that were successfully solved with topical corticosteroids, without leaving sequelae. In the epi-off group, only one case of small epithelial defects that completely closed on the 3rd postoperative day was reported. No cases of infectious keratitis or stromal scars were reported in any patient from both groups. Koller et al[62] and Ghanem et al[63] reported sterile infiltrate rates after epi-off CXL in 7.6% and 0.97% of eyes in their series, respectively. Stulting et al[51] reported a rate of 5% for small epithelial defects the day after treatment, but almost all were closed the next day. Furthermore, in our study, stromal haze was present in 8.8% of the patients in the epi off group (3 patients), which was minimized at around 6 months in all patients. The incidence of postoperative corneal haze after epi-off CXL varies significantly from studies, since values around 10%[8,64] to values over 20%.[65]

In the epi-on group, mean 3-month change in CDVA was significantly correlated with preoperative ACT, CCT and anterior corneal asphericity. Specifically, these correlations revealed that more visual improvement was expected in those eyes with less prolate and thicker corneas. In contrast, in the epi-off group, mean 3-months change in CDVA was found to be significantly correlated with preoperative ACT, CCT, ISV, IVA, anterior total RMS and anterior LOA RMS, with more improvement expected in thinner corneas, with more anterior aberrations and higher values of ISV and IVA at baseline. This confirms that the predictive factors for the visual change induced with the two techniques of CXL evaluated were clearly different and consequently that differential mechanisms of action were present with both techniques. There are previous studies that have investigated some potential predictive factors for the effect of epi-off CXL, but not for the effect of epi-on CXL. Some of them are consistent with those found in the epi-off group in the current series. Wisse et al[1] confirmed that cone

eccentricity was the sole predictor of keratometry outcomes at 1 year after epi-off CXL, demonstrating also that pretreatment CDVA could be used to reliably predict CDVA 1 year after treatment. Toprak et al[3] observed that a preoperative CDVA < 20/40 was significantly related with postoperative visual improvement after epi-off CXL. Likewise, these authors confirmed that corneas with a thinnest corneal pachymetry below 450 μm experienced significantly more flattening in maximum K. In the study conducted by Greenstein SA et al, the only independent predictor of the change in postoperative CDVA after CXL was the preoperative CDVA.[28] Badawi et al[5] demonstrated that higher K-max, worse CDVA, and relative thinner corneas were associated with greater improvement after epi-off CXL, whereas Peyman et al[2] observed that lower pretreatment logMAR CDVA, thinner pretreatment CCT, and higher pretreatment KI was associated to higher postoperative logMAR CDVA reduction. In addition, Koller et al[27] observed that a higher baseline K-max was associated with a greater degree of flattening.

Besides the analysis of the correlation of the visual change in each group with preoperative data, a multiple linear regression analysis was performed to obtain a linear expression allowing the clinician to obtain an estimation of the visual change expected after epi-on and epi-off CXL techniques. Likewise, the validity of the two predictive models obtained was investigated. This analysis revealed that the visual change induced by the epi-on CXL techniques could be predicted from the following preoperative variables: age, oblique component of refractive astigmatism (J_{45}), anterior corneal asphericity, and the RMS value of posterior corneal high order aberrations. In contrast, in the epi-off group, other different variables were involved in the predicting equation: preoperative MCT and Zernike term corresponding to the vertical coma of the anterior corneal surface. This confirms, as happened in the correlation analysis, the presence of differential factors for the prediction of the visual change after epi-on and epi-off CXL, suggesting the presence of clearly different mechanisms of action. Specifically, age was only found to be a critical factor of the prediction equation of the visual change induced in the epi-on group despite an extremely weak correlation found between age and visual change in both Epi-on and Epi-off groups. This may be related to the different

mechanism of action and level of penetration with Epi-on CXL, leading to differences in the response of the treatment in those eyes with weaker corneas or with more predisposition to progression. It has been previously reported that the factors possibly contributing to a potentially lesser response of CXL with the transepithelial approach include alterations of the epithelium and basement membrane, epithelial absorption of ultraviolet A radiation, and other patient's variables, such as refraction, Kmax and pachymetry.[14] The riboflavin solution used in the transepithelial study group was formulated with benzalkonium chloride 0.01%, which has been reported to enhance ocular surface penetration by increasing epithelial permeability and bioavailability of topical medication to the corneal stroma.[66] Rush et al[9] concluded that the ocular surface penetration of riboflavin into the corneal stroma in a transepithelial CXL study group was inferior to a epithelium-off control group despite the application of a more concentrated riboflavin formulation and the frequent instillation of benzalkonium chloride. However, this different level of penetration does not necessarily mean a lower capability of controlling the keratoconus progression or less visual impact. It can only be related to a different mode of modifying the mechanical properties of the cornea and generating clinical changes. Indeed, no correlation has been found between demarcation line depth (level of penetration of riboflavin) and visual or topographic outcomes after epi-on and epi-off CXL techniques.[67] More research is needed in the future to understand better the exact mechanism of action of each CXL technique to strengthen the corneal structure.

The multiple linear regression analysis revealed that more significant visual improvement was present at 3 months after epi-on CXL in younger people with higher preoperative levels of posterior HOA RMS, less anterior corneal prolateness and more positive J_{45} refractive component. In contrast, more significant visual improvement was expected at 3 months after epi-off CXL in those eyes with thinner corneas and significant levels of primary coma on the anterior corneal surface. Therefore, as suggested in previous series,[1-3,5,27,28] more visual improvement was expected in those eyes with moderate to severe keratoconus when using epi-off CXL, but not when using epi-on CXL. With the epi-on CXL technique, the visual change induced with surgery does not seem to be related to the level of severity of keratoconus.

This should be considered when selecting the type of CXL to apply in a specific case, being potentially more recommendable the epi-off technique in more advanced keratoconus to also induce a positive impact on visual acuity. In any case, more studies in other keratoconus populations should be conducted to validate and refine these two models of prediction of the visual change after CXL. Finally, it should be mentioned that the use of contact lens was not found to be a critical or confounding factor in these predicting equations, confirming its minimal influence on the outcomes obtained. Furthermore, it should be considered that only a minor portion of patients were contact lens wearers in the current sample.

Our study had several limitations that must be mentioned and acknowledged. First, more cases of moderate to advanced keratoconus were included in the epi-on group, being recommendable to perform in the future comparative studies including more comparable samples in terms of keratoconus severity. Second, although this study provides useful information about proper patient's selection according to the CXL technique, the predictors proposed should be used with care as they cannot be generalizable to all patients, especially to those falling outside the range of the study population; therefore, this study should be validated in future studies for a proper implementation in clinical practice. Third, the retrospective design might be considered as a limitation of the study. It should be considered that information about atopy and familiarity were not available in most of the clinical histories revised and therefore its role as potential confounding factors was not investigated.

In conclusion, changes in logMAR CDVA at 3 months after epi-on CXL were significantly associated with the preoperative magnitude of posterior HOA RMS, age, level of anterior corneal prolateness and the J_{45} refractive component. In contrast, visual changes after epi-off CXL was significantly associated with corneal thickness and the level of primary coma which is present on the anterior corneal surface. These significant differences in the predictive factors of the visual change associated with each CXL technique suggests that the mechanism of action for modifying the mechanical strength of the cornea may differ significantly. There is no clear benefit for a 1-year follow-up of one CXL technique over the other, but more visual improvement might be expected in more severe keratoconus cases. These factors can provide

new insights into the mechanism of action of each CXL technique and provide new insights into prediction of CXL effect for a better patient selection. However, more studies are still needed to validate and refine these predictive models.

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SECCIÓN 3: ARTÍCULOS NO PUBLICADOS

En esta sección se adjunta el cuarto artículo de la actual tesis doctoral que se encuentra en revisión actualmente (revista Journal of Ophthalmology) denominado CAPÍTULO 4.

3.1 CAPÍTULO 4: CHARACTERIZATION AND PREDICTION OF THE CLINICAL RESULT WITH A SPECIFIC MODEL OF MINI-SCLERAL CONTACT LENS IN CORNEAS WITH KERATOCONUS

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Abstract

Purpose: To investigate which factors are correlated with the visual improvement achieved with a specific model of scleral contact lens (ScCL) in keratoconus (KC) eyes and to define a model to predict such improvement according to the pre-fitting data.

Methods: Longitudinal retrospective study including 30 eyes of 18 patients (age, 14-65 years) with KC fitted with the ScCL ICD16.50 (Paragon Vision Sciences). Visual, refractive, corneal tomographic and ocular aberrometric changes were evaluated during a 3-month follow-up. Likewise, the characterization of the post-lens meniscus was performed by optical coherence tomography (OCT) with the measurement of central, nasal and temporal vaults.

Results: The visual acuity (VA) increased significantly from a mean pre-fitting value with spectacles of 0.23±0.07 logMAR ((logarithm of minimal angle of resolution) to a mean value of 0.10±0.04 after 1 month of ScCL wear ($p<0.001$). An improvement of 1 or more lines of VA (visual acuity) with the ScCL occurred in 62.1% of the eyes. A significant decrease in central, nasal, and temporal vault was observed after 1 month of ScCL wear ($p\leq0.046$). Likewise, there was a significant difference between nasal and temporal vaults during the first month of ScCL use ($p=0.008$). Furthermore, a significant reduction of ocular high order ($p=0.028$) and primary coma root mean square ($p=0.018$) was found with the ScCL. A predicting linear equation of the change in VA achievable with the ScCL was obtained ($p<0.001$, $R^2 = 0.878$) considering the pre-fitting spectacle corrected distance visual acuity, and the power and sagittal lens of SCL.

Conclusions: The scleral contact lens evaluated provides an efficacious visual rehabilitation in KC due to the improvement of VA and the correction of the low and high order ocular aberrations. This VA improvement can be predicted from some pre-fitting variables.

Keywords: keratoconus; corneal ectasia; scleral contact lens; miniscleral contact lens; aberrometry; visual acuity.

Introduction

ScCL are currently reaching a great impact due to their indication in irregular corneas such as KC, pellucid marginal degeneration, keratoglobus, post-keratoplasty or postsurgical ectasia, and in patients with severe ocular surface disease, such as extreme dry eye syndrome, Sjögren syndrome, Stevens-Johnson syndrome, scarring ocular pemphigoid, neurotrophic corneal disease, and atopic keratoconjunctivitis.[1-6] ScCL have increased in popularity in the last decade, and it was estimated that 70,000 individuals in the United States wore a scleral lens in 2016.[7,8] As ScCL are large-diameter gas-permeable devices specially designed to rest on the sclera and vault over the entire corneal surface, not bearing on the corneal structure and consequently respecting it, they are an ideal option for visual rehabilitation in KC.[9] Indeed, KC is the main indication of the use of these lenses.[7,8,10-12] Koppen et al[13] reported that scleral lenses mitigated the need for corneal transplant in 80% of patients with severe KC.

Several studies have demonstrated that a successful visual rehabilitation can be achieved with ScCL in KC,[6,7,14-16] even in cases with previous surgical treatments, such as intracorneal ring segments.[17,18] However, the visual improvement achieved with ScCL can vary significantly between individuals.[6,7,14-18] Several factors may account for this, such as the selection of the vault.[19,20] Otchere et al[19] concluded in a clinical study that a scleral lens fitted adding 375 µm to the corneal sagittal height measured by optical coherence tomography (OCT) gave the best combination of visual acuity and comfort ratings. However, Sonsino and Mathe[20] did not find a correlation between magnitude of vault and LogMAR visual acuity, including in their study patients fitted with scleral lenses with vaults up to 600 µm of vault and as low as 220 µm of vault. Therefore, other factors are involved in the level of visual recovery provided by a ScCL in KC. The aim of the current study was to investigate which factors are correlated with the visual improvement achieved with a specific model of ScCL and to define a model to predict such improvement according to the pre-fitting data.

Methods

Study population

The study was designed as a longitudinal retrospective study of the subjects with keratoconus examined at the Advanced Clinical Optometry Unit of the Department of Ophthalmology of the Vithas Medimar International Hospital (Alicante, Spain) and fitted with a specific model of ScCL (ICD16.50, Paragon Vision Sciences, distributed in Spain by Lenticon, Madrid, Spain). The research was carried out in accordance with the principles of the Declaration of Helsinki, obtaining written consent from all patients for the use of their data in this retrospective analysis. The study was approved by the ethics committee for medical research of the Health Department of Alicante (General Hospital, Alicante, Spain) (CEIm 2020-048, ISABIAL 200045).

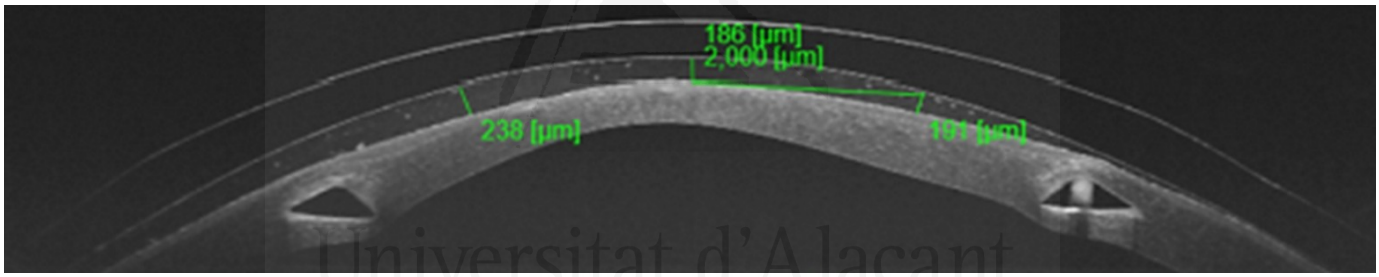
The inclusion criteria for the study were patients with KC in any degree of progression, registered in our database, and fitted with the ICD16.50 scleral contact lens. Patients with or without previous corneal collagen cross-linking (CXL) surgery or implantation of intracorneal ring segments were included. The exclusion criteria were keratoplasty, post-refractive surgery corneal ectasia, contact lens (CL) fitting with another design of ScCL or a follow-up of the CL wear of less than 3 months.

Clinical examinations

All patients had undergone a complete pre-fitting examination including measurement of uncorrected (UDVA) and corrected distance visual acuity (CDVA), manifest refraction, slit lamp biomicroscopy, corneal topography and pachymetry with the Sirius tomographer (CSO, Firenze, Italy), and ocular aberrometry for a 5-mm pupil with the i-Trace system (Tracey Technologies Corp., Houston, TX, USA). After the selection of the first trial lens according to the manufacturer guideline and subsequent trials if needed, the visual acuity with the scleral lens (SLVA) was measured as well as the over-refraction and the central vault by means of optical coherence tomography (DRI OCT Triton, Topcon). Once received the scleral lens with the

appropriate optical power and the adjustments of the periphery required, measurements of SLVA, ocular aberrometry and post-lens meniscus was performed. The post-lens meniscus was characterized by means of the measurement of the central vault and the vault at 2 mm nasally and temporally from the center (Figure 1). These measurements were performed along the horizontal meridian considering the pupillary center as a central reference. These measurements were taken with the OCT caliper option by a single researcher and supervised by a professional with experience in CL field. All these measurements were performed in the afternoon-evening after 6 hours of CL wear during the day.

Figure 1.- Example of characterization of the post-lens meniscus by measuring the vault centrally and at 2 mm nasally and temporally.



After this first assessment with the final CL prescribed, additional examinations were performed after 1 and 3 months of CL wearing. In these two post-fitting visits, SLVA measurement, slit lamp biomicroscopy, OCT-based post-lens meniscus characterization, and corneal tomography without the CL were performed.

Concerning the data extracted from the Sirius tomography system, the following parameters were collected and recorded: anterior (KMa) and posterior mean keratometry (KMp) for the central 3-mm area, anterior (ASTa) and posterior corneal astigmatism (ASTp) for the central 3-mm area, anterior (Qa) and posterior corneal asphericity (Qp) for the central 8-mm area, central (CCT) and minimal corneal thickness (MCT), and anterior and posterior corneal surface aberrations (6-mm pupil), including high order aberration (HOA), primary coma, and

residual aberration (all HOAs except primary coma and spherical aberration) RMS (root mean square) as well as the Zernike term corresponding to the primary spherical aberration (SA).

Scleral contact lens

The ICD16.50 lens is a miniscleral contact lens manufactured by Paragon with the Paragon HDS 100 (Paflufocon D) material that have a Dk of 100 Fatt units, forward wetting and backward wetting angles of 42º and 70º, respectively, specific gravity of 1.10, hardness (Shore D) of 79 and water content of <1%.[21] The lens has a diameter of 16.50 mm, thickness of 0.29 mm and is available in powers from -40 D to +30 D in 0.25-D steps, and in sagittal heights from 3900 to 5600 μm.[16] For a customized optimal adjustment, the lens has 4 differentiated zones that can be modified: central clearance zone (CCZ), peripheral corneal clearance zone (PCCZ), limbal clearance zone (LCZ) and scleral landing zone (SLZ).[16] This ScCL has been designed to be fitted mainly in irregular corneas.[6,16,22-25] The fitting was performed following the manufacturer guidelines: selection of the initial diagnostic lens according to the fitting table, insertion of the CL, evaluation of CCZ, assessment of central clearance, slit lamp examination of the ScCL after 60 minutes of wearing and finally measurement of the over-refraction (ORx) to determine the final power of the CL.[16]

Statistical analysis

All data were analyzed by IBM-SPSS version 24.0 statistical software (SPSS Inc., Chicago, IL). Frequency distribution tables were used to describe the data. To summarize the information of the variables, average measures (mean and median) and dispersion measures (variance, standard deviation, SD, and range) were used. The normality of the data distributions was checked using the Kolmogorov-Smirnov test. When the variables followed a normal distribution, the Student t test was for paired samples was used to compare the data between consecutive visits. In the case of non-normalized distributions, the Wilcoxon rank test was used to compare parameters between consecutive visits. Likewise, the correlation between different

clinical variables was analyzed, using the Pearson or Spearman correlation coefficients depending on whether the analyzed data distributions followed normality or not.

Finally, a multiple linear regression analysis was carried out to check whether the achieved change in visual acuity could be estimated based on different pre-fitting clinical variables. This analysis was performed using the backward step technique. Once the predictive formula was obtained, it was verified whether it met the necessary conditions for its use: homoscedasticity (normal distribution of non-standardized residuals), absence of multicollinearity (tolerance and inflation variance factor), absence of outliers (Cook's distance) and absence of correlation between errors (Durbin-Watson test).

Results

A total of 30 eyes form 18 patients (12 men and 6 women) with KC were included. A total of 17 (56.7%) right eyes and 13 (43.3%) left eyes were considered for the analysis. The age of patients ranged from 14 to 65 years old, with a mean value of 34.5 years (SD: 6.7 years). Of the 30 eyes studied, 15 (50%) had KC without previous treatment, 10 (33.3%) had been treated previously with CXL, 5 (16.7%) had been previously treated with implantation of intracorneal ring segments. The initial sphero-cylindrical refraction and CDVA data are shown in Table 1.

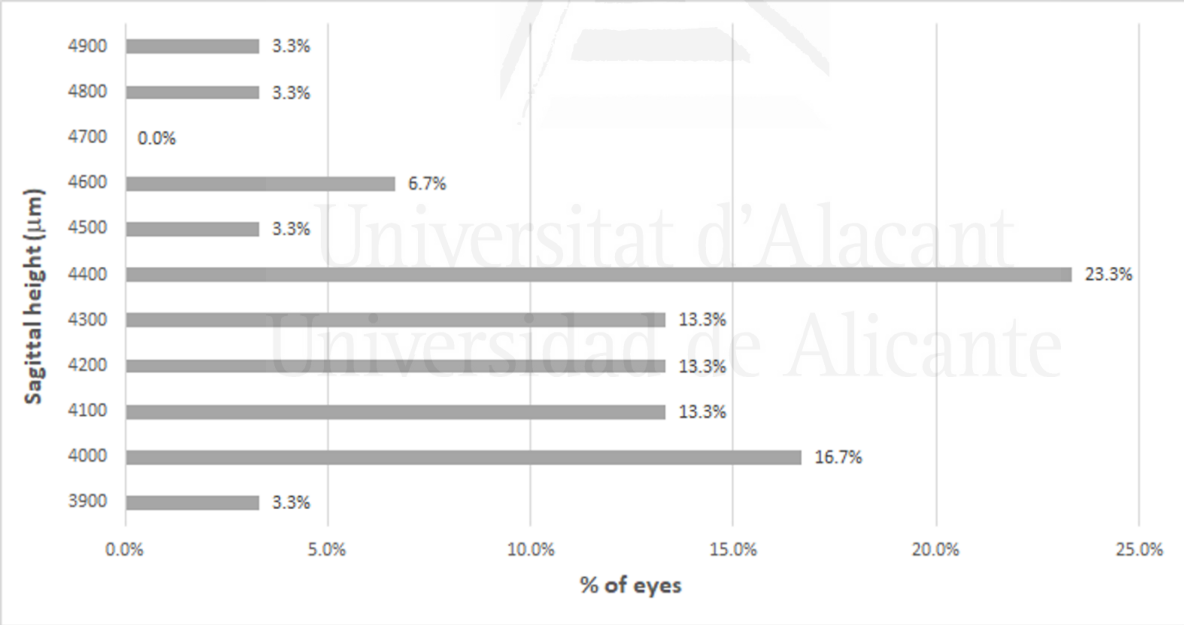
Table 1. Pre-fitting visual and refractive data

Variable	Mean (SD)	Median (Range)
Sphere (D)	-2.64 (1.42)	-1.37 (-12.00 to 3.00)
Cylinder (D)	-3.01 (0.65)	-3.00 (-6.50 to 0.00)
CDVA (logMar)	0.23 (0.07)	0.22 (0.00 to 0.70)

Abbreviations: CDVA, corrected distance visual acuity; logMAR, logarithm of minimal angle of resolution

The mean power of the fitted lenses was -3.04 D (SD: 1.78; median: -2.38; range: -15.50 to 4.25 D). The ScCL used were mostly spherical and only 5 (16.66%) eyes required peripheral toricity. Regarding the design of the lenses, the sagittal height used ranged from 3,900 to 4,900 µm. The distribution of the sagittal heights used in the study is shown in Figure 2. Adjustments of SLZ were needed in a total of 12 eyes (40.0%).

Figure 2.- Distribution of the sagittal heights of the scleral lenses fitted in the study.



Visual acuity changes

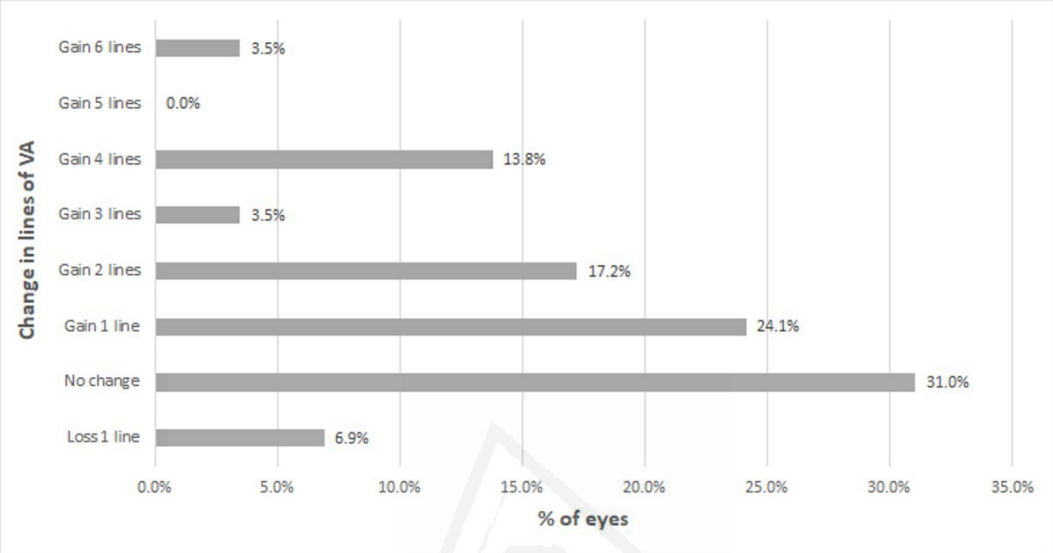
The VA increased significantly from a mean pre-fitting value of 0.23 logMAR (SD: 0.07) to a mean value of 0.10 logMAR (SD: 0.04) after 1 month of CL wear (p<0.001) (Table 2). The mean VA difference was -0.13 logMAR (SD: 0.07) after 1 month of CL wear and the median was -0.10 logMAR, indicating a mean increase in VA with the CL of around one line. However, the increase in VA ranged from -0.60 to 0.10, and patients could gain in some cases 6 lines of VA (Figure 3). An improvement of 1 or more lines of VA (logMAR) occurred in 62.1% of the eyes, whereas only one case showed a lost 1 of line of VA. Between the first and third month of CL wear, no significant changes were detected in visual and refractive outcomes (p≥0.180) (Table 2).

Table 2. Visual acuity and over-refraction data with the final scleral contact lens fitted during the follow-up

Variable	***1 month follow-up***			***3 months follow-up***		
	Mean (SD)	*Median (Range)*	*P-value*	*Mean (SD)*	*Median (Range)*	*P-value*
SLVA	0.10 (0.04)	0.10 (-0.08 to 0.30)	<0.001	0.10 (0.06)	0.10 (-0.08 to 0.40)	0.219
Sphere ORx (D)	0.22 (0.16)	0.00 (-0.50 to 1.50)	<0.001	0.18 (0.21)	0.00 (-0.50 to 1.00)	0.357
Cylinder ORx (D)	-0.05 (0.08)	0.00 (-1.00 to 0.00)	<0.001	-0.14 (0.20)	0.00 (-1.25 to 0.00)	0.180
SLVA with ORx (logMar)	0.09 (0.04)	0.10 (-0.08 to 0.30)	---	0.07 (0.05)	0.04 (-0.08 to 0.30)	0.753

Abbreviations: SLVA, scleral lens corrected distance visual acuity; ORx: Over-refraction; logMAR, logarithm of minimal angle of resolution; SD, standard deviation; D, diopters.

Figure 3.- Distribution of the VA changes achieved with the scleral lenses fitted in the study after 1 month of CL use.



Post-lens meniscus characterization

Measurement of the post-lens meniscus by OCT showed a statistically significant decrease in central, nasal, and temporal vault after 1 month of CL wear ($p \leq 0.046$) (Table 3). Mean decrease in central vault after one month of CL wear was -84.09 µm (SD: 82.45). However, between the first and third month of CL wear, there was a tendency of these vault measures to increase, but without statistical significance ($p \geq 0.131$) (Table 3).

Table 3.- Measurements of the central, nasal and temporal vault of the scleral contact lens over the cornea in the initial fitting and after 1 and 3 months of contact lens wear.

Variable	*First trial*		*1 month follow-up*				*3 months follow up*			
	Mean (SD)	*Median (Range)*	*Mean (SD)*	*Median (Range)*	*Change compared to first trial*	*P-value*	*Mean (SD)*	*Median (Range)*	*Change compared to first trial*	*P-value*
Central vault (µm)	294.46 (33.13)	267.00 (167 to 543)	200.09 (36.85)	207.00 (111.0 to 307)	-84.09 (82.45)	0.046	228.0 (60.04)	207.50 (122 to 361)	+19.55 (30.22)	0.174
Nasal vault (µm)	278.50 (51.00)	276.50 (176 to 441)	194.45 (27.32)	198.0 (126 to 240)	-80.64 (63.89)	0.018	227.50 (42.47)	228.0 (137 to 328)	+26.22 (35.98)	0.131
Temporal vault (µm)	344.42 (58.28)	306.50 (267 to 587)	257.36 (48.32)	245.0 (150.0; 394.0)	-80.36 (87.21)	0.021	269.70 (67.34)	249.5 (143 to 417)	+3.89 (38.05)	0.820

Abbreviations: SD, standard deviation

As shown in Table 3, the vault values showed a variation along the horizontal axis, with lower values for the nasal area and higher for the temporal area in all visits. The difference between nasal and temporal vault was statistically significant in the first trial and after 1 month of CL wear, with mean values of 65.92 µm (SD: 43.35; median: 84.50; range: 58 to 152 µm) (p=0.01) and 62.91 µm (SD: 42.60; median: 55.50; range: 24 to 167 µm) (p=0.008), respectively. After 3 months of CL wear, this difference between nasal and temporal vaults decreased, not reaching statistical significance (Mean: 42.40; SD: 47.30; median: 40.00; range: 55 to 172 µm) (p=0.074).

Corneal tomographic and aberrometric changes

No statistically significant changes were detected in the tomographic data evaluated (p≥0.276) (Table 4). There was a tendency for asphericity towards more negative values after 3 months of CL wear, but it did not reach statistical significance (p≥0.635). Concerning aberrations, there was a trend of HOAs towards higher values after 3 months of CL wear, but it did not reach statistically significance either (p≥0.110) (Table 5).

Table 4.- Tomographic data before-fitting and after 3 months of contact lens wear.

Variable	*Pre-fitting*		*After 3 months of CL wear*		
	Mean (SD)	*Median (Range)*	*Mean (SD)*	*Median (Range)*	*P-value*
Km_{ant} (D)	48.91 (1.64)	48.80 (42.03 to 63.24)	50.28 (5.08)	48.87 (42.86 to 64.47)	0.594
Ast_{ant} (D)	4.60 (0.98)	4.11 (1.12 to 12.55)	6.55 (3.44)	5.20 (0.87 to 13.69)	0.513
Q_{ant}	-0.93 (0.22)	-0.92 (-2.28 to 0.61)	-1.23 (0.54)	-1.06 (-2.56 to 0.43)	0.813
Km_{post} (D)	-7.54 (0.39)	-7.54 (-11.32 to -6.17)	-7.83 (1.17)	-7.89 (-11.32 to -6.22)	0.575
Ast_{post} (D)	0.93 (0.17)	1.03 (0.09 to 1.66)	1.07 (0.37)	1.14 (0.40 to 1.90)	0.735
Q_{post}	-1.15 (0.25)	-0.98 (-3.18 to -0.44)	-1.41 (0.61)	-1.21 (-3.04 to -0.49)	0.635
MCT(µm)	442.79 (24.98)	455 (313 to 554)	421.89 (48.52)	432 (322 to 551)	0.276
CCT (µm)	485.38 (26.05)	484.0 (340 to 558)	457.55 (42.27)	481 (342 to 556)	0.343

Abbreviations: SD, standard deviation; D, diopters; Q_{ant}, asphericity of the anterior corneal surface; Q_{post}, asphericity of the posterior corneal surface; Km_{ant}, anterior mean keratometry; Km_{post}, posterior mean keratometry; Ast_{ant}, anterior astigmatism; Ast_{post}, posterior astigmatism; MCT: minimal corneal thickness; CCT, central corneal thickness

Table 5.- Corneal aberrometric data before- fitting and after 3 months of contact lens wear.

Variable	*Pre-fitting*		*After 3 months of CL wear*		
	Mean (SD)	*Median (Range)*	*Mean (SD)*	*Median (Range)*	*P-value*
Anterior corneal surface					
HOA RMS (µm)	3.02 (0.56)	3.28 (0.55 to 7.28)	4.14 (2.65)	2.38 (1.06 to 10.77)	0.380
Coma RMS (µm)	2.47 (0.53)	2.66 (0.11 to 5.58)	2.94 (1.68)	2.08 (0.50 to 5.82)	0.653
SA (µm)	-0.21 (0.23)	-0.17 (-2.01 to 1.41)	-0.30 (0.82)	-0.06 (-2.99 to 0.51)	0.110
Residual RMS (µm)	1.50 (0.30)	1.32 (0.53 to 4.22)	2.51 (2.22)	1.10 (0.67 to 9.70)	0.779
Posterior corneal surface					
HOA RMS (µm)	0.76 (0.16)	0.7 (0.13; 1.99)	0.89 (0.43)	0.84 (0.21; 1.73)	0.765
Coma RMS (µm)	0.60 (0.13)	0.59 (0.06; 1.54)	0.68 (0.33)	0.70 (0.14; 1.25)	0.806
SA (µm)	0.08 (0.08)	0.04 (-0.46; 0.63)	0.01 (0.22)	-0.06 (-0.21; 0.77)	0.634
Residual RMS (µm)	0.38 (0.10)	0.33 (0.11; 1.31)	0.48 (0.29)	0.36 (0.11; 1.21)	0.399

Abbreviations: SD, standard deviation; RMS, root mean square; HOA, high order aberrations; SA, spherical aberration.

Ocular aberrometric changes

A significant reduction of ocular HOA RMS (p=0.028) and primary coma RMS (p=0.018) was found with the scleral contact lens. Specifically, mean HOA RMS changed from a pre-fitting value of 1.84 μm (SD: 1.40; median: 1.24; range: 0.36 to 5.04 μm) to a mean value with the CL of 0.73 μm (SD: 0.25; median: 0.72; range: 0.08 to 1.81 μm), whereas mean primary coma RMS changed from a pre-fitting value of 1.57 μm (SD: 1.33; median: 0.99; range: 0.23 to 4.81 μm) to a mean value with the CL of 0.45 μm (SD: 0.15; median: 0.49; range: 0.03 to 0.82 μm). Median HOA RMS was reduced by 41.93% and median primary coma RMS was reduced by 50.50%. There was a significant correlation between the change in VA with the CL and the change in primary coma RMS (r=0.775, p=0.041).

Correlation of visual changes with pre-fitting variables

Statistically significant correlations of the change in VA achieved with the CL and a great variety of pre-fitting variables were found: CDVA (r=-0.774, p<0.001), ASTa (r=-0.449, p=0.016), KMp (r=0.417, p=0.027), ASTp (r=-0.477, p=0.010), MCT (r=0.473, p=0.011), anterior corneal surface HOA (r=-0.545, p=0.003), primary coma (r=-0.425, p=0.024) and residual RMS (r=-0.550, p=0.002), posterior corneal surface HOA (r=-0.470, p=0.012), primary coma (r=-0.460, p=0.014) and residual RMS (r=-0.497, p=0.007), and the power of the CL (r=0.427, p=0.021).

Multiple linear regression analysis

A statistically significant linear relationship of the visual change in VA (L'lVA) with CL with different pre-fitting variables was obtained according to the following expression (p<0.001, R^2 = 0.878, adjusted R^2: 0.862, Durbin-Watson: 1.856):

L'lVA (LogMAR)= -1.104 - 0.766 x CDVA (LogMAR) + 0.018 x CLP + 0.000281 x SHCL

where CDVA is the pre-fitting spectacle corrected distance visual acuity, CLP is the contact lens power of the scleral lens and SHCL is the sagittal lens of the scleral lens.

The normality of the unstandardized residuals distribution (p=0.187) and the absence of influential points or outliers (mean Cook's distance=0.036 ± 0.057) confirmed the homoscedasticity of this model. Likewise, no multicollinearity was detected in the model (variance inflation factor between 1.277 and 2.650).

Discussion

In this study, changes occurring with the fitting of a specific model of ScCL during a period of 3 months in corneas with KC have been investigated. A statistically significant improvement in VA has been observed in our sample of KC eyes, which is consistent with the results of previous clinical studies.[6,16,22,26-26] This good efficacy in terms of visual rehabilitation with the SCL was consistent with the efficacy in terms of optical correction, with mean ORx close to 0.00 D during the entire follow-up. Suarez et al[6] evaluated the efficacy and safety of the same ScCL used in the current study, reporting a mean SLVA of 0.16 ± 0.25 logMAR and an improvement in VA of 2 or more lines in 56% of the eyes. This finding is consistent with those obtained in the current series in which mean SLVA was 0.10 ± 0.04 and 44.76% of the eyes reached an improvement in VA of 2 or more lines. This percentage was lower than that reported in the study by Suarez et al.[6] This can be explained by the fact that these authors started from a worse mean baseline VA (0.44 ± 0.45), which is, according to our analysis, an advantageous situation for VA improvement. It should be remembered that a negative correlation between VA change and pre-fitting CDVA was found, which implies that subjects with worse pre-fitting CDVA experienced more improvement in VA with the ScCL evaluated. Regarding VA changes

between 1 and 3 months of CL wear, they were small in magnitude and not statistically significant, suggesting a stability of the VA during this period. This stability should be also confirmed in the long term.

The characterization of the post-lens meniscus by OCT showed that the central, nasal, and temporal vaults decreased significantly after 1 month of ScCL wear. This is the result of the progressive indentation of the periphery of ScCL onto the conjunctival tissue.[30] Vincent et al[31] found that the central vault of the ICD16.50 ScCL significantly decreased an average of 76 ± 8 μm after 8 hours of use. Furthermore, they observed that 50% of the reduction occurred in the first 45 minutes, 75% in 2 hours and after 4 hours of use the decrease was not statistically significant.[31] Likewise, these authors found a statistically significant but not clinically relevant change associated in ORx.[31] Similarly, a reduction of the vault have been reported with other ScCL designs. Bray et al. showed a decrease in the vault of 83 ± 22 μm after 6-8 hours of CL use, with statistically significant changes in ORx associated.[32] Rathi et al[33] observed a decrease in the central vault in 90% of their sample after 4 hours of use of a ScCL, ranging from an initial value of 680 ± 421 μm to 589 ± 355 μm SD: 355). Courey and Michaud[34] showed a decrease in the central vault of 70 ± 9.8 μm after 6 hours of use of a specific model of ScCL. Otchere et al[35] evaluated the decrease in the central vault of 3 different types of ScCLs, obtaining a mean value of 34 ± 48 μm after 1 hour of use. Furthermore, these authors observed that the vault loss depended on the initial magnitude of the vault. These mean decreases reported in previous studies were close to those obtained in our sample after 1 month of CL wear. Furthermore, as in previous studies indicating that most of changes in ScCL vault occurred in the initial period of CL wear, no significant changes were found in our sample in the characterization of horizontal post-lens meniscus between the first and third month of CL wear.

A significant difference between the nasal and temporal vault was found in our sample during the initial post-fitting period which could be due to a temporal decentration of the ScCL, a greater indentation in the nasal area or a decentered CL position as a consequence of the asymmetry of the corneal surface in KC.[36] Courey and Michaud[34] showed a smaller vault on the

nasal side than on the temporal that was attributed by the authors to the toric nature of the sclera.[46] Concerning the difference in nasal-temporal vault in our study over time, it was not statistically significant after 3 months of CL use, which could indicate that the ScCL stabilizes over time. This may be related to some level of conjunctival molding with the use of the ScCL over time, as has been demonstrated using Fourier-domain profilometry to characterize the corneo-scleral profile.[30]

Concerning the evaluation of corneal tomographic changes, they did not reach statistical significance. This contrasts with other studies reporting significant changes in corneal shape and thickness in the short term.[23,24] Serramito et al[24] demonstrated that there was a statistically significant corneal thinning in the inferior region of KC eyes fitted also with the ICD16.50 ScCL and in the superior region of KC eyes implanted with intracorneal ring segments. A trend to a decrease in MCT and CCT was observed in our series, but both did not reach statistical significance. Vincent et al[37] reported a small and statistically significant amount of edema after 8 hours of use of the ICD16.50 ScCL in healthy adults. Specifically, a mean increase of 10.23 ± 5.77 μm in corneal thickness was observed which corresponded to 2% edema.[37] In another similar study, these same authors investigated the variation of edema over time, observing that the corneal thickness swelled after 15 minutes of CL use, stabilizing 45 minutes after CL insertion, reaching its maximum point after 90 minutes with a 1.18 ± 0.20% of edema, and existing a gradual thinning after 2 hours of use.[38] Possibly, in our sample, changes in corneal thickness associated to the initial use of the lens had been already stabilized when they were evaluated after 1 and 3 months of CL use. Similarly, minimal and no significant changes in anterior and posterior corneal shape and aberrations were found, confirming a stability of the cornea with the use of the ScCL during the first three months. Serramito et al[23,24] only found significant changes in anterior and posterior spherical aberrations after 8 hours of ScCL use, although more HOAs changed significantly when intracorneal ring segments had been implanted. In any case, a high variability was observed in corneal tomographic changes in the sample evaluated in the current study, confirming that the impact of the ScCL on the cornea may vary between KC individuals.

The improvement in VA observed in our sample was associated to a significant change in ocular HOAs. Specifically, a significant decrease was observed with the CL in HOA and primary coma RMS, confirming the ability of this type of CL to neutralize the aberrations that are present in KC eyes and to improve the ocular optical quality. Indeed, a string significant correlation was found between the decrease in comatic aberration and the improvement in VA. Thus, a large part of the improved VA is produced by the masking of aberrations by the tear meniscus formed between the lens and the cornea. Montalt et al[27] also showed a decrease in ocular coma and HOAs with the use of a ScCL, with a 55% decrease of total HOAs. These authors commented that despite this reduction, the aberration values with the ScCL in KC were still higher than in normal corneas, suggesting that despite masking the irregularities of the corneal surface, aberrations on the posterior surface of the cornea and internal aberrations are not compensated.[27] Alipour et al[18] observed a statistically significant reduction in coma and trefoil aberrations with the use of ScCL in eyes with KC implanted with intracorneal ring segments.[30]

Concerning the correlations of pre-fitting variables with the VA change achieved with ScCL evaluated, they were statistically significant for spectacle CDVA, anterior and posterior corneal astigmatism, posterior keratometry, MCT, anterior and posterior HOAs and the power of the CL. This confirms that a great variety of variables can be used to predict with different levels of accuracy the VA change that can be achieved with the ScCL evaluated. The strongest correlation was found between the VA change and the pre-fitting CDVA value and it was negative. This means that patients with the worst initial VA were those who presented the greatest visual improvement with the fitting of the ScCL. Considering that those eyes with worse VA are normally KC eyes with more aberrated corneas, it is normal that more VA would be expected as more ocular optical quality can be induced.[16] Indeed, the rest of significant correlations detected revealed that more VA improvement could be achieved in those eyes with more significant signs associated to moderate to severe stages of KC, such as higher levels of anterior and posterior corneal astigmatism, higher amounts of HOAs, greater curvature of the posterior corneal surface and lower MCT.[39,40]

Finally, a multiple linear regression equation was obtained to predict the final VA through a series of initial data. This equation proposes the prediction of the VA change with the ScCL evaluated from 3 variables that can be obtaining in the pre-fitting and first trial visits. These variables were pre-fitting spectacle CDVA, lens power, and lens sagittal height. Therefore, more VA improvement can be expected when fitting this ScCL in those eyes with worse pre-fitting VA and fitted with scleral lenses with lower sagittal heights and optical power. According to this, the ideal candidate for optimizing the visual quality with this type of scleral contact lens would be an advanced KC eye requiring a moderate to high myopic correction using a moderate to low sagittal height of the lens. Possibly, the combination of the aberrometric profile of a negative powered ScCL with a low sagittal height potentially associated to a low central vault (lower optical contribution of the post-lens meniscus as it would be thinner) may be associated to a potentially better optical quality and consequently may explain the contribution of these two factors to the predicting equation. This should be investigated in future investigations analyzing the optical profile of these ScCLs as well as the optical impact of the post-lens meniscus. It should be considered that it was verified that this prediction model fulfilled the requirements to ensure its validity and it was shown that the equation predicted with very good results the VA of the patients in the sample, with only 10.3% of cases in which the error would be greater than 0.1 logMAR.

Our study had several limitations that must be mentioned and acknowledged. First, the retrospective design might be considered as a limitation of the study. Second, the sample size could be considered another limitation of the study. Especially for the development of predicting models. For this reason, this model represents a prototype that must be validated and optimized with a larger sample.

In conclusion, the ICD 16.50 ScCL provides an efficacious visual rehabilitation in KC due to the improvement of VA and the correction of the low and high order ocular aberrations. The visual result achievable with this ScCL is predictable from a linear equation relating pre-fitting spectacle CDVA, and power and sagittal height of the ScCL fitted

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40. Piñero DP, Alió JL, Alesón A, et al. Corneal volume, pachymetry, and correlation of anterior and posterior corneal shape in subclinical and different stages of clinical keratoconus. J Cataract Refract Surg 2010; 36: 814-25.

SECCIÓN 4: DISCUSIÓN DE LOS RESULTADOS

En este apartado se realiza la discusión de los cuatro artículos, incluyendo el que se encuentra en proceso de revisión. Los cuatro artículos que componen la actual tesis doctoral componen una investigación sobre la efectividad de las diferentes técnicas de CXL, basándonos en la evidencia disponible actualmente, e igualmente una investigación sobre el manejo del QC. De esta manera, se han analizado 3 puntos clave en el tratamiento del QC: 1) Efectividad de los ACI de F, con la optimización de un nomograma para la implantación de los ACI, 2) Efectividad de las técnicas de CXL epi-on y epi-off en el QC progresivo y la descripción de un modelo de predicción del efecto del CXL, tanto en la técnica epi-on como epi-off y, 3) Efectividad de las LCE y la definición de un modelo para predecir el efecto del ajuste de las LCE.

4.1. Discusión de la publicación científica: "Comparison of Different Methods of Corneal Collagen Crosslinking: A Systematic Review"

La primera publicación científica de la que se compone esta tesis doctoral trata de una revisión sistemática crítica, mediante el empleo de una herramienta para analizar la calidad científica de los ECA incluidos en esta revisión. Además, se ha llevado a cabo una descripción de las diferentes técnicas de CXL valorando la efectividad de las mismas.

La metodología, resultados, conclusiones, limitaciones y sesgos de cada uno de los ECA incluidos se han evaluado mediante la herramienta, "Programa de Habilidades de Evaluación Crítica Español" (por sus siglas en inglés, CASPe).[134] Se trata de un instrumento de lectura crítica que permite el análisis mediante preguntas sobre la validez interna del estudio y sus resultados, y si estos son extrapolables a la población.[134] En la revisión sistemática de la actual tesis doctoral, se ha empleado el cuestionario CASPe para la evaluación de ensayos clínicos (EC), el cual consta de 11 ítems, para poder entender un EC.[134] A la hora de valorar un EC, tenemos que considerar tres grandes epígrafes: ¿Son válidos los resultados del ensayo?, ¿Cuáles son los resultados? y ¿Pueden ayudarnos estos resultados? Las 11 preguntas están diseñadas para ayudar a centrarse en esos epígrafes de modo sistemático.[134] Las primeras 3 preguntas son de eliminación, de manera que si la respuesta a las tres es "sí", entonces vale la pena continuar con las preguntas restantes.[134] Esas tres preguntas de eliminación son las siguientes:[134] ¿Se orienta el ensayo a una pregunta claramente definida?, ¿Fue aleatoria la asignación de los pacientes a los tratamientos?, ¿Fueron adecuadamente considerados hasta el final del estudio todos los pacientes que entraron en él? Las 8 preguntas restantes son las siguientes:[134] ¿Se mantuvo el cegamiento?, ¿Fueron

similares los grupos al comienzo del ensayo?, al margen de la intervención en estudio, ¿los grupos fueron tratados de igual modo?, ¿Es muy grande el efecto del tratamiento?, ¿Cuál es la precisión de este efecto?, ¿Puede aplicarse estos resultados en tu entorno o población local?, ¿Se tuvieron en cuenta todos los resultados de importancia clínica? y por último, ¿Los beneficios a obtener justifican los riesgos y los costes? Un resultado de 7/11 se consideró en nuestra revisión sistemática, como un valor de calidad mínimo aceptable para cualquier estudio evaluado con la herramienta CASPe,[134] y si el valor fuera menor de 7/11, se adopta una actitud crítica hacia el estudio. En la revisión sistemática que compone esta tesis doctoral, los 14 artículos incluidos han superado la barrera de los 7 puntos sobre 11, lo que permite catalogarlos de buena calidad científica.

En nuestra revisión sistemática, se han incluido 14 estudios, de los cuales 2 compararon la RB-hipotónica (H) vs (versus) RB-dextrano (D) y en estos 2 trabajos, se ha utilizado la técnica de CXL-S, 5 estudios compararon CXL-S vs CXL-Acelerado (A), 2 compararon CXL-TE vs CXL-S, 1 estudio comparó CXL-S vs CXL-I, 1 estudio comparó diferentes técnicas de CXL-A, 1 estudio comparó PiXL vs CXL pulsado uniforme y, 1 estudio comparó CXL-S, CXL-A y CXL-TE.

Rosenblat y cols., han demostrado que el empleo de RB-H en córneas sometidas a CXL reducía en un 30% el adelgazamiento corneal, pero sin afectar a la eficacia, funcionalidad o cambios del recuento de células endoteliales.[81] En otro trabajo, se ha demostrado que el empleo de la RB-H supone un menor adelgazamiento corneal que la RB-D.[76] Hagem y cols. han demostrado un mayor aplanamiento topográfico tras CXL-A con RB-hidroxipropil-metilcelulosa (HPMC) respecto a la RB-D, probablemente causado por la mayor facilidad de difusión de ciertas moléculas en la córnea e igualmente podría ser la responsable de una línea de demarcación (LDD) más profunda,

por consiguiente, un tratamiento más eficiente que la RB-D.[77] Mesen y cols. observaron que a pesar de que la LDD fue más profunda con CXL-A y CXL-S respecto a CXL-TE, no observaron correlación entre la LDD y los cambios topográficos inducidos.[79]

En dos estudios se ha demostrado que CXL-S es más efectivo para detener la progresión del QC que CXL-TE, aunque esta última técnica se caracteriza por la comodidad para los pacientes que se someten a la misma.[72,82]

Hashemi y cols.,[78] Sadoughi y cols.[83] y Sherif y cols.[84] han demostrado un efecto similar sobre la progresión del QC empleando tanto CXL-S como CXL-A, pero Choi y cols.[75] observaron un mayor efecto de aplanamiento con CXL-S respecto al CXL-A. En este último trabajo, se ha observado que el menor efecto de CXL-A probablemente sea debido, al mayor uso de oxígeno (O_2) respecto a la cantidad restaurada por difusión, con el consiguiente agotamiento del O_2 y secundariamente impediría el efecto del CXL.[75] Además, en otro trabajo, se ha demostrado que aumentar la radiación UV-A total administrada a la córnea durante la técnica de CXL, no significa que aumente la eficacia de la técnica.[85]

En un estudio comparativo de CXL-S vs CXL-I, se ha demostrado que CXL-I, a pesar de ser eficaz para detener la progresión del QC, es menos efectivo que CXL-S, con menor reducción de la paquimetría y Kmax.[74]

Tras la revisión sistemática de esta tesis doctoral, se ha observado que son necesarios más estudios con tamaños muestrales y períodos de seguimiento mayores para comparar las complicaciones de las técnicas de CXL-TE y CXL-S, e igualmente son necesarios más estudios para poder determinar la forma más efectiva de administrar la RB a la córnea durante la radiación UV-A. Además, sería muy interesante establecer

unos factores comunes de estudio a la hora de realizar los trabajos, para que no sean tan variables a la hora de definir los parámetros para demostrar la efectividad de las técnicas.

En resumen, CXL-S continúa siendo el tratamiento de elección para el QC progresivo, siendo más eficaz que CXL-TE para detener la progresión de la enfermedad. Sin embargo, sería conveniente analizar de forma comparativa las complicaciones entre las técnicas de CXL para confirmar si CXL-TE presenta beneficios respecto a CXL-S.

4.2. Discusión de la publicación científica: "Evaluation of a new nomogram for Ferrara ring segment implantation in keratoconus"

Actualmente existe evidencia suficiente que ha demostrado la capacidad de los ACI para reducir el nivel de AAO e irregularidades corneales, lo que conduce a una mejora de la calidad visual.[135] Sin embargo, existe una gran variabilidad y discrepancias entre los estudios, siendo los principales factores responsables que la mayoría de los trabajos no son controlados, sin disponer de ensayos clínicos comparativos aleatorizados y la gran variabilidad en el nomograma o criterios de implantación, basados en datos empíricos o experiencias personales.[135] Al inicio la de la implantación de los ACI, los nomogramas eran empíricos, utilizando la refracción y la queratometría como factores más importantes para la selección del ACI a implantar en cada caso y con el tiempo se optimizaron significativamente en base al patrón topográfico.[101,102-104] Estas optimizaciones fueron la base para el desarrollo de un nomograma altamente optimizado en el que, además de otros factores, tuvo gran importancia el patrón topográfico para la selección del ACI a implantar.[135] De esta manera, el nuevo nomograma, desarrollado en el segundo artículo de la actual tesis doctoral, pretende ofrecer niveles más altos de previsibilidad y superar las experiencias anteriores.[135]

El segundo artículo de esta tesis doctoral consistió en evaluar los resultados de la implantación de los ACI en QC, mediante el empleo de un nomograma optimizado, teniendo en cuenta el nivel de astigmatismo corneal anterior, coma primario, asfericidad corneal y el nivel de desalineación entre los ejes topográfico y comático, para seleccionar el grosor del ACI y la LA a implantar.[135] Este estudio se ha llevado a cabo en 2 centros diferentes, con 2 métodos diferentes de creación del túnel para la inserción de los ACI, con el objetivo de evaluar todos los factores potenciales que pudieran influir

en el resultado, que se pudiera alcanzar con el nuevo nomograma optimizado descrito en este artículo.[135]

En este segundo estudio, cabe destacar que se ha observado que un 33,7% de los casos han ganado 2 líneas de AVLC, siendo un resultado mejor que los informados por otros autores previos, con el uso de otros nomogramas de implantación. Alfonso y cols.[108] han observado una mejora de más de 2 líneas de la AVLC en el 26,83% de los casos con una versión previa del nomograma, y Fernández Vega y cols.[105] han observado una mejora de más de 2 líneas de la AVLC en el 25,7% de los pacientes con QC. Además, en este segundo estudio, un 88,4% de los ojos han mejorado o han mantenido la AVLC tras la cirugía y el 53,5% de los ojos mejoraron la AVLC a los 3 meses del posoperatorio, con la peculiaridad de que en este trabajo se han incluido casos de todo tipo de patrones topográficos. En otro estudio, con otro nomograma, se ha demostrado una mejora del 64% de los ojos en la AVLC en pacientes con QC de moderado a severo.[136] En otro trabajo, se ha demostrado que el 84,5% de los ojos con QC habían mantenido o mejorado la AVLC a los 5 años tras la cirugía.[105]

Fernández Vega y cols.[105] incluyeron pacientes con QC con el punto más delgado en el mapa de paquimetría corneal ubicado a una distancia de > 0,8 mm y < 1,6 mm del centro de la pupila, un espesor en el ápex corneal (EAC) de > 400 μm y diferencias entre el eje del cilindro refractivo, meridiano corneal más plano y mapa de aberraciones comáticas inferior a 30º. Se implantaron ACI de F tipo AFR6 en todos los ojos estudiados.[105] El protocolo utilizado para la implantación de los ACI se basó en el nomograma desarrollado por Mediphacos Inc. (Keraring CalculationGuidelines2009;http://smmedical.cl/wpcontent/uploads/2013/10/Agrupado.pdf).[105] El eje de implantación del ACI coincidía con el eje topográfico plano y el grosor del ACI era dependiente de la paquimetría intraoperatoria en la zona de implantación de

6 mm, y los ACI fueron implantados mediante láser de femtosegundo.[105] Los autores no consideraron la progresión del QC como criterio de inclusión en el estudio, por lo tanto, no se sabe si el QC se encontraba en progresión en el momento de la cirugía.[105]

En el segundo artículo de esta tesis, se han incluido pacientes mayores de 18 años de edad, con QC según los criterios estándar (patrón topográfico asimétrico y al menos uno de los siguientes signos clínicos en la LH: adelgazamiento del estroma, protrusión cónica de la córnea en el ápex, anillo de Fleischer, estrías de Vogt o cicatriz del estroma anterior)[137] y diagnóstico de QC de leve a moderado según el sistema de Amsler-Krumeich (grados I a III).[138] En este trabajo se ha desarrollado un nuevo nomograma optimizado para la implantación de los ACI, donde la asfericidad corneal anterior, la magnitud del astigmatismo corneal anterior y el nivel de discrepancia entre las orientaciones de astigmatismo y coma, justificarían el numero de segmentos de ACI a implantar.[135] Específicamente cada caso se ha clasificado según 16 patrones corneales o fenotipos diferentes (ver figura 12), y en función de cada uno de ellos, se recomienda la implantación de un segmento de ACI específico o combinación de segmentos de ACI.[135] La creación del túnel, ya sea de forma mecánica o mediante láser de femtosegundo, se ha llevado a cabo en el meridiano más curvo según el mapa topográfico, para la posterior inserción de los ACI de F.[135] El ACI más implantado fue el de 250 μm de espesor y 150º de LA, seguido del ACI de 250 μm de espesor y 210º de LA; los ACI AFR se implantaron en 33 ojos, mientras que los ACI AFR6 se implantaron en 55 ojos.[135]

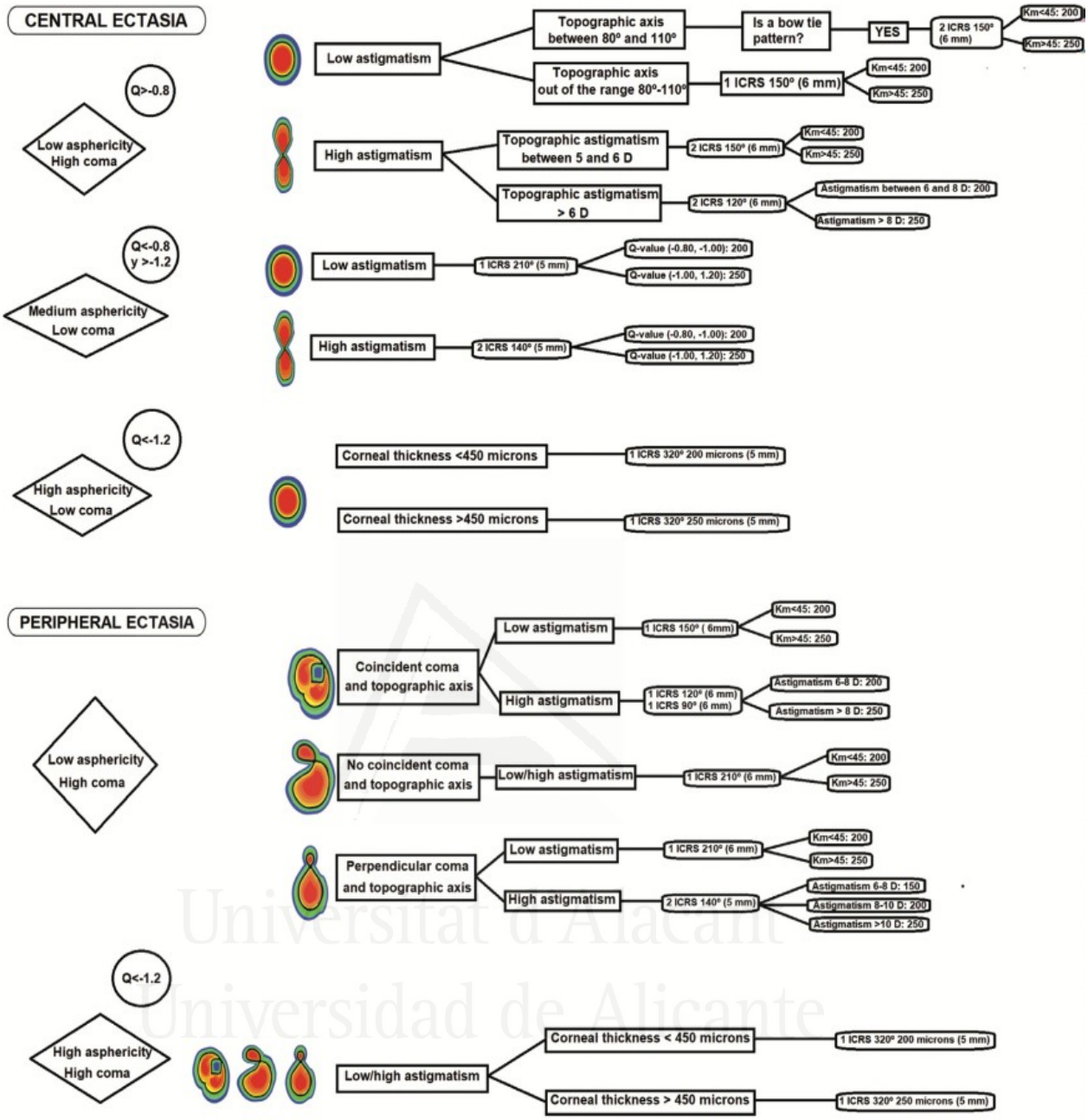

Figura 12. Nomograma personalizado desarrollado para los ACI de F. Muestra como se clasifica cada caso para la selección del ACI más adecuado a implantar. Primero, se considera la asfericidad corneal y el nivel de coma primario en la superficie anterior de la córnea (columna izquierda). Segundo, se evalúa la posición relativa de los ejes de coma y astigmatismo corneal (columna central). Finalmente, se considera la magnitud del astigmatismo (columna derecha). De esta forma, se definen en total 16 fenotipos o

patrones topográficos corneales diferentes. Extraída de la referencia bibliográfica número 135.

Con el nuevo nomograma optimizado descrito en el segundo artículo de la actual tesis doctoral, se ha observado un cambio significativo en la magnitud del cilindro manifiesto y el EE tras la implantación del ACI de F, y son los principales factores responsables de la mejora en la AVLC tras la implantación de los ACI.[135] Se ha demostrado una reducción del EE superior al 50% en el 41,5% de los ojos, desde un valor medio preoperatorio de -3,24 ± 3,51 dioptrías (D), a un valor medio postoperatorio de -2,12 ± 3,11 D, a los 3 meses tras la implantación de los ACI.[135] Hamdi y cols. demostraron una reducción en el EE desde un valor medio de -3,60 ± 3,10 D, a un valor medio de -2,52 ± 3,10 D, sin ser estadísticamente significativo.[136]

La implantación de ACI siguiendo este nomograma optimizado genera una corrección miópica por la reducción en la curvatura central de la superficie corneal anterior observada en los meridianos más curvo y plano, con una reducción adicional de la magnitud del astigmatismo corneal anterior y la Kmax.[135] Además, los ACI generan cambios importantes en la curvatura corneal central posterior, confirmando que los ACI de F inducen un modelado de la estructura corneal global.[135] Asimismo, los ACI generan un cambio significativo en la asfericidad de la superficie cornal anterior de la córnea, pasando a un valor menos prolato.[135]

La aberración del coma primario es la aberración de alto orden que más degrada la calidad visual en el QC. El nomograma optimizado ha generado un cambio en el coma primario total de forma significativa, desde un valor preoperatorio medio de 3,66 ± 3,04 μm, a un valor postoperatorio de 2,33 ± 2,26 μm, para una pupila de 6 mm.[135]

La implantación de ACI de F con un nuevo nomograma optimizado ha demostrado un aumento paquímetrico alrededor de 10 μm, probablemente secundario a una redistribución del tejido corneal.[65] En este estudio, no se observaron diferencias significativas estadísticamente en las aberraciones corneales, aplanamiento corneal o complicaciones, implantando los ACI de forma mecánica o mediante láser de femtosegundo.[135]

En resumen, este nuevo nomograma considera los siguientes parámetros para la implantación de los ACI: asfericidad corneal anterior, astigmatismo corneal, coma primario y la desalineación entre los ejes topográficos y comáticos. La ventaja fundamental de este nomograma es la mejora de la calidad visual, por el mayor control de las AAO.

4.3. Discusión de la publicación científica: "Preliminary Characterization of Predictive Factors of the Visual Change after Epi-On and Epi-Off Corneal Collagen Crosslinking Techniques"

El tercer artículo de la actual tesis doctoral describe los factores predictivos de la técnica de CXL, tanto epi-on como epi-off y establece modelos de predicción del efecto final del CXL.

Se han definido múltiples factores predictivos, tales como la AV preoperatoria, la excentricidad del cono y la Kmax previo al tratamiento con CXL, pero los pocos estudios que los describen presentan una gran variabilidad entre ellos y no describen modelos de predicción.[98,139,140]

En el tercer artículo se han investigado los factores predictivos del cambio visual inducido tras CXL epi-on y CXL epi-off acelerados. En el grupo epi-on, el cambio medio en la AVLC se ha correlacionado con la asfericidad corneal anterior, espesor corneal mínimo (ECM) y el EAC preoperatorios. Por tanto, era de esperar una mayor mejora en la AVLC en pacientes con córneas menos prolatas y mas gruesas. Sin embargo, en el grupo epi-off, el cambio en la AVLC se ha correlacionado con el ECC, EAC, índice de varianza superficial (IVS), índice de asimetría vertical (IAV), RMS (error cuadrático medio) total anterior y RMS de las ABO (aberraciones de bajo orden) anterior preoperatorios. De manera que era de esperar una mayor mejoría en córneas más delgadas, con más aberraciones anteriores y valores más altos de IVS e IAV. Esto significa que los factores predictivos del cambio visual fueron totalmente diferentes entre las dos técnicas, por lo tanto, los mecanismos de acción parecen ser distintos.

En este estudio, para facilitar la tarea al clínico, intentamos llegar más lejos estimando el cambio visual esperado después de las dos técnicas, mediante una expresión lineal con la validación previa de los modelos de predicción obtenidos (ver figuras 13 y 14). Mediante este análisis se pudo demostrar que el cambio visual inducido por la técnica epi-on se puede predecir a partir de una serie de variables: edad, J_{45} (vector de potencia del astigmatismo refractivo), asfericidad corneal anterior y el valor del RMS de las AAO posteriores. Sin embargo, en el grupo epi-off, la ecuación de predicción fue diferente, a partir de otras variables: ECM y coma vertical de la superficie corneal anterior. De igual forma, esto sugiere que el mecanismo de acción de las dos técnicas es totalmente diferente. No debemos pasar por alto que en este trabajo de investigación, a pesar de encontrar una correlación muy débil entre la edad y el cambio visual en los dos grupos de estudio, en el grupo epi-on la edad es un factor crítico de la ecuación de predicción del cambio visual.

$$\Delta CDVA = 0.063 - 0.006 \times Age - 0.075 \times J_{45} - 0.203 \times Q\text{-}val - 0.140 \times HOA_{post}\ RMS$$

Figura 13.- Ecuación lineal del cambio de agudeza visual tras CXL en el grupo epi-on. Abreviaciones: DCDVA, cambios a los 3 meses de la AVLC; Age, edad del paciente; J_{45}, vector del poder astigmático refractivo; Q-val, asfericidad corneal anterior; HOA_{post} RMS, RMS de la AAO posterior. Extraída de la referencia bibliográfica 148.

$$\Delta CDVA = -1.551 + 0.003 \times MCT + 0.171 \times Z_3^{-1}$$

Figura 14.- Ecuación lineal del cambio de agudeza visual tras CXL en el grupo epi-off. Abreviaciones: MCT, espesor corneal mínimo; Z_3^{-1}, término de Zernicke correspondiente al coma primario vertical anterior. Extraída de la referencia bibliográfica 148.

En este artículo además de estudiar los factores predictivos, se ha demostrado que los resultados visuales y refractivos, no difirieron de forma significativa, de manera que las dos técnicas fueron comparables en lo que respecta a los cambios visuales, refractivos y en la capacidad de detener la progresión del QC durante 1 año de seguimiento. En este estudio, partimos de peores condiciones basales en el grupo epi-on, pacientes con QC más avanzados, por lo tanto, córneas más delgadas, que se han sometido a CXL epi-on, con el objetivo de proteger el endotelio corneal de la penetración excesiva de RB y la radiación UV-A. De esta manera, esperábamos mejores resultados al final del seguimiento en el grupo epi-off por tener pacientes con QC menos avanzado, pero los resultados fueron comparables entre ambas técnicas de CXL.

En resumen, tras CXL epi-on se presenta una mejoría de la AV más significativa a los 3 meses, en pacientes más jóvenes, con niveles preoperatorios más altos de RMS de las AAO posterior, córneas menos prolatas y componente refractivo J_{45} más positivo. Sin embargo, una mejoría visual más significativa se espera a los 3 meses tras CXL epi-off en pacientes con córneas más delgadas y niveles altos de coma primario en la superficie corneal anterior.

4.4. Discusión del estudio en revisión: "Characterization and prediction of the clinical results with a specific model of mini-scleral contact lenses in corneas with keratoconus"

Las LCE pueden lograr una rehabilitación visual buena, pero esta mejora de la AV puede variar de forma importante entre individuos por varios factores, como es el "vault" de la LCE adaptada.[111,120,132] El cuarto artículo de la actual tesis doctoral, que actualmente se encuentra en revisión, trata de definir los factores predictivos para facilitar el ajuste de un modelo concreto de LCE (ICD 16.50 de la casa Paragon) y predecir el efecto de mejora de la AV. Esta LCE es una LC mini-escleral, disponible en potencias de -40 D a +30 D en pasos de 0,25 D y en alturas sagitales de 3900 a 5600 µm.[141] En este cuarto trabajo, la potencia media de las lentes ajustadas fue de -3,40 D, esféricos en su mayoría, y solo 5 ojos necesitaron toricidad periférica.

Se han incluido pacientes con QC en cualquier grado de progresión, independientemente de si fueron sometidos previamente a CXL o ACI, pero se excluyeron a los pacientes sometidos previamente a trasplante corneal.

En este artículo se ha observado una mejora significativa de la AV a los 3 meses tras el ajuste de la LCE y una correlación negativa entre el cambio de la AV y la AVLC antes de la adaptación, lo que implica que los pacientes con peor AVLC pre-ajuste experimentaron más mejoría en la AV con la LCE.

En este cuarto artículo, se ha demostrado una diferencia significativa entre el "vault" nasal y temporal en la post-adaptación inmediata de la LCE, probablemente debido a un descentramiento temporal de la LCE, mayor indentación en el área nasal o

una posición de la LC descentrada por la asimetría de la superficie corneo-escleral en el QC. Sin embargo, a los 3 meses, la diferencia en el "vault" nasal-temporal, no fue significativa, probablemente debido a la estabilización de la LCE con el tiempo, como consecuencia de un moldeado conjuntival con el uso de la LCE a lo largo del tiempo, y que se ha demostrado previamente usando perfilometría de dominio de Fourier.[142]

En la muestra de este estudio, de la misma manera que en otros estudios,[131,143] se ha observado una mejora de la calidad visual, por una disminución significativa de las AAO y coma primario, demostrando una correlación significativa entre la aberración comática y la mejora de la AV. De esta manera, un parte importante de la mejora de la AV se produce por el enmascaramiento de las aberraciones, por el menisco lagrimal entre la LCE y la córnea.

Además, en este artículo, se ha demostrado que las variables pre-ajuste que se han correlacionado con el cambio de la AV tras el ajuste de la LCE ICD 16.50 y que, por lo tanto, se podrían utilizar para predecir el cambio de la AV una vez ajustada la LCE son las siguientes: AVLC en gafas, astigmatismo corneal anterior y posterior, queratometría posterior, ECM, AAO anterior y posterior y el poder de la LC.

Las probables limitaciones de nuestro estudio son el diseño retrospectivo y el tamaño muestral.

Se ha demostrado una potente correlación negativa entre el cambio de la AV tras el ajuste de la LCE y el valor de la AVLC previo a la adaptación de la LCE, de manera que los pacientes con peor AV inicial fueron los que más mejoría visual presentaron con el ajuste de la LCE. De igual manera, se ha obtenido una ecuación lineal (ver figura 15) para predecir el cambio de AV a partir de 3 variables (AVLC en gafas, potencia y altura

sagital de la lente); así pues, se esperaría una mayor mejora de la AV al colocar una LCE en ojos con QC, con peor AV pre-adaptación y con LCE ICD 16.50 que tenga una altura sagital y potencia óptica más baja.

$$\Delta VA\ (LogMAR) = -1.104 - 0.766 \times CDVA\ (LogMAR) + 0.018 \times CLP + 0.000281 \times SHCL$$

Figura 15.- Ecuación lineal del cambio de AV tras el ajuste de la LCE. Abreviaciones: CDVA, agudeza visual a distancia corregida; LogMAR, logaritmo del ángulo mínimo de resolución; CLP, potencia de la LCE; SHCL, altura sagital de la LCE. Referencia: cuarto artículo de la actual tesis doctoral, en revisión actualmente.

En definitiva, el paciente ideal para el implante de la LCE ICD 16.50 sería un ojo con QC avanzado, que requiera una corrección miópica moderada a alta, utilizando una altura sagital de la LCE moderada a baja

SECCIÓN 5. CONCLUSIONES Y LÍNEAS FUTURAS DE INVESTIGACIÓN

5.1. CONCLUSIONES

Los trabajos realizados en esta tesis doctoral han brindado conclusiones de gran importancia en el manejo del tratamiento del QC y específicamente en el campo del CXL, ACI y LCE. Los cuatro estudios de esta tesis son esenciales para obtener resultados, aclarar controversias y dudas respecto al manejo de los pacientes con QC progresivo. Estos artículos ofrecen información de gran utilidad para la práctica clínica diaria de los profesionales y aportan información necesaria a los pacientes, para determinar con más exactitud, las posibilidades de manejo de las córneas con QC.

Conforme a los resultados obtenidos en la tesis y teniendo en cuenta los objetivos planteados al comienzo de la tesis, se establecen las siguientes conclusiones:

1. La calidad científica de todos los ECA comparativos de distintas técnicas de CXL es buena (analizada a través de la herramienta CASPe) y el CXL-S es la técnica "gold standard", siendo más eficaz que CXL-TE en el QC progresivo.
2. La implantación de ACI de F basada en un nuevo nomograma optimizado, considerando el nivel de asfericidad corneal anterior, astigmatismo, aberración del coma primario y la desalineación entre los ejes topográfico y del coma, es seguro y eficaz para promover una rehabilitación visual en el QC progresivo, con un control importante del coma primario.
3. Los cambios en la AVLC tras CXL epi-on se asocian significativamente con 3 variables: EAC, ECC y asfericidad corneal anterior. Sin embargo, con la técnica epi-off, los cambios se asocian con las siguientes variables: EAC, ECC, IVS, IAV, RMS de las ABO anterior y el RMS total anterior. Además, el efecto del CXL sobre el cambio de la AV es predecible mediante una ecuación lineal. En el grupo epi-on, dicha ecuación, depende de la magnitud preoperatoria del RMS

posterior (para las AAO), edad, curvatura corneal anterior y el componente refractivo J_{45}; mientras que en el grupo epi-off, depende del grosor corneal y el nivel de coma primario presente en la superficie anterior de la cornea.

4. Los cambios en la AVLC tras la adaptación de la LCE ICD 16.50, a pesar de que se han relacionado significativamente con varias variables, tales como el astigmatismo corneal anterior y posterior, queratometría posterior, AAO anterior y posterior, poder de la lente de contacto y el ECM, se hallan fuertemente correlacionados con el valor de la AVLC previo a la adaptación. Además, se ha podido comprobar que se puede predecir el cambio de la AV con la LCE evaluada, mediante una ecuación lineal en base a tres variables, AVLC en gafas pre-adaptación, potencia y altura sagital de la LCE.

5.2. LÍNEAS FUTURAS DE INVESTIGACIÓN

Los diferentes trabajos realizados en esta tesis doctoral han permitido alcanzar los objetivos que se presentaron al comienzo de este proyecto. La investigación ha demostrado un gran avance en la optimización del tratamiento del QC, facilitando la labor a los profesionales encargados del manejo de esta patología. La existencia de modelos de predicción del efecto de CXL, tanto epi-on como epi-off y del efecto de las LCE ICD 16.50 y el desarrollo de un nomograma optimizado para la implantación de ACI, ha supuesto un gran logro en la actualidad para el manejo del QC.

Los modelos de predicción y nomogramas de estos trabajos han sido desarrollados siguiendo una metodología detallada, pero son necesarios estudios con otras muestras de pacientes que permitan validar e incluso refinar estos modelos de predicción, si fuera necesario.

Las investigaciones futuras podrían estar focalizadas en el empleo de suplementos durante la técnica de CXL y valorar la eficacia y seguridad de dichos suplementos. Además, sería muy interesante que las líneas futuras de investigación se centren en los factores que se correlacionan con la mejor AV lograda con determinados modelos de LCE y definir modelos para predecir esta mejora con los datos de ajuste previo. Finalmente, considero oportuno focalizar los trabajos futuros, en la adaptación de LCE guiadas por frente de onda personalizadas para eliminar las AAO y lograr una calidad visual satisfactoria.

La eficacia y seguridad del CXL-S esta ampliamente respaldado por pruebas sólidas.[144] Sin embargo, el principal problema de este protocolo sería la larga duración del tratamiento.[144] De esta manera, se han recomendado los protocolos acelerados, que según la Ley de Bunson-Roscoe establece que cambios en la duración y la intensidad no alteran el efecto fotoquímico de la luz UV-A, a menos que la cantidad total de energía se mantenga constante.[144] Sin embargo, existe incertidumbre de la técnica acelerada, probablemente por el papel del O_2 durante la técnica de CXL, ya que el O_2 se consume rápidamente y es posible que el agotamiento del O_2 impida la formación de ERO, dificultando las reacciones fotoquímicas efectivas.[144] El O_2 ambiental se agota rápidamente en segundos, aumentando a niveles normales después de 3 minutos y por este motivo se propuso el CXL pulsado, para de esta forma permitir la re-oxigenación de los tejidos.[145] Richoz y cols. demostraron que en las córneas porcinas sometidas a CXL a una intensidad de 9 mW/cm^2 en condiciones de baja concentración de O_2, el efecto final era similar al de una córnea que no se sometía a CXL.[83] Más tarde, Hill y cols. demostraron en córneas porcinas ex vivo que el suplemento con O_2, suponía un aumento de 5 veces los niveles de O_2 estromales, aumentando significativamente el efecto del CXL-A.[146]

El ozono (O_3) es una molécula de tri-oxígeno inestable que al descomponerse en O_2 da lugar a radicales libres de O_2, que son agentes oxidantes muy reactivos y potentes. De esta manera, el O_3 sólo o junto con la RB y la luz UV-A tiene el potencial de aumentar el efecto de entrecruzamiento.[145]

En varios estudios se ha demostrado que en las técnicas epi-on, la penetración de la RB en el estroma es insuficiente, pero la absorción de la luz UV-A del epitelio y la membrana basal, y las características antioxidantes del epitelio, pueden proporcionar

una contribución adicional, ya que el CXL es un procedimiento básicamente oxidativo.[147] Los antioxidantes más importantes en el ojo contra las ERO son el glutatión y el ácido ascórbico (vitamina C).[147] El glutatión se encuentra fundamentalmente en el cristalino y el ácido ascórbico en el epitelio corneal.[147] El ácido ascórbico ni se sintetiza ni se almacena en el cuerpo humano, así pues la ingesta dietética es esencial.[147]

Faramarzi y cols. han demostrado que el O_2 sistémico suplementario administrado durante la técnica de CXL-A, mejora la eficacia del procedimiento respecto al CXL-A sin suplemento de O_2 y también respecto al CXL-S.[144] Los autores de este trabajo administraron el O_2 a una concentración de 5 litros/minuto (min), a través de unas gafas nasales durante 10 min, a los pacientes sometidos a CXL-A.[144]

Dogan y cols. han demostrado en córneas de ovejas cadavéricas que el uso de O_3 durante el CXL-A, supone un aumento de los niveles de O_2 y mejor reorganización (más regulares y paralelas) de las fibras de colágeno, de las córneas sometidas a CXL.[145]

Koc y cols. han demostrado en córneas de conejos que la suplementación con ácido ascórbico sistémico, antes de la aplicación de CXL-TE, no parece disminuir la eficacia del CXL-TE, por lo tanto, no existe razón para detener o reducir la suplementación con vitamina C entes de la terapia con CXL-TE.[147]

Sin embargo, se requieren datos a largo plazo para tener más información sobre la estabilidad y seguridad de la técnica suplementada con O_2, investigar la seguridad y eficacia de la aplicación de O_3 durante la técnica de CXL e igualmente verificar los resultados del efecto de ácido ascórbico en el CXL en el ámbito clínico.

Son muchos los estudios que han demostrado que se puede lograr una rehabilitación visual óptima con las LCE, pero la mejora de la AV con las LCE puede variar significativamente entre pacientes, y esto se debe fundamentalmente a que son múltiples los factores que influyen en la mejora de la AV y probablemente dependa en gran medida de la LCE empleada.[115,132,143] De esta manera, resulta importante llevar a cabo estudios con LCE específicas para determinar las variables que influyen significativamente en la mejora de la AV con la LCE en cuestión y, de igual forma, establecer modelos de predicción, para así facilitar a los profesionales el trabajo en la práctica clínica diaria.

Como bien sabemos, la zona óptica de las LCE presenta la corrección refractiva de dichas lentes y se pueden personalizar de forma similar a las LCR.[149] La zona óptica puede tener forma de elipse para optimizar el ajuste o estar desplazada del centro geométrico de la lente para mejorar la alineación de la óptica con la pupila.[150,151] Además, aunque las LCE neutralizan una proporción significativa de las anomalías ópticas de la córnea anterior, los pacientes pueden presentar una visión subóptima debido a las aberraciones que surgen de la superficie corneal posterior o del cristalino.[152,153] De esta manera, se puede utilizar una superficie frontal tórica para corregir el astigmatismo interno o incorporar un diseño asférico de superficie frontal para minimizar la aberración esférica.[154,155] Sin embargo, para eliminar las AAO, como el coma que es común en el QC, se requiere un diseño de superficie frontal guiado por frente de onda personalizado.[156] Este enfoque no ha tenido éxito en gran medida en las LC blandas y las LCR por el movimiento y la rotación de las lentes.[156] Sin embargo, las LCE, gracias a la zona de apoyo escleral, son una plataforma ideal que aseguran la alineación de la corrección con la pupila y un movimiento o rotación mínimos.[156] De esta manera, los diseños iniciales de las LCE personalizadas han supuesto una reducción

significativa en las AAO y una mejora en los resultados visuales, con correcciones de la superficie frontal personalizada, en comparación con las LCE convencionales.[157,158] Sin embargo, los datos de mejora de la AV son inferiores en los estudios a la AV óptima esperada para los datos de la población de la misma edad.[159] Además, hay estudios que sugieren que la AV con LCE guiadas por frente de onda puede mejorar tras un período de adaptación más largo,[159] de manera que serían necesarios estudios a largo plazo que nos informen de los resultados de seguridad y eficacia de las LCE personalizadas a largo plazo.

Es probable que comiencen a surgir nuevas técnicas de CXL suplementado, y cada vez sean más los trabajos que nos informen de los factores de predicción de la AV, así como los modelos de predicción de la mejora de AV con un tipo concreto de LCE. Además, probablemente tengamos más información acerca de la adaptación de las LCE personalizadas. Todo este arsenal terapéutico se convertirá gradualmente en una parte clave del tratamiento del QC, logrando un manejo adecuado de las expectativas de estos pacientes.

SECCIÓN 6. CONTRIBUCIÓN A CONGRESOS NACIONALES E INTERNACIONALES

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1. **Autores:** CR de Lossada, RR Anil, CA Linero, FA Aliste, MC Jiménez, M Contreras, SM Hamida Abdelkader, MR Calvo de Mora

   Título: Evaluación de la gravedad tomográfica del queratocono pediátrico al primer diagnóstico según rangos de edad

   Congreso: LII Congreso Nacional de la Sociedad Andaluza de Oftalmología, Málaga, los días 23,24 y 25 de enero de 2020.

2. **Autores:** SM Hamida Abdelkader

   Título: Crosslinking: Riboflavinas, Protocolos y Técnicas

   Congreso: Contact Lenses of the Americas Specialists Symposium (CLASS) 2020. Presentación (on-line) el día 7 de diciembre de 2020. Enlace de la presentación: https://www.youtube.com/watch?v=HD9766MIRWU&t=39s

3. **Autores:** SM Hamida Abdelkader

   Título: Protocolos de Dresden vs Protocolos Actuales

   a. **Congreso:** Keratoconus Forum (on-line). 2 de agosto de 2020. Enlace de la presentación: https://www.youtube.com/watch?v=3SbqFNduUvI&t=2519s

4. **Autores:** SM Hamida Abdelkader, J Fernández, MR Vallejo, AS García, DP Piñero

Título: Comparison between different methods of corneal collagen crosslinking: a systematic review

a. **Congreso:** 39th Congress of the European Society of Cataract & Refractive Surgeons (ESCRS). Amsterdam, los días 8-11 de octubre de 2021.

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ANEXOS

ANEXO 1. INFORMES DE APROBACIÓN DEL COMITÉ ÉTICO

ANEXO 1.1. INFORME DEL COMITÉ ÉTICO DEL

ARTÍCULO 2: Fernández J, Martínez CP, Rueda AP, Hamida Abdelkader SM, Revert MJR and Piñero DP. Evaluation of a new nomogram for Ferrara ring segment implantation in keratoconus. Int J Ophthalmol 2021; 14(9): 1371-1383. DOI: 10.18240/ijo.2021.09.12. PMCID: PMC8403859

Servicio Andaluz de Salud
CONSEJERÍA DE SALUD

CARMEN FERNÁNDEZ SÁNCHEZ, Presidenta del Comité de Ética de la Investigación de Almería

CERTIFICA

Que este Comité actuando como **referencia** ha evaluado en reunión celebrada el día 20 de diciembre de 2017, el Estudio Clínico titulado: **"Evaluación de la eficacia de un nomograma personalizado frente al convencional para el implante de los segmentos de anillos de Ferrara en pacientes con Queratocono". Código de** protocolo **QC-CHT-2017 Código** interno **46/2017** y considera que:

Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio.

La capacidad del investigador y los medios disponibles son apropiados para llevar a cabo el estudio.

El protocolo presentado respeta los principios éticos de la Declaración de Helsinki de 2013 y otros Códigos Internacionales.

Y que se acepta que dicho Estudio Clínico sea realizado en la UGC de Oftalmología del Complejo Hospitalario Torrecárdenas, por el Dr. Joaquin Fernández Pérez, como investigador principal.

Lo que firmo en Almería, a cinco de marzo de dos mil dieciocho.

CONSEJERÍA DE SALUD
Servicio Andaluz de Salud
JUNTA DE ANDALUCIA
COMITÉ ÉTICA
INVESTIGACIÓN
CENTRO ALMERÍA
COMPLEJO HOSPITALARIO TORRECÁRDENAS

Fdo.: Carmen Fernández Sánchez

NOTA: El suplemento a la póliza de responsabilidad civil Nº 0630000121, es correcto. Por otro lado le informamos que la vigencia de la PÓLIZA, tal y como consta en el suplemento es desde el 20/02/2018 hasta el 30 /06/2018 por tanto la inclusión de pacientes debe ser posterior al 20/02/2018.

ANEXO 1.2. INFORME DEL COMITÉ ÉTICO

DEL ARTÍCULO 3: Hamida Abdelkader SM, Férnandez J, Sebastián J, Piñero DP. Preliminary Characterization of Predictive Factors of the Visual Change after Epi-On and Epi-Off Corneal Collagen Crosslinking Techniques. J Ophthalmol 2021; 9680253. DOI: 10.1155/2021/9680253; PMCID: PMC8670975.

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DICTAMEN DEL COMITÉ DE ÉTICA DE LA INVESTIGACIÓN PROVINCIAL DE ALMERÍA

Ref: EMC/apg

D. EMILIO MOLINA CUADRADO, Secretario Técnico del Comité de Ética de la Investigación Provincial de Almería. CEI/CEIm, acreditado y constituido conforme a los requisitos establecidos en la legislación vigente.

CERTIFICA

Que dicho Comité, en su reunión celebrada con fecha **31/03/2021**, con la asistencia de los miembros recogidos en el anexo, ha ponderado los aspectos metodológicos, éticos y legales del proyecto de investigación cuyos datos identificativos se refieren a continuación, el balance de riesgos y beneficios anticipados dimanantes del estudio, y evaluado la cualificación del investigador principal y la del equipo investigador, así como la factibilidad del proyecto, conforme a lo dispuesto en el artículo 12 de la Ley 14/2007, de 3 de julio, de Investigación Biomédica (B.O.E núm 159, de 4/7/2007) ha acordado la emisión de ***INFORME FAVORABLE,*** con las consideraciones que son expuestas y con los efectos derivados de los establecidos en el apartado e), del artículo 2, de la citada Ley, según consta todo recogido en el Acta de la reunión del Comité, número 3 ***de*** 31 ***de marzo de*** 2021

Título del estudio: **" Factores predictivos de la eficacia de cross-linking en córneas con queratocono"**

Código del Estudio: **FACCROSS-2021**

Código interno del estudio: **26/2021**

Versión y fecha de protocolo: **1.0 de fecha 09/03/2021**

Tipo de Estudio: **Tesis Doctoral**

Investigador Principal: **Sidi Mohamed Hamida Abdelkader**

Tutor Académico: **David Pablo Piñero Llorens**

Almería a 31 de marzo de 2021

Fdo: Emilio Molina Cuadrado
Secretario del CEI/CEIm

ANEXO 1.3. INFORME DEL COMITÉ ÉTICO DEL ARTÍCULO 4 (en revisión): Characterization and prediction of the clinical results with a specific model of mini-scleral contact lense in corneas with keratoconus

COMITÉ DE ÉTICA PARA LA INVESTIGACIÓN CON MEDICAMENTOS DEL DEPARTAMENTO DE SALUD DE ALICANTE - HOSPITAL GENERAL
C/. Pintor Baeza, 12 – 03010 Alicante
http://www.dep19.san.gva.es
Teléfono: 965-913-952
Correo electrónico: ceim_hgua@gva.es

Ref. CEIm: PI2020-048 - Ref. ISABIAL: 200045

INFORME DEL COMITE DE ETICA PARA LA INVESTIGACION CON MEDICAMENTOS

Reunidos los miembros del Comité de Ética para la Investigación con medicamentos del Departamento de Salud de Alicante – Hospital General, en su sesión del día 29 de Julio de 2020 (Acta 2020-8), y una vez estudiada la documentación presentada por **D. David Pablo Piñero** del Departamento de Optica, Farmacología y Anatomía de la Universidad de Alicante, tiene bien a informar que el proyecto de investigación titulado **"Efecto a nivel de la calidad óptica del incremento del vault en sujetos sanos",** se ajusta a las normas deontológicas establecidas para tales casos.

Y para que conste a los efectos oportunos, firmo la presente en Alicante con fecha 1 de Septiembre de 2020.

Fdo. Dr. Luis Manuel Hernández Blasco
Secretario Técnico CEIm Departamento de Salud de Alicante – Hospital General

ANEXO 2. CERTIFICADOS DE ASISTENCIA A CONGRESOS Y PRESENTACIONES EN CONGRESOS

ANEXO 2.1. Certificado asistencia congreso EUROPEAN SOCIETY OF CATARACT & REFRACTIVE SURGEONS

39th Congress of the ESCRS

AMSTERDAM

CERTIFICATE OF ATTENDANCE

This is to certify that

Sidi Mohamed HAMIDA ABDELKADER

attended the 39th Congress of the European Society of Cataract & Refractive Surgeons, held in Amsterdam, The Netherlands, and online, from 8 - 11 October 2021.

ESCRS 2021 has been accredited by the European Accreditation Council for Continuing Medical Education {EACCME®) for a maximum of **23 European CME credits (ECMEC®s)**.

Each medical specialist should claim only those credits that he/she actually spent in the educational activity.

The EACCME® is an institution of the European Union of Medical Specialists {UEMS), www.uems.eu.

Through an agreement between the European Union of Medical Specialists and the American Medical Association, physicians may convert EACCME® credits to an equivalent number of AMA PRA Category 1 Credits™. Information on the process to convert EACCME® credits to AMA credits can be found at www.ama-assn.org/education/earn-credit-participation-international-activities.

Live educational activities occurring outside of Canada, recognised by the UEMS-EACCME® for ECMEC® credits are deemed to be Accredited Group Learning Activities {Section 1) as defined by the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada.

Prof. Dr. Rudy MMA Nuijtss
President

ANEXO 3. PÓSTER EN CONGRESOS

ANEXO 3.1 Póster presentado en el congreso de la EUROPEAN SOCIETY OF CATARACT & REFRACTIVE SURGEONS

ANEXO 3.2 Póster presentado en el LII congreso de la SOCIEDAD ANDALUZA DE OFTALMOLOGÍA

P0165

LII CONGRESO Sociedad Andaluza de Oftalmología

23, 24 y 25 de Enero, 2020 Málaga

SAO

Evaluación de la gravedad tomográfica del queratocono pediátrico al primer diagnóstico según rangos de edad.

Autores: **Carlos Rocha de Lossada**; Rahul Rachwani; Carmen Alba Linero; Federico Alonso Aliste; Margarita Cabanás Jiménez; Miguel Contreras; Sidi Mohamed Hamida Abdelkader; Marina Rodríguez Calvo de Mora

INTRODUCCIÓN

El queratocono (QC) es normalmente una enfermedad corneal inflamatoria bilateral y asimétrica caracterizado por un adelgazamiento corneal progresivo que resulta en una protrusión central o paracentral originando una disminución progresiva de la agudeza visual como resultado de un aumento en el astigmatismo y en las aberraciones de alto orden. La edad de inicio suele estar entre la segunda y la tercera década de la vida y tiene una tendencia a progresar hasta los 35-40 años antes de estabilizarse. En los niños, es una enfermedad rara y hasta la fecha existen pocos estudios extensos de caracterización a estas edades en comparación con los adultos. En la población pediátrica (edad 0-17 años), se informa que la prevalencia es del 0.16% . La edad temprana parece estar asociada con formas más graves de QC y con una progresión más rápida del mismo, con una correlación inversa entre la edad y la gravedad. De hecho es actualmente una de las principales indicaciones de trasplante de córnea en edad juvenil.

Propósito

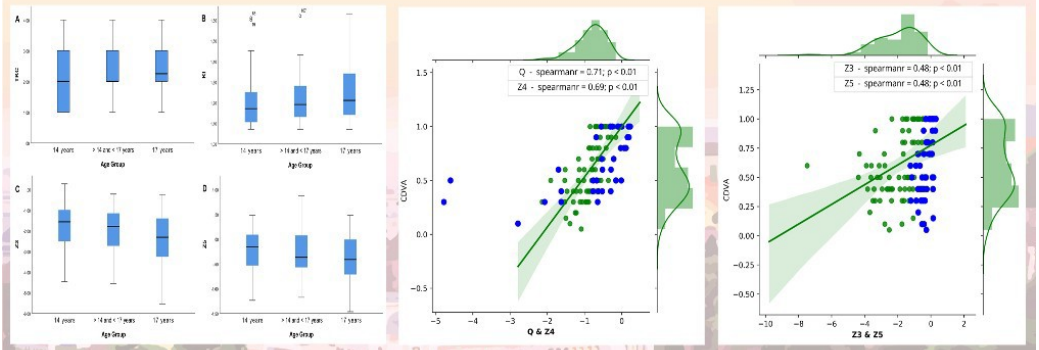
Caracterizar a los pacientes con QC pediátrico mediante el análisis de las características tomográficas con Pentacam en la muestra pediátrica más alta, según nuestro conocimiento, disponible en la literatura científica.

Métodos

Se trata de un estudio retrospectivo, transversal, multicéntrico (6 centros, 3 países diferentes). Se evaluaron 278 ojos de 139 pacientes con QC pediátrico. Entre los criterios de selección estaban; (1) 18 años o menos, (2) mapas tomográficos del primer diagnóstico de QC antes de los 18 años, (3) QC unilateral o bilateral. Para el diagnóstico y clasificación del QC, seleccionamos los parámetros del Pentacam: Índice de QC (KI ≥ 1.07) y Clasificación de QC topográfico (TKC ≥ 1). Los pacientes se dividieron en dos y tres grupos, según los rangos de edad. El análisis estadístico se realizó con estadísticas SPSS 25.0. Se realizó la prueba t student. El factor ANOVA se realizó en la comparación de tres grupos

Resultados:

230 ojos fueron diagnosticados de QC pediátrico. La edad media fue de 15.48 ± 2.33 (6 a 18) años. Nuestros resultados mostraron que había diferencias en términos de TKC (2.08 ± 0.89 y 2.35, P <0.05), KI (1.20 ± 0.12 y 1.25 ± 0.16, P <0.05), coma primario (-1.88 ± 1.39 y -2.40 ± 1.26, P <0.05) y coma secundario (-0.24 ± 0.40 y -0.37 ± 0.41, P <0.05) entre menores de 14 años y mayores de 17 años, respectivamente. Igualmente observamos una fuerte correlación positiva entre la MAVC y asfericidad (Sperman=0.71) y aberración esférica (Sperman=0.69), así como una correlación moderada entre la MAVC y aberración comática (Sperman= 0.48). Esto significa, que un queratocono pediátrico central tendría un peor pronóstico visual que uno paracentral/periférico.

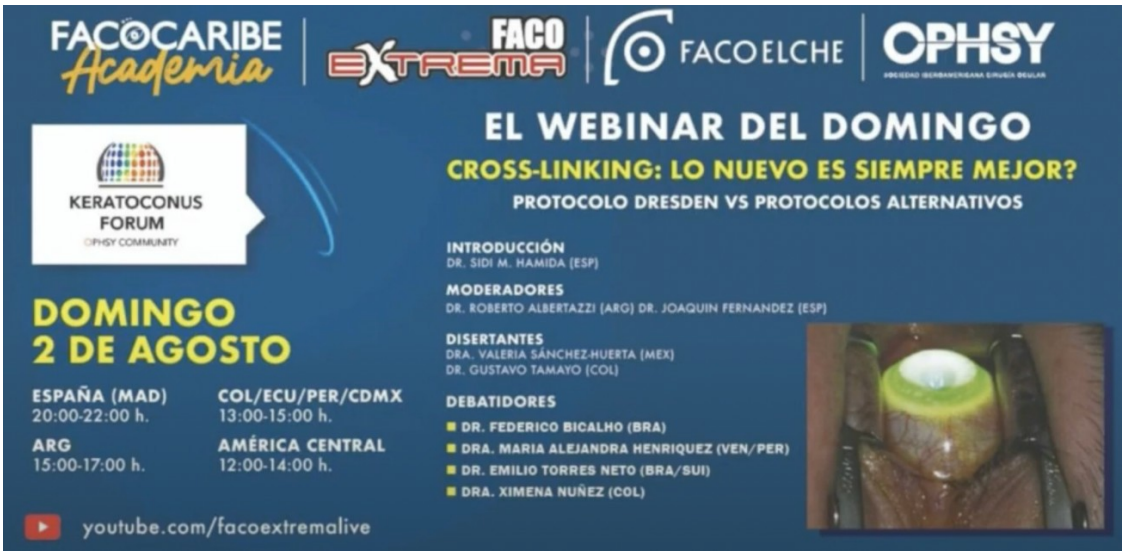


Conclusiones:

Nuestros hallazgos revelaron que el QC es agresivo en la población pediátrica y juvenil con un alto grado de gravedad al primer diagnóstico; por lo tanto, recomendamos que sean monitoreados de cerca y tratados de manera intensiva. Sugerimos que la tomografía corneal debería realizarse sistemáticamente en todos los niños con astigmatismo corneal de inicio reciente.

ANEXO 4. TÍTULOS DE LAS COMUNICACIONES ON-LINE EN CONGRESOS INTERNACIONALES

ANEXO 4.1. Comunicación on-line en el KERATOCONUS FORUM



ANEXO 4.2. COMUNICACIÓN ON-LINE EN CONTACT LENSES OF THE AMERICAS SPECIALISTS SYMPOSIUM (CLASS 2020)

ANEXO 5. CERTIFICADOS DE PREMIOS EN CONGRESOS

ANEXO 5.1. CERTIFICADO PRIMER PREMIO EN EL LII CONGRESO DE LA SOCIEDAD ANDALUZA DE OFTALMOLOGÍA

LII Congreso Sociedad Andaluza de Oftalmología
23, 24 y 25 de Enero, 2020
Málaga

SAO

Certificado de 1er Premio

Autores

Carlos Rocha de Lossada, Rahul Rachwani Anil , Carmen Alba Linero , Federico Alonso Aliste , Margarita Cabanás Jiménez , Miguel Contreras , Sidi Haida Adelkader y Marina Rodríguez Calvo de Mora

Han resultado los ganadores del Primer Premio con la comunicacion

EVALUACIÓN DE LA GRAVEDAD TOMOGRÁFICA DEL QUERATOCONO PEDIÁTRICO AL PRIMER DIAGNOSTICADO SEGÚN RANGOS DE EDAD

En el LII Congreso Nacional de la Sociedad Andaluza de Oftalmología, celebrado en el hotel Ilunion Málaga, los días 23, 24 y 25 de Enero de 2020

Dr. Ignacio Montero de Espinosa Escoriaza
Presidente Sociedad Andaluza de Oftalmología

Dr. Jesús Hernández-Barahona Palma
Vocal Coordinador Científico