ANÁLISIS MORFOGEOMÉTRICO DE LA ESTRUCTURA HEMIESFÉRICA DEL SEGMENTO ANTERIOR DEL OJO HUMANO Y SU APLICACIÓN CLÍNICA

Programa de Doctorado en Tecnologías Industriales

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Universidad Politécnica de Cartagena
Departamento de Estructuras, Construcción y
Expresión Gráfica

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Tesis Doctoral

2020

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**CONFORMIDAD DE SOLICITUD DE AUTORIZACIÓN DE DEPÓSITO DE
TESIS DOCTORAL POR EL/LA DIRECTOR/A DE LA TESIS**

D. Francisco Cavas Martínez y D. Jorge Luís Alió del Barrio, Director y Co-Director respectivamente de la Tesis doctoral *Análisis morfogeométrico de la estructura hemiesférica del segmento anterior del ojo humano y su aplicación clínica*.

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Que la referida Tesis Doctoral, ha sido realizada por D. José Sebastián Velázquez Blázquez, dentro del Programa de Doctorado en Tecnologías Industriales, dando nuestra conformidad para que sea presentada ante el Comité de Dirección de la Escuela Internacional de Doctorado para ser autorizado su depósito.

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D. Juan Suardíaz Muro, Presidente/a de la Comisión Académica del Programa de Doctorado en Tecnologías Industriales

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Que la Tesis Doctoral titulada, “*Análisis morfogeométrico de la estructura hemiesférica del segmento anterior del ojo humano y su aplicación clínica*”, ha sido realizada, dentro del mencionado Programa de Doctorado, por D. José Sebastián Velázquez Blázquez, bajo la dirección y supervisión de los Dres. Francisco Cavas Martínez y Jorge Luís Alió del Barrio.

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Autorizar la presentación de la Tesis Doctoral a D. José Sebastián Velázquez Blázquez en la modalidad de “compendio de publicaciones”.

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*A Ana, Quique y Noelia,
por su infinita paciencia
y su incondicional apoyo*

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1D:	Unidimensional
2D:	Bidimensional
3D:	Tridimensional
AIC:	Criterio de información de Akaike (Akaike Information Criteria)
AUC o AUROC:	Área bajo la curva ROC
BMU o UBM:	Biomicroscopía ultrasónica (Ultrasound Biomicroscopy)
CAD:	Diseño asistido por ordenador (Computer-Aided Design)
CCT:	Espesor corneal Central
CDVA:	Agudeza visual lejana corregida (Corrected Distance Visual Acuity)
CM:	Microscopía confocal (Confocal Microscopy)
D:	Dioptrías
CAGD o DGAO:	Diseño geométrico asistido por ordenador
DOI:	Identificador digital de objetos (Digital Object Identifier)
e:	Excentricidad
FDM:	Tecnología de deposición de material fundido
GUI:	Interfaz gráfica de usuario
HOA:	Aberraciones de alto orden (High Order Aberrations)
IC 95%:	Intervalo de confianza al 95%
IQR:	Rango intercuantílico
JCR:	Journal Citations Report
K:	Potencia corneal central
KC o KCN:	Queratocono

LASIK:	Queratomileusis in-situ asistida por láser (Laser-Assisted In-Situ Keratomileusis)
MCT:	Espesor corneal mínimo (Minimum Corneal Thickness)
μm:	Micras
mm:	Milímetros
MRI:	Resonancia magnética (Magnetic Resonance Imaging)
MTP:	Punto de mínimo espesor
NURBS:	Curvas B-spline racionales no uniformes
OCT:	Tomografía de coherencia óptica (Optical Coherence Tomography)
p:	Factor de forma
PET:	Tereftalato de polietileno (Polyethylene Terephthalate)
PIO:	Presión intraocular
PLA:	Ácido poliláctico (Polylactic Acid)
Q:	Asfericidad corneal
RMS:	Valor cuadrático medio (Root Mean Square)
ROC:	Curva característica receptor-operador
ROI:	Región de interés
SD:	Desviación estándar (Standard Deviation)
SJR:	Scimago Journal Rank
SLB:	Biomicroscopía con lámpara de hendidura (Slit-lamp Biomicroscopy)
SM:	Microscopía especular (Specular Microscopy)
UDVA:	Agudeza visual sin corregir (Uncorrected Distance Visual Acuity)
USP:	Paquimetría por ultrasonidos (Ultrasound Pachymetry)
VHF:	Biomicroscopía por ultrasonidos de alta frecuencia (Very High Frequency)

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Resumen

La superficie refractiva más importante del ojo humano es la córnea, que presenta una estructura de forma hemiesférica localizada en el segmento ocular anterior. Esta estructura, incluso en un escenario no patológico, no es perfecta, dado que presenta asimetrías que provocan deformaciones, desalineamientos y descentramientos entre ambos ojos del mismo individuo. Cuando además existen patologías corneales, como pueden ser las ectasias, esta asimetría, y por tanto sus efectos, se acentúan, provocando en el paciente un deterioro ciertamente importante de la capacidad visual, lo que da cuenta de la importancia de disponer de sistemas que permitan una caracterización corneal precisa que facilite la detección, diagnóstico y clasificación de las ectasias.

En esta tesis doctoral se ha propuesto un sistema integrado capaz de detectar (fase preclínica) y diagnosticar (fase clínica), de manera eficiente y desde un punto de vista óptico-geométrico, la progresión de la ectasia corneal, permitiendo de esta forma incidir de manera directa en el proceso de toma de decisiones relativas a la calidad visual de los pacientes.

Para ello, y partiendo de un modelo sólido personalizado en 3D generado con herramientas de Diseño Asistido por Ordenador, se han propuesto diversos parámetros morfogeométricos macroscópicos de tipo lineal, superficial, volumétrico y angular, con el objetivo de caracterizar la progresión de la ectasia corneal más importante, el denominado queratocono. La estructura microscópica también se ha estudiado, programando una aplicación que permite cuantificar el polimegatismo y el pleomorfismo de las células endoteliales corneales.

Posteriormente, se han revisado los distintos sistemas univariantes y multivariantes de diagnóstico y clasificación del queratocono, y se ha comprobado que los parámetros morfogeométricos permiten tanto la detección como la clasificación del queratocono en base a su grado de severidad de acuerdo con las escalas RETICS, Amsler-Krumeich y Alió-Shabayek.

Además, se han propuesto dos modelos predictivos (demográfico-óptico-geométricos) de clasificación del grado de la enfermedad en base a la escala RETICS, que han dado lugar al desarrollo de dos aplicaciones informáticas denominadas EMKLAS y KERATOSCORE, que a su vez dan cuenta de la dificultad inherente a la detección de esta enfermedad en la fase preclínica.

Por último, se ha aplicado un modelo sólido personalizado obtenido mediante impresión 3D a la educación del paciente, comprobándose que la percepción visual y táctil del modelo permite a los pacientes entender mucho mejor su enfermedad y el tratamiento indicado para ella, mejorando la percepción de calidad del servicio prestado en las clínicas oftalmológicas.

Abstract

The most important refractive surface of the human eye is the cornea, which has a hemispherical-shaped structure located in the anterior ocular segment. This structure, even in a non-pathological scenario, is not perfect, since it presents asymmetries that cause deformations, misalignments and decenterings between the two eyes of the same individual. When there are also corneal pathologies, such as ectasias, this asymmetry, and therefore its effects, are accentuated, causing in the patient a certainly significant deterioration of the visual capacity, something that shows the importance of having systems that allow precise corneal characterization to facilitate the detection, diagnosis and classification of ectasias.

In this doctoral thesis, an integrated system capable of efficiently detecting (preclinical phase) and diagnosing (clinical phase), from an optical-geometric point of view, the progression of corneal ectasia, has been proposed, thus allowing a direct impact on the decision-making process concerning the visual quality of patients.

To do so, and starting from a solid model customized in 3D generated with tools of Computer Assisted Design, several macroscopic morphogeometrical parameters of linear, superficial, volumetric and angular type have been proposed, with the aim of characterizing the progression of the most important corneal ectasia, the so-called keratoconus. The microscopic structure has also been studied, having programmed an application that allows to quantify the polymegatism and pleomorphism of the endothelial corneal cells.

Subsequently, several univariate and multivariate diagnostic and classification systems for keratoconus have been revised, and it has been proven that morphogeometrical parameters allow both the detection and classification of keratoconus, basing on its degree of severity according to the RETICS, Amsler-Krumeich and Alió-Shabayek scales.

In addition, two classification predictive models (demographical-optical-geometrical) of the disease degree based on the RETICS scale have been proposed, resulting in the development of two computer applications called EMKLAS and KERATOSCORE, which show the inherent difficulty of detecting this disease in its preclinical phase.

Finally, a 3D printed personalized solid model has been applied to patient's education, showing that the visual and tactile perception of the model allows patients to better understand their illness and the treatment indicated for it, improving the perception of quality of service provided in ophthalmological clinics.

Publicaciones que conforman la tesis

0.1. Publicaciones que conforman la tesis

La presente tesis doctoral es un compendio de doce documentos, todos ellos previamente publicados o aceptados para publicación. En concreto, 9 corresponden a artículos en revistas listadas en el ISI-JCR del Sciences Citation Index, mientras que los 3 restantes corresponden a capítulos de libro de la editorial Springer (Ranking Scholarly Publishers Indicators 4/200). Dichos documentos se enumeran a continuación de acuerdo con el orden cronológico en que han sido publicados durante el desarrollo de la investigación:

1. Cavas-Martínez F, Fernández-Pacheco DG, Cañavate FJF, Velázquez-Blázquez JS, Bolarín JM, Alió JL. Study of Morpho-Geometric Variables to Improve the Diagnosis in Keratoconus with Mild Visual Limitation. *Symmetry*. 2018;10(8):306. DOI: [10.3390/sym10080306](https://doi.org/10.3390/sym10080306) (Rango JCR: Q2, FI: 2.143)
2. Cavas-Martínez F, Fernández-Pacheco DG, Cañavate FJF, Velázquez-Blázquez JS, Bolarín J, Tiveron M, Alió J. Early keratoconus detection by patient-specific 3D modelling and geometric parameters analysis. *Dyna*. 2019. 94(2). DOI: [10.6036/8895](https://doi.org/10.6036/8895) (Rango JCR: Q4, FI: 0.629)
3. Velázquez-Blázquez JS, Cavas-Martínez F, Alió del Barrio J, Fernández-Pacheco DG, Cañavate FJF, Parras-Burgos D, Alió J. Detection of Subclinical Keratoconus Using Biometric Parameters. In: Rojas I., Valenzuela O., Rojas F., Ortuño F. (eds) *Bioinformatics and Biomedical Engineering. IWBBIO 2019. Lecture Notes in Computer Science*, vol 11466. Springer, Cham. DOI: [10.1007/978-3-030-17935-9_44](https://doi.org/10.1007/978-3-030-17935-9_44) (Rango Citescore: Q2, SJR: 0.283)
4. Velázquez JS, Cavas F, Alió Del Barrio J, Fernández-Pacheco DG, Alió J. Assessment of the Association between In Vivo Corneal Morphogeometrical Changes and Keratoconus Eyes with Severe Visual Limitation. *J Ophthalmol*. 2019;2019:8731626-8731626. DOI: [10.1155/2019/8731626](https://doi.org/10.1155/2019/8731626) (Rango JCR: Q3, FI: 1.580)
5. Velázquez-Blázquez JS, Cavas-Martínez F, Campuzano VA, Alió del Barrio J, Cañavate FJF, Alió J. Automatic image processing applied to corneal endothelium cell count and shape characterization. *Dyna*. 2020;95(2). DOI: [10.6036/9275](https://doi.org/10.6036/9275) (Rango JCR: Q4, FI: 0.629)
6. Velázquez-Blázquez JS, Fernández-Pacheco DG, Alió del Barrio J, Alió JL, Cavas-Martínez F. Efficacy of Morpho-Geometrical Analysis of the Corneal Surfaces in Keratoconus Disease According to Moderate Visual Limitation. In: Cavas-Martínez F., Sanz-Adan F., Morer Camo P., Lostado Lorza R., Santamaría Peña J. (eds) *Advances in Design Engineering. INGEGRAF 2019. Lecture Notes in Mechanical Engineering*. Springer, Cham. [10.1007/978-3-030-41200-5_29](https://doi.org/10.1007/978-3-030-41200-5_29) (Rango Citescore: Q4, SJR: 0.134)

7. Velázquez JS, Cavas F, Bolarín JM, Alió JL. 3D Printed Personalized Corneal Models as a Tool for Improving Patient's Knowledge of an Asymmetric Disease. *Symmetry*. 2020;12(1):151. [10.3390/sym12010151](https://doi.org/10.3390/sym12010151) (Rango JCR: Q2, FI: 2.143)
8. Bolarín JM, Cavas F, Velázquez JS, Alió JL. A Machine-Learning Model Based on Morphogeometric Parameters for RETICS Disease Classification and GUI Development. *Applied Sciences*. 2020;10(5):1874. [10.3390/app10051874](https://doi.org/10.3390/app10051874) (Rango JCR: Q2, FI: 2.217)
9. Velázquez JS, Cavas F, Bolarín JM, Alió JL. Comparison of Corneal Morphologic Parameters and High Order Aberrations in Keratoconus and Normal eyes. In: Rojas I., Valenzuela O., Rojas F., Ortuño F. (eds) Bioinformatics and Biomedical Engineering. IWBBIO 2020. Lecture Notes in Computer Science, vol 12108. Springer, Cham. DOI: [10.1007/978-3-030-45385-5_8](https://doi.org/10.1007/978-3-030-45385-5_8) (Rango Citeseer: Q2, SJR: 0.283)
10. Toprak I, Cavas F, Velázquez JS, Alió del Barrio JL, Alió JL. Subclinical keratoconus detection with three-dimensional (3-D) morphogeometric and volumetric analysis. *Acta Ophthalmologica*. (in press). [10.1111/aos.14433](https://doi.org/10.1111/aos.14433) (Rango JCR: Q1, FI: 3.153)
11. Velázquez JS, Cavas F, Piñero DP, Cañavate FJF, Alió del Barrio J, Alió JL. Morphogeometric analysis for characterization of keratoconus considering the spatial localization and projection of apex and minimum corneal thickness point. *Journal of Advanced Research*. (in press). DOI: [10.1016/j.jare.2020.03.012](https://doi.org/10.1016/j.jare.2020.03.012) (Rango JCR: Q1, FI: 5.045)
12. Velázquez-Blázquez JS, Bolarín JM, Cavas-Martínez F, Alió JL. EMKLAS: A New Automatic-Scoring System for Early and Mild Keratoconus Detection. *Translational Vision Science & Technology*. (in press). (2020). (Rango JCR: Q2, FI: 2.399)

Además, de la presente investigación se han derivado tres conjuntos de programas informáticos, cuya propiedad intelectual se ha solicitado registrar, enumerados a continuación:

- A. Cavas F, Velázquez JS, Campuzano VM, Cañavate FJF. CoEnCell. Número de solicitud: MU-164-2020. Fecha de Registro: 28/02/2020. Entidad titular de los derechos: Universidad Politécnica de Cartagena.
- B. Cavas F, Velázquez JS, Bolarín JM. KERATOSCORE. Número de solicitud: MU-170-2020. Fecha de Registro: 02/03/2020. Entidad titular de los derechos: Universidad Politécnica de Cartagena.
- C. Cavas F, Velázquez JS, Bolarín JM. EMKLAS. Número de solicitud: MU-171-2020. Fecha de Registro: 02/03/2020. Entidad titular de los derechos: Universidad Politécnica de Cartagena.

1

Introducción

1.1. Introducción

El ojo humano tiene cuatro superficies refractivas, cinco índices de refracción y cuatro espesores.¹ La variación de cualquiera de estos parámetros afecta al estado refractivo del conjunto. De todas ellas y desde el punto de vista refractivo, la más importante es la córnea, que presenta una estructura hemisférica en el segmento anterior del ojo.²

Una córnea perfecta sería completamente simétrica. Sin embargo, la córnea como estructura biológica no es perfecta, debido a que los ápices (puntos de máxima curvatura) de las superficies corneales no se encuentran alineados respecto de un mismo eje, y por tanto ambas superficies no presentan simetría de revolución en ellas, aunque sí podrían presentarla de forma individual.

Esta asimetría lleva aparejada la existencia de deformaciones, desalineamientos y descentramientos entre las estructuras superficiales de ambos ojos.³ Además, esta caracterización asimétrica se desarrolla en un escenario sano, y por lo tanto refleja una estrategia biológica más que un defecto óptico-geométrico.

Sin embargo, en un escenario patológico, la progresión de la asimetría en la estructura hemisférica contribuye a una disminución de su capacidad óptica, provocando una pérdida de la calidad visual de los pacientes⁴. Esta progresión puede tener su origen en varios mecanismos fisio-patológicos como son las ectasias corneales. En el caso de las ectasias corneales (queratocono, queratoglobo, degeneración marginal pelúcida, ectasia post cirugía refractiva y post queratoplastia penetrante), donde cada una de ellas presenta un característico patrón geométrico, y desde el punto de vista morfogeométrico, se caracterizan por una descompensación geométrica de la curvatura corneal en el punto de máxima curvatura, y un aumento del perfil anular de paquimetría a partir del punto de mínimo espesor.⁵

Este desorden multifactorial y progresivo característico de las ectasias, es típicamente percibido durante la segunda década de vida, con una prevalencia estimada de 50-230 casos por cada 100.000 individuos², por ello los diferentes tipos de ectasias son considerados enfermedades raras.

Dentro de la baja prevalencia de las ectasias, el queratocono⁶ es la más frecuente de todas, atribuyéndosele uno enormes impactos:

- Clínico, al ser la primera causa de trasplantes de córnea en pacientes menores de 40 años, según la American Corneal Bank Association (Annual Report 2018).
- Social, pues afecta de forma notable a la calidad de vida (productividad, seguridad vial, etc.) de los pacientes.

La literatura científica describe numerosos sistemas para el diagnóstico y la clasificación del grado de severidad, en función del tipo de ectasia. Concretamente en el caso del queratocono, existen varias clasificaciones que consideran diferentes fenotipos óptico-

geométricos. Sin embargo, se precisa de mejoras adicionales en la detección del queratocono en su fase preclínica (queratocono subclínico), para aumentar las estrategias de diagnóstico de esta enfermedad, y evitar el riesgo de ectasia iatrogénica progresiva en pacientes que se someten a cirugía refractiva corneal (ectasia post quirúrgica).^{7,8}

Las cirugías refractivas se utilizan para cambiar la curvatura de la superficie corneal y para modificar su potencia óptica, por una variada cantidad de razones. A pesar de los avances quirúrgicos en los últimos años, existen estudios que demuestran la existencia de un cierto grado de imprevisibilidad en los resultados obtenidos, por la aparición de efectos secundarios debidos a una corrección insuficiente o excesiva durante la cirugía, que dan lugar a su vez a una alteración de la agudeza visual o a la aparición del denominado ojo seco.⁹ Esto es debido a que puede existir alguna enfermedad oculta en la córnea que no ha sido identificada durante la fase de exploración clínica, por lo tanto, puede ser necesario un segundo procedimiento refractivo de “mejora”.

Recientemente, un grupo mundial de expertos en ectasias corneales, reunidos en el proyecto “Global Consensus on Keratoconus and Ectatic Diseases”¹⁰ definió un nuevo concepto denominado “Ectasia Progression”, que describe la progresión de las ectasias en sus diferentes fases, en función de los cambios de magnitud de, al menos, los siguientes puntos singulares: ápex de la superficie corneal anterior, ápex de la superficie corneal posterior y puntos de mínimo espesor de las superficies corneales anterior y posterior. Igualmente, Belin et al.¹¹ han demostrado la importancia del punto de mínimo espesor de la córnea y de su zona de influencia en la superficie corneal anterior y posterior, por ser éste un punto local y no centrado, donde inicialmente se manifiesta el encurvamiento característico de la patología ectásica.

De este modo, se propuso un primer modelo geométrico computacional de la córnea como método de análisis para el estudio y la caracterización del queratocono¹², sin embargo este primer modelo apenas presenta variables geométricas de caracterización, y no ha sido desarrollado como una herramienta de análisis dinámico para el estudio de la evolución de la enfermedad en los diferentes grados de ectasia en fases incipiente (no existen síntomas de deterioro visual), desarrollada (en sus diferentes grados de progresión, si existen diferentes grados de deterioro visual), y tratada mediante tratamientos invasivos (quirúrgicos) y no invasivos (lentes duras, blandas, etc.).

Esta investigación se propone ser la primera en crear una infraestructura capaz de desarrollar, por una parte, una alternativa clínica mejorada para el diagnóstico evolutivo de la patología, basada en software de propietario y código abierto; y por otra, una nueva tecnología de simulación morfogeométrica, implementable en cuasi-tiempo real, capaz de intervenir favorablemente en la evolución clínica corneal.

Así pues, el principal reto de esta tesis doctoral ha sido crear un sistema integrado y eficiente capaz de detectar (fase preclínica) y diagnosticar (fase clínica), desde un punto de vista óptico-geométrico, la progresión de la ectasia corneal, ya que su evolución incide de forma directa en la calidad visual de los pacientes.

La presente tesis doctoral se enmarca dentro de las prioridades temáticas fijadas por el reto social Salud, Cambio Demográfico y Bienestar de los objetivos estratégicos del programa Horizonte 2020 de la Unión Europea y la Estrategia Española de Ciencia, Tecnología y de Innovación 2013-2020, al promover el desarrollo de una tecnología y sus aplicaciones, buscando la mejora de la competitividad, así como al intentar resolver el desafío específico de una mayor integración de la información clínica del paciente, permitiendo de esta forma la extracción del conocimiento, y el apoyo a la decisión clínica.

Estado del Arte

2.1. El ojo humano

El ojo humano es uno de los órganos más complejos e importantes del cuerpo, puesto que es el que nos permite mantener una conexión con el entorno.¹³ Desde un punto de vista óptico, se podría definir como un conjunto de órganos con una capacidad refractiva determinada, que, actuando de manera análoga a lentes, hacen converger la luz hacia la zona interior del conjunto, en la que se encuentran los receptores electroquímicos, estimulándolos. Estos a su vez transforman dichos estímulos en señales, que son conducidas al cerebro a través del nervio óptico.^{13,14}

El ojo presenta tres capas claramente distinguidas (Figura 2.1, áreas I, II y III).¹⁵

Figura 2.1 Capas del ojo humano. Extraída de Willoughby¹⁵

La córnea y la esclerótica conforman la llamada capa externa (I). En ella, la córnea es la encargada de refractar y transmitir la luz al cristalino y a la retina, a la vez que protege de infecciones y daños estructurales a las partes internas del ojo. La esclerótica, forma un recubrimiento de tejido conectivo que protege el ojo de las fuerzas externas e internas, manteniendo su forma. Ambas, quedan conectadas por el limbo esclerocorneal. La parte visible de la esclerótica está cubierta de una membrana mucosa transparente, la conjuntiva.^{14,15}

La capa interna (II) del ojo es la retina, una estructura compleja y estratificada de neuronas que capturan y procesan la luz.^{14,15}

La capa media (III) se compone del iris, el cuerpo ciliar y la coroides. El iris determina el tamaño de la pupila, y por tanto la cantidad de luz que alcanza la retina; el cuerpo ciliar controla la potencia y la forma de la lente, y es el lugar en que se produce el humor acuoso; y la coroides es la capa vascular que proporciona oxígeno y nutrientes a las capas retinales más externas.^{14,15}

Por último, existen tres estructuras transparentes que quedan envueltas por estas capas oculares citadas, y que reciben el nombre de humo acuoso, humor vítreo y cristalino.¹⁵

Desde un punto de vista anatómico-fisiológico, el ojo puede dividirse de forma general en dos segmentos, denominados anterior y posterior (Figura 2.2). El segmento anterior consta de estructura hemiesférica o córnea, conjuntiva, humor acuoso, iris, cuerpo ciliar y cristalino. La parte restante, esto es, el segmento posterior, incluye la esclerótica, la coroides, la membrana de Bruch, el epitelio retinal pigmentario, la retina y el humor vítreo.¹³

Figura 2.2 Segmentos del ojo. Extraída de internet¹⁶

El ojo humano cuenta con cuatro superficies refractivas, cinco índices de refracción y cuatro espesores¹⁷. La variación de cualquiera de estos parámetros repercute en el estado funcional del ojo, pero desde el punto de vista refractivo, el elemento más importante de todos ellos es la estructura hemiesférica situada en el segmento anterior.

2.2. Estructura hemiesférica del segmento anterior

La estructura hemiesférica del segmento anterior, también conocida como córnea, es un tejido avascular, altamente innervado, diferenciado y multifuncional, aunque por sus propiedades intrínsecas de curvatura y transparencia, ser el primer elemento refractivo ocular sería su función más importante.¹⁷ Su morfología es muy variable, sobre todo cuando presenta alguna patología¹⁸, por lo que resulta vital:

- Caracterizar su anatomía y morfología tanto a nivel macroscópico como microscópico.
- Estudiar en profundidad las tecnologías que permiten actualmente dicha caracterización morfológica, y las variables o parámetros utilizados para ello.

- Conocer los distintos sistemas de clasificación usados en la actualidad por la comunidad médica para la ectasia corneal conocida como queratocono, la nomenclatura de los distintos grados, y los parámetros en los que se basan.

Por lo tanto, se ha estructurado este epígrafe en cuatro sub-epígrafes: en el primero se describe la anatomía de la estructura hemiesférica, tanto a nivel general (nivel macroscópico) como desde un punto de vista histológico (nivel microscópico); en el segundo, se elabora una caracterización morfológica, desde un punto de vista geométrico; en el tercero, se describen las distintas tecnologías existentes para la caracterización morfogeométrica, y se exponen las diferencias encontradas entre ojos sanos y enfermos con la tecnología aplicada en esta tesis (tomografía Scheimpflug); y en el cuarto, se describen las distintas clasificaciones existentes para el queratocono, con particular detalle las de Amsler-Krumeich, Alió-Shabayek y RETICS, que han sido las usadas en los artículos que componen este documento.

2.2.1 Anatomía

La estructura hemiesférica del segmento anterior, o córnea, presenta dos superficies claramente definidas, denominadas anterior y posterior. La superficie anterior está en contacto con la película lagrimal, mientras que la posterior está en contacto con el humor acuoso. En un estado sano, se caracteriza por su transparencia.

2.2.1.1 Análisis a nivel macroscópico

El espesor promedio, para un humano adulto, es en la región central de aproximadamente 0.52 mm, mientras que en la periferia alcanza los 0.65 mm (Figura 2.3)

Su diámetro medio horizontal es de 11.5 mm y el vertical de 10.5 mm.¹⁹ La zona óptica, que proporciona la mayor parte de su función refractiva, tiene un diámetro de 4 mm y se localiza en la zona central de la misma, anterior a la pupila, en condiciones fotópicas.¹⁵

Su potencia refractiva es de 43 dioptrías (D)²⁰, lo que supone el 70% del total ocular, manteniéndose su curvatura esencialmente constante a lo largo de la vida.¹

Figura 2.3 Corte sagital de una córnea sana con sus parámetros promedio. Extraída de Cavas²¹

2.2.1.2 Análisis a nivel microscópico

La córnea consta de cinco capas bien diferenciadas a nivel microscópico (Figura 2.4): epitelio, membrana de Bowman, estroma, membrana de Descemet y endotelio.^{1,22}

2.2.1.2.1 Epitelio

La superficie del epitelio corneal está cubierta por la película lagrimal, que la protege de los agentes químicos, tóxicos u objetos extraños que puedan dañarla, así como de las infecciones microbianas, suavizando además las micro-irregularidades presentes en la superficie epitelial.^{13,14}

El epitelio corneal posee un complejo y denso entramado intercelular, que lo convierte en una capa extremadamente impermeable y estable¹⁵, confiriéndole la propiedad de resistencia mecánica a la abrasión por el parpadeo o uso de lentes de contacto. Con un espesor de 40 a 50 μm ¹, se compone de: de dos a tres capas de células superficiales, dos a tres capas de células intermedias y una capa basal.^{1,13,14} Las células epiteliales se renuevan cada 7-10 días desde una población de células madre pluripotentes ubicadas en las empalizadas de Vogt, en el limbo esclerocorneal.²³

Figura 2.4 Capas histológicas de la córnea humana (200x). Extraída de Fernández²⁴

2.2.1.2.2 Membrana de Bowman

La membrana de Bowman se sitúa bajo la capa basal epitelial y justo antes del estroma, y no es estrictamente una membrana, sino más bien un condensado acelular de la parte superior de este último, formado principalmente por fibras de colágeno. Tiene un espesor aproximado de 15 μm y su función es la de ayudar a la córnea a mantener su forma. Cuando se daña, no se regenera, pudiendo aparecer cicatrices.^{1,15}

2.2.1.2.3 Estroma

El estroma corneal constituye el grueso de la red estructural de la córnea, y supone aproximadamente un 80-85% de su espesor, que toma valores de entre 500 y 540 μm en el área central y de casi unas 700 μm en el área más periférica. La principal diferencia del estroma con otras estructuras de colágeno es su transparencia, que resulta de una organización concreta de las fibras estromales y la matriz extracelular. Las fibras de colágeno se agrupan en grupos paralelos llamados fibrillas, y estas a su vez agrupan en capas paralelas llamadas lamelas. El estroma del ojo humano contiene entre 200 y 250 lamelas distintas medidas de limbo a limbo, cada capa con el ángulo correcto con respecto a la lamela adyacente.^{1,25} En la zona pre-pupilar, las fibrillas se agrupan de una forma más compacta que en la periferia de la córnea, lo que probablemente contribuye a la resistencia mecánica y la estabilidad dióptrica de la misma.²⁶

2.2.1.2.4 Membrana de Descemet

Es la capa base del endotelio corneal, compuesta por una fina capa de fibrillas de colágeno, que es secretada de forma continua por las células endoteliales.^{1,15} Tiene un espesor aproximado de unos 10 μm , siendo sus principales características la elasticidad, la capacidad de regenerarse rápidamente y la resistencia a las enzimas proteolíticas.

2.2.1.2.5 Endotelio

El endotelio es la monocapa de entre 4 y 10 μm de espesor responsable de mantener una hidratación corneal constante (y por tanto, la transparencia), presentando en su forma no degradada un aspecto de mosaico hexagonal que recuerda a un panal de abejas²⁷. Por el proceso natural de envejecimiento, así como por ciertas patologías o disfunciones, tanto el número de celdas como su forma van cambiando a lo largo de la vida, de 3000/4000 células/ mm^2 en la segunda década de vida hasta unas 2600 células/ mm^2 al sobrepasar la octava. El número de celdas con forma hexagonal se modifica de forma similar, desde aproximadamente el 75% hasta solo el 60% del total^{1,28}. Esta reducción del número de celdas crea huecos que fuerzan al resto de células a aumentar su tamaño (polimegatismo) y/o perder su forma hexagonal (pleomorfismo) para rellenarlos^{1,29}, de ahí la gran importancia del conteo de células y la caracterización de su forma para detectar algunas anomalías, tales como el glaucoma o el queratocono.

2.2.2 Morfología

El segmento anterior del ojo humano posee una geometría y una estructura singulares, que varían al pasar del escenario natural al patológico.

Caracterizar desde el punto de vista clínico su morfogeometría es vital para el diagnóstico de patologías relacionadas con él, así como para la toma de decisiones acerca de la conveniencia o no de aplicar técnicas invasivas en el caso de un posible tratamiento correctivo.

El enfoque tradicional para el estudio de la morfogeometría de la córnea ha sido el bidimensional, y consecuentemente, aspectos morfológicos y geométricos como el

volumen, el espesor corneal o el área de las superficies de sus caras anterior y posterior no han sido tenidas en cuenta. Además, oftalmológicamente la córnea se consideraba como un único ente refractivo, sin distinguir entre sus superficies anterior y posterior.

El advenimiento de nuevas tecnologías en los últimos años ha permitido la caracterización corneal en un entorno tridimensional, pasando de la percepción simplista bidimensional a otra más compleja, donde la córnea se considera un elemento refractivo tridimensional.

2.2.2.1 La córnea sana

La regularidad que presentan las superficies de la estructura hemiesférica del segmento anterior hace que estas actúen como lentes, confiriendo al conjunto la máxima importancia, desde el punto de vista refractivo, en el esquema ocular. Así, la superficie de la cara anterior de la córnea aporta dos tercios de la potencia óptica total del ojo humano (43 D) en el punto corneal de mayor altimetría respecto al plano de referencia, definido como ápex corneal.

Una córnea sana puede caracterizarse morfológicamente de la siguiente forma:

- En su cara anterior. muestra un intervalo de curvatura superficial promedio entre 7.75 mm y 7.89 mm,³⁰⁻³² y para la zona central un valor medio de 7.79 mm.³⁰
- En su cara posterior. muestra un intervalo de curvatura superficial promedio entre 6.34 mm y 6.48 mm³⁰⁻³² y para la zona central un valor medio de 6.53 mm.^{30,33}

La paquimetría o espesor corneal queda definido por el espacio inter-superficial, alcanzando un valor promedio en su centro geométrico en torno a 0.54 mm.³³⁻³⁵

Se ha comprobado que los valores promedio de curvatura y espesor corneal muestran una tendencia clara a mantenerse estables en un escenario sano.³³

Pero además de los parámetros ópticos y paquimétricos descritos, es preciso conocer la morfología de ambas superficies corneales si se desea alcanzar una caracterización morfogeométrica completa de la misma. Ambas superficies pueden asemejarse, desde un punto de vista geométrico, a la superficie de un esferoide (Figura 2.5), figura geométrica cuya curva generatriz se obtiene al girar una elipse alrededor de uno de sus ejes principales. Un esferoide cuenta con dos ejes dominantes, el llamado “eje de simetría”, designado habitualmente con la letra “c” y localizado sobre el eje cartesiano Z; y el denominado “eje perpendicular al de simetría”, designado con la letra “a”. La elección de las letras de designación ha sido establecida por convenio Internacional.

Un esferoide puede adoptar tres configuraciones distintas, dependiendo de la relación existente entre sus ejes principales “c” y “a” (Figura 2.5):

- Esferoide oblato. Si $a > c$, el eje de simetría es el menor.
- Esferoide prolato. Si $a < c$, el eje de simetría es el mayor.

- Esfera. Si $a=c$, el eje de simetría es igual. Este es un caso particular, dado que la curva generatriz sería una elipse cuyos semiejes mayor y menor son iguales, es decir, una circunferencia. Por tanto, la superficie obtenida por rotación de la curva generatriz, será una esfera.

Figura 2.5 Elipsoide prolato, oblato y esfera. Extraída de internet³⁶

De vuelta al campo de la oftalmología, y en base a lo expuesto, se podría afirmar que la córnea presenta un comportamiento geométrico muy similar al de un perfil de naturaleza elíptica:^{32,34}

$$X^2 - Y^2 + (1 + Q)Z^2 - 2ZR = 0 \quad (2.1)$$

Esta ecuación utiliza tres coordenadas espaciales (X, Y, Z), y basándose en ellas se interpreta la superficie corneal actualmente como un elemento refractivo 3D, caracterizado por medio de tres parámetros:

- Asfericidad corneal (Q): parámetro que caracteriza la naturaleza de la curva cónica que define la superficie corneal (Figura 2.6).
- Eje de revolución conocido (Z).
- Radio del conoide (R): es el radio del punto más alto de la superficie de la cara anterior o del ápex corneal

 Figura 2.6 Tipos de curvas cónicas. Adaptada de Calossi³⁴

La asfericidad corneal puede definirse como la tasa de cambio de la curvatura de la córnea desde la zona central hasta la periferia.³⁴ Esta tasa puede incrementarse, caso de una córnea patológica, o bien reducirse, como sucedería en una córnea sana.

El coeficiente de asfericidad corneal (Q) puede ser calculado matemáticamente a partir de la relación entre los hemiejes centrales (b) y periféricos (a) del perfil elíptico corneal (Figura 2.7).

 Figura 2.7 Asfericidad corneal. Extraída de Cavas²¹

Como puede percibirse, el perfil elíptico de la superficie corneal puede corresponderse con cualquiera de los siguientes:³⁷

- Esférico ($Q = 0$). Es un caso singular, donde los hemiejes horizontal o periférico y central o vertical (b) de la elipse son iguales, es decir la superficie corneal tiene la misma curvatura en la región central que en la región periférica.^{21,37}
- Elipse prolata ($0 > Q > -1$). En este caso, el perfil elíptico de la superficie corneal se aplana conforme se aleja del punto más alto o ápex de la superficie corneal. Este comportamiento se da en un escenario sano, lo que implica desde el punto de vista refractivo que la córnea posee una baja aberración esférica.^{21,37}
- Elipse oblata ($Q > 0$). En este otro caso, el perfil elíptico de la superficie corneal se hace más curvo conforme se aleja del punto más alto o ápex corneal. Este comportamiento se da en un escenario patológico, lo que implica desde el punto de vista refractivo que la córnea posee una aberración esférica proporcional al factor Q .^{21,37}
- Parábola o hipérbola ($Q \leq -1$). Es un caso excepcional en los ojos sanos, y exclusivo de las patologías ectásicas centrales de la córnea. Desde el punto de vista de la superficie refractiva, la córnea posee un índice de aberración esférico negativo proporcional al factor Q .^{21,37}

Además, existen otros parámetros, aparte del ya mencionado coeficiente de asfericidad, capaces de dar cuenta del grado de curvatura de la córnea²¹:

- Factor de excentricidad (e): $e = -\sqrt{Q}$ (2.2)
- Factor de forma (p): $p = 1 - e^2$ ó $p = Q + 1$ (2.3)

Todos ellos se relacionan entre sí de acuerdo a las expresiones de la Tabla 2.1:

Tabla 2.1 Relación entre los distintos tipos de curvas cónicas, en función de “e”, “p” y “Q”.
Adaptada de Montalbán³⁷

Sección córnea	Excentricidad e^2	Factor de forma $p = 1 - e^2$ ó $p = Q + 1$	Asfericidad $Q = -e^2$
Esfera	$e^2 = 1$	$p = 1$	$Q = 0$
Elipse oblata	$e^2 < 1$	$p > 1$	$Q > 0$
Elipse prolata	$0 < e^2 < 1$	$0 < p < 1$	$1 < Q < 0$
Parábola	$e^2 = 1$	$p = 0$	$Q = -1$
Hipérbola	$e^2 > 1$	$p < 1$	$Q < -1$

Otra relación matemática útil es la que permite definir el perfil de la sección elíptica corneal en función del radio de curvatura central (R_c):

$$p = \left(\frac{a}{b}\right)^2 = \frac{R_c}{a} \quad (2.4)$$

De todos los parámetros definidos, el más usado en la caracterización morfogeométrica de la córnea es la asfericidad, que toma como valores promedio más usuales para la cara anterior el rango de -0.29 a -0.13,^{31,38,39} mientras que para la cara posterior oscila entre -0.34 y -0.38,^{30,35} lo que pone de manifiesto que ambas superficies presentan una caracterización morfológica de naturaleza prolata.

Finalmente, es importante señalar que el valor de la asfericidad cambia dependiendo de la región corneal analizada, de manera que dentro de la misma córnea pueden presentarse distintos valores de asfericidad.

2.2.2.2 Modelado de la estructura hemiesférica del segmento anterior

El conocimiento de la morfología de la estructura hemiesférica del segmento anterior ha sido adquirido a lo largo de la historia del ser humano en función del objetivo del análisis a realizar, pudiendo tener diferentes finalidades, como ópticas o de diagnóstico clínico de una determinada patología, entre muchas otras. En cualquiera de los casos, se suele afrontar el problema del modelado desde dos estrategias diferentes: usando modelos genéricos, o por el contrario, recurriendo a modelos personalizados.

2.2.2.2.1 Modelos geométricos genéricos

Estos modelos se basan en dimensiones promedio y se utilizan en la reproducción y extracción de resultados aplicables a la totalidad de la población. En este contexto, se puede encontrar una amplia variedad de modelos ópticos, siguiendo cada uno un enfoque diferente, tales como número de componentes anatómicos,^{40,41} dispersión cromática,^{40,42} calidad óptica e imagen,^{40,43} índice de refracción,^{44,45} amplitud del campo visual,^{46,47} nivel de alojamiento o acomodación,^{48,49} y alteraciones morfológicas relacionadas con la edad.⁵⁰

Esta enorme variedad de modelos geométricos existentes no hace sino evidenciar el hecho de que todos los modelos genéricos son incompletos, ya que el ojo humano real contiene, además de la estructura hemiesférica, otros elementos anatómicos, trabaja con luz policromática, presenta un rendimiento óptico limitado (aberraciones ópticas), posee un campo visual amplio, utiliza un mecanismo de acomodación para enfocar los objetos en función de la proximidad o lejanía de estos y evoluciona a lo largo de la vida, por lo que cualquier modelo debe de considerar a corto plazo el alojamiento y a largo plazo los cambios asociados al envejecimiento.²¹

En el ámbito de la biomecánica, desde los primeros trabajos basados en modelos bidimensionales asimétricos,⁵¹ hasta los más actuales,⁵² se han empleado aproximaciones a la geometría en base a los distintos modelos ópticos anteriormente referidos. Un estándar ampliamente aceptado en la comunidad oftalmológica consiste en utilizar como aproximación a la superficie un modelo que esté basado en una superficie cónica o bicónica,⁵³ tales como esferas,⁵⁴ elipses,⁵⁵ toros,⁵⁶ biconos,⁵⁷ o elipsoides de no revolución.⁵⁸

Esta abundancia de modelos genéricos puede entenderse si se tiene en cuenta el hecho de que la superficie de la córnea no se ajusta perfectamente a ninguna superficie analítica. En todos los casos se pretende que el modelo geométrico de base propuesto sea capaz de capturar las características morfológicas esenciales de la estructura media, y al mismo tiempo, haga que los valores residuales obtenidos, es decir las irregularidades que presenta la superficie, sean menores que la superficie base.

De esta forma se consigue que la superficie geométrica de base presente una descripción global de la morfología corneal de forma aceptable. En referencia al ajuste del residuo, éste se realiza normalmente por métodos matemáticos basados en los polinomios de Zernike.

En resumen, estos modelos son válidos cuando analizamos o reproducimos los resultados que le son de aplicación a un conjunto de la población en los campos de la óptica y la biomecánica corneal.

Sin embargo, estos modelos no son válidos para estudiar el diagnóstico clínico de determinadas patologías corneales, al prescindir de las características individuales de cada paciente en particular.

2.2.2.2.2 Modelos geométricos personalizados

Estos modelos, a diferencia de los genéricos, permiten estudiar el caso de un paciente en concreto con distintos fines, tales como: ópticos, para la valoración de la agudeza visual de un paciente; diagnósticos, para categorizar una patología ectásica; o biomecánicos, para analizar el comportamiento de los tejidos que forman la estructura hemiesférica, entre muchos otros. Generalmente, en estos casos la caracterización puede acometerse a partir de información:

- i) Obtenida mediante técnicas de tratamiento de imágenes,
- ii) Aportada por unos equipos específicos denominados tomógrafos corneales.

2.2.2.2.2.1 Caracterización a partir de técnicas de tratamiento de imágenes

Estas técnicas cuentan con un amplio uso en los campos de la óptica, el diagnóstico clínico de ectasias o lesiones oculares, la anatomía ocular y de la biomecánica de la estructura hemiesférica.

La fiabilidad de estos modelos viene determinada en gran medida por el proceso de adquisición de imagen, y el posterior tratamiento de éstas realizado por el propio software de equipos diagnósticos tales como los microscopios especulares (SM), los tomógrafos de coherencia óptica (OCT), los equipos de biomicroscopía ultrasónica (BMU) o los de resonancia magnética (MRI en inglés).

Los modelos personalizados generados con fines ópticos se fundamentan principalmente en el tratamiento de imágenes adquiridas por un OCT, logrando cuantificar la influencia del espesor en el índice de refracción,⁵⁹ o la influencia de la inclinación y del descentrado de una lente intraocular en la potencia refractiva⁶⁰.

El tratamiento de imágenes obtenidas por OCT ha sido también empleado con éxito para diagnosticar patologías relativas a la morfogeometría de la estructura hemiesférica del segmento anterior, concretamente para el diagnóstico y tratamiento de la ectasia corneal.⁶¹⁻⁶³

En la revisión de la literatura científica existente aparecen algunos trabajos en los cuales, ante la falta de datos que permitan reconstruir la imagen capturada, se emplea software comercial (Adobe Photoshop® o similares) en el proceso de reconstrucción de la imagen, lo que pudiera dar lugar a un sesgo significativo en los resultados obtenidos.^{64,65}

Otros autores se centran en la caracterización morfológica solamente para refinar el conocimiento acerca de la morfología real,^{66,67} pero con respecto a la estructura hemiesférica del segmento anterior, no se ha constatado hasta el momento la existencia de una tecnología de adquisición y tratamiento de imágenes que permita generar un modelo virtual de acceso abierto y universal.

El análisis de la biomecánica del segmento anterior es otro de los campos con un interés creciente en los modelos personalizados,⁶⁸ por su utilidad en el análisis del comportamiento mecánico de los tejidos que constituyen la estructura hemiesférica en córneas patológicas, y estudio de sus posibles tratamientos.

La información necesaria para la generación del modelo biomecánico a partir de imágenes puede obtenerse mediante equipos OCT,⁶⁹ de microscopía óptica,⁷⁰ o de rayos X.⁷¹ Otros autores definen la geometría a partir de un equipo específico diseñado para la realización de ensayos mecánicos.⁷²

2.2.2.2.2 Caracterización mediante tomografía corneal

El otro enfoque que permite la creación de un modelo específico de caracterización personalizado para cada paciente es la tomografía. Esta consiste en una técnica exploratoria no invasiva que posibilita el análisis cualitativo y cuantitativo de la morfogeometría corneal, permitiendo la detección de patrones normalizados y la discriminación de alteraciones cuyos efectos pueden ser devastadores para la visión, provenientes de trastornos patológicos ectásicos.⁷³

La tomografía se lleva a cabo mediante los denominados tomógrafos corneales, instrumentos con amplia extensión y aceptación entre la comunidad médica oftalmológica, que logran una caracterización anatómica y geométrica del segmento anterior a partir de la reconstrucción de su superficie.⁷⁴

En el proceso seguido por la mayoría de los tomógrafos para la presentación de los datos al profesional de la oftalmología, se distinguen claramente dos fases:

- La primera fase correspondería al proceso de adquisición y tratamiento interno de los datos. En esta se adquieren los datos altimétricos, en forma de matriz de elevaciones o en forma de datos de curvatura, sobre un conjunto discreto y finito de puntos representativos de la superficie de la córnea, denominados datos en

bruto o “raw data”.¹² Es en esta etapa donde pueden presentarse dos tipos de errores de adquisición, los llamados intrínsecos, atribuibles al equipo (ruido de fondo, precisión, etc.); y los extrínsecos, asociados a los que puede cometer el examinador en el proceso de adquisición (errores de apreciación, de centrado, descuelgue de película lagrimal, etc.)

- La segunda fase correspondería a la reconstrucción de la córnea, partiendo de los datos que constituyen la matriz de elevaciones, para su posterior comparación con una superficie de referencia, generalmente de forma esférica, y hallar por tanto el mapa topográfico que caracteriza la superficie corneal.

En la actualidad, los tomógrafos se basan generalmente en dos principios: i) la reflexión de la luz sobre las distintas capas de la estructura hemiesférica y ii) la proyección de una hendidura de luz sobre la córnea. Ambas tecnologías proporcionan diferentes mapas topográficos de la superficie corneal anterior, posterior y paquimétricos, así como unos índices resumen para el seguimiento y la valoración clínica de las tomografías corneales.

2.2.3 Herramientas para la caracterización morfogeométrica

Dadas sus muchas aplicaciones y su relevancia para la optimización de los procedimientos quirúrgicos corneales e intraoculares, se han desarrollado durante las últimas décadas diferentes técnicas encaminadas a caracterizar la morfogeometría del segmento anterior y su estructura hemiesférica, aportando cada una de ellas sus ventajas y sus inconvenientes.

En general, la gran mayoría de equipos de imagen permiten un análisis más o menos preciso de uno o varios parámetros anatómicos o geométricos, pero pocos aportan un análisis integral y una evaluación pormenorizada del segmento anterior, incluyendo curvatura, asfericidad y análisis de espesor de la córnea, así como medida de las dimensiones del espacio del segmento anterior.⁷⁴

2.2.3.1 Biomicroscopía con lámpara de hendidura

La biomicroscopía con lámpara de hendidura (SLB) consiste en la combinación de un sistema de observación que permite visualizar de manera directa la córnea a diferentes aumentos (desde 6x hasta 40x, dependiendo del modelo), y un sistema de iluminación independiente, que hace posible modificar el ángulo, la anchura del haz y el nivel de iluminación (Figura 2.8).⁷⁵

La SLB permite evaluar la estructura tanto del segmento anterior como del posterior. Existen numerosas técnicas de iluminación para el diagnóstico de las diversas patologías, la evaluación pre y post operativa, o el uso de lentillas.^{76,77} Otro uso de la SLB sería la exploración detallada de la retina o el nervio óptico mediante una lente condensadora adicional que aporta una vista estereoscópica ampliada de la retina.⁷⁸

Figura 2.8 Biomicroscopio de lámpara de hendidura. Extraída de internet⁷⁹

2.2.3.2 Microscopía especular

La microscopía especular (SM) es una técnica que permite visualizar el endotelio corneal *in vivo*, mediante el uso de una luz reflejada especular y una lámpara de hendidura. Las células endoteliales son visibles porque su índice refractivo es mayor que el del humor acuoso.⁸⁰

Los microscopios especulares modernos (Figura 2.9) son instrumentos sin contacto que usan técnicas de autoenfoco de imagen, lo que permite su uso con pacientes de un amplio rango de edades, desde niños pequeños a ancianos.⁸¹ Suministran medidas paquimétricas y de análisis del endotelio corneal, tales como evaluación de pérdida de células, polimegatismo (incremento de tamaño) y pleomorfismo (modificación de su forma hexagonal), por lo que son muy útiles para la investigación y la práctica clínica relacionada con el queratocono⁸², lentes de contacto,⁷⁵ o el diagnóstico de diferentes desórdenes endoteliales (distrofia de Fuchs, distrofia polimorfa posterior y síndrome iridocorneal endotelial).

Figura 2.9 Microscopio especular Topcon SP-1P. Extraída de internet⁸³

2.2.3.3 Paquimetría por ultrasonidos

El concepto de paquimetría corneal hace referencia a la medida del espesor de la córnea. Por lo tanto, la paquimetría por ultrasonidos (USP) mide el espesor de la córnea, usando para ello la energía emitida por la punta de una sonda, que se refleja en forma de eco. El tiempo que tarda en retornar a la punta de la sonda permite calcular el espesor corneal. La Figura 2.10 muestra un paquímetro por ultrasonidos de mano.

Figura 2.10 Paquímetro por ultrasonidos de mano DGH Pachmate-2. Extraída de internet⁸⁴

El espesor corneal es un importante indicador de la salud de la córnea, y permite el diagnóstico y seguimiento de diversas enfermedades corneales, como el edema corneal, o la ectasia corneal provocada por el queratocono o la degeneración marginal pelúcida. También es importante esta tecnología en la evaluación de pacientes sospechosos de sufrir glaucoma, puesto que la presión intraocular se ha demostrado que depende del espesor corneal central y periférico.³⁸ Por último, cabe destacar que es uno de los parámetros que determinan si un paciente puede someterse a cirugías refractivas como el LASIK.⁸⁵

Sin embargo, para la medida del espesor corneal con USP es preciso aplicar anestesia, y existe contacto directo con la córnea, aumentando el riesgo de infecciones y disminuyendo la repetitividad. Esto ha hecho que se esté reemplazando actualmente por tecnologías que permiten una mayor repetitividad y reproducibilidad, y que eviten el contacto directo con el ojo, como la tomografía de coherencia óptica, los sistemas de escaneo de lámpara de hendidura, o los basados en fotografía Scheimpflug.^{75,86-90}

2.2.3.4 Microscopía confocal

La microscopía confocal (CM) permite evaluar el estado de la córnea a nivel celular, lo que permite un diagnóstico temprano y confiable de diversas patologías por la detección de cambios en las estructuras normales (Figura 2.11).^{77,91}

La principal diferencia entre la CM y la microscopía con luz convencional, es que esta última está limitada por los reflejos y la luz dispersada desde las estructuras que están fuera del plano focal del microscopio, lo que disminuye la calidad de imagen. La técnica de la CM se basa en el principio de confocalidad: los caminos de iluminación y de detección comparten el mismo plano focal, solventando el problema de la luz desenfocada.⁷⁵

Figura 2.11 Microscopio confocal Konan NSP-9900. Extraída de internet⁹²

La resolución y ampliación de las imágenes tomadas con CM permite detectar *in vivo* los cambios morfológicos en células, o la presencia de estructuras anómalas. Esta calidad permite la detección de distintas distrofias corneales, entre las que se encuentra el queratocono.^{77,93} También permite la observación no invasiva de los nervios corneales, la medida del espesor epitelial y de la densidad de queratocitos estromales, o la presencia de puntos altamente reflectantes.⁹³⁻⁹⁵

El uso de la CM se utiliza ampliamente en cirugía refractiva para el estudio de los efectos de distintos procedimientos con el tiempo, tales como la respuestas curativa, evaluación estromal, espesor corneal o los mecanismos de halo corneal tras intervenciones LASIK.⁷⁵

2.2.3.5 Biomicroscopía por ultrasonidos de alta frecuencia

Esta tecnología es la base del equipo Artemis (ArcScan Inc, Morrison, Colorado, EEUU), siendo el único que la usa. Los sistemas de ultrasonidos permiten la visualización de las estructuras del segmento anterior incluso con presencia de opacidades. En general, la resolución y profundidad de penetración viene determinada por la frecuencia del transductor. La ultrasonografía tradicional del ojo completo usa un transductor de 10 MHz con una resolución aproximada de 150 μm . En la biomicroscopía por ultrasonidos de alta frecuencia (VHF), la mayor frecuencia de un transductor de 50 MHz incrementa la resolución en tejido hasta las 50 μm , pero a expensas de reducir la profundidad de penetración hasta los 4-5 mm, suficiente para tomar imágenes del segmento anterior (Figura 2.12). Para el escaneo corneal se pueden usar transductores de 100 MHz, aumentando la resolución hasta menos de 20 μm .

Figura 2.12 Córnea analizada con un ultrasonógrafo de alta frecuencia. Reproducida de Piñero⁷⁴

Se han descrito distintos usos de esta tecnología, entre los que se encuentran: análisis de tumores intraoculares⁹⁶, determinación de la posición de lentes fáquicas intraoculares⁹⁷, planificación de tratamientos de cirugía refractiva⁹⁸, estudio de patologías intraoculares⁹⁹ y análisis de algunas estructuras del segmento posterior.¹⁰⁰

La principal ventaja de esta tecnología es su precisión y su repetitividad, mientras que su principal inconveniente es el método de medida, que requiere contacto entre la córnea y la sonda, o en su caso poner al paciente en posiciones poco confortables y examinadores muy experimentados para llevar a cabo el procedimiento. Además, este aparato no aporta medidas de la curvatura corneal, sino simplemente un análisis anatómico del segmento anterior.⁷⁴

2.2.3.6 Tomografía de coherencia óptica

La tomografía de coherencia óptica (OCT) es un método de análisis transversal basado en la reflexión y la dispersión de la luz en las estructuras contenidas en la córnea. Medir las distintas reflectividades por métodos de interferometría óptica produce imágenes transversales de las estructuras corneales y del segmento anterior (Figura 2.13).¹⁰¹

En la interferometría óptica, la fuente de luz se separa en los haces de referencia y de medida. El haz de medida se refleja desde las estructuras oculares e interactúa con la luz de referencia reflejada desde el espejo de referencia, un fenómeno llamado interferencia. La interferencia coherente o positiva, caracterizada por una señal resultante incrementada, es medida por el interferómetro y, a continuación, se puede calcular la posición de la estructura reflejante del ojo.¹⁰¹ De esta forma, se pueden visualizar las estructuras del segmento anterior con grados de resolución muy altos. Esto permite obtener de forma sencilla imágenes de estructuras tan finas como las aletas de LASIK, el canal de Schlem, o las lentejas de la cirugía de queratoplastia lamelar.⁷⁵

Figura 2.13 Imagen corneal obtenida con OCT. Recuperada de Mehtani¹⁰²

Existen dos tipos de OCTs: los de dominio del tiempo, en los que variando la posición del espejo de referencia se producen imágenes transversales; y los del dominio de Fourier, en los que el espejo de referencia es fijo, y la transformación de Fourier del interferograma espectral da lugar a las imágenes transversales. Estos últimos tienen tiempos de adquisición más rápidos, y mayor resolución.⁷⁵

Sus principales ventajas son que el procedimiento de medida es rápido y fácil para el examinador y el paciente, y que no hay contacto corneal o con interfase específica para la medida. Sin embargo, esta tecnología tiene una importante limitación: no detecta estructuras situadas tras el iris, ni cualquier otra estructura opaca.⁷⁴

2.2.3.7 Oftalmómetro o queratómetro

El oftalmómetro aprovecha la capacidad de la superficie anterior de la córnea para comportarse como un espejo convexo. El oftalmómetro Helmholtz (Figura 2.14) proyecta cuatro puntos sobre la córnea (Figura 2.15), creando una imagen reflejada que puede ser analizada y convertida a datos de radios corneales, por medio de una ecuación que considera la distancia de la mira a la córnea, la imagen, y el tamaño de la mira.

Figura 2.14 Oftalmómetro Takagi KM-1 Led. Extraída de internet¹⁰³

Aunque aún se usan en la práctica oftalmológica, tienen importantes limitaciones, ya que:

- Miden solo en los 3 mm centrales, teniendo en cuenta solo el 6% de la superficie corneal
- Consideran que la córnea tiene una forma esfero-cilíndrica perfecta, lo que no es cierto.
- No aporta información de la zona periférica.
- No aportan información de la zona central fuera de los 4 puntos medidos.

Figura 2.15 Típico aspecto del queratocono detectado mediante oftalmómetro. Extraída de internet¹⁰⁴

2.2.3.8 Queratoscopia basada en discos de Plácido

Este sistema, desarrollado por Antonio Plácido en 1880, se basa en una diana circular que alterna círculos concéntricos de colores claros y oscuros, conocida como Disco de Plácido (Figura 2.16), que contiene a su vez una apertura central que permite observar los reflejos de estas bandas sobre la córnea del paciente, tomando estas una apariencia no circular si existe alguna anomalía en la superficie corneal anterior (como puede ser astigmatismo, queratocono o cicatrices corneales)¹⁰⁵.

Figura 2.16 Disco de Plácido. Extraída de internet¹⁰⁶

Los sistemas de medida actuales basados en discos de Plácido, colocan al paciente sentado mirando a una superficie con forma de semiesfera cóncava, que contiene el patrón de proyección, el cual se enfoca sobre la superficie anterior de la córnea. El patrón reflejado (Figura 2.17) es procesado por un ordenador que proporciona los datos de la configuración geométrica corneal en distintos formatos numéricos y gráficos.^{74,75}

Figura 2.17 Queratoscopia sobre la superficie corneal anterior

La clave para una medida precisa en este sistema, es contar con un alineamiento, un centrado y un enfoque certeros, lo que depende en gran medida de la pericia del examinador. Además, estos sistemas presentan algunas limitaciones:^{107,108}

- El disco central es oscuro, y por tanto no se puede obtener información de esta área central.
- Están diseñados para obtener información a lo largo de los meridianos de forma radial, no proporcionando información directa de la geometría corneal de forma circunferencial.
- Se usan aproximaciones basadas en algoritmos, lo que nos es adecuado si las corneas a analizar son muy irregulares.

2.2.3.9 Topografía de elevación por escaneo de hendidura

En los sistemas de escaneo por hendidura, también denominados sistemas basados en la reflexión de la luz sobre la córnea, se proyecta un haz de luz sobre la córnea a distintos ángulos. Este es el principio sobre el que se basa el equipo Orbscan II (Figura 2.18) (Bausch and Lomb Inc., Rochester, NY, EEUU), en el que una cámara de vídeo de alta resolución captura 40 hendiduras proyectadas sobre la córnea. La reflexión difusa se obtiene de la córnea, el iris y la lente. Por triangulación, se obtiene la información de las superficies corneales anterior y posterior, permitiendo así el cálculo de la profundidad de la cámara anterior, o la paquimetría corneal completa. Además, el equipo aporta información sobre la curvatura y la elevación de la superficie corneal posterior.

Figura 2.18 Orbscan II de Bauch & Lomb. Extraída de internet¹⁰⁹

2.2.3.10 Sistemas de imagen Scheimpflug

En los sistemas basados en la fotografía estándar, también denominados sistemas basados en la proyección de una hendidura de luz sobre la córnea, existen dos variantes en función de la disposición espacial del sistema de captura fotográfica.

Por un lado, se dispone de los sistemas basados en la fotografía estándar, que se caracterizan porque la profundidad de campo sobre el plano del motivo cuando las prolongaciones imaginarias de este, las del objetivo y las de la imagen no coinciden en punto alguno, es decir, las prolongaciones son paralelas (Figura 2.19-superior),¹¹⁰ siendo su principal limitación que si el sujeto no está situado paralelo al plano de imagen, solo queda enfocada una pequeña parte.

Por otro lado, estarían los sistemas basados en la imagen Scheimpflug, que se caracterizan porque una cámara fotográfica de gran formato consigue la máxima profundidad de campo en el plano del objeto cuando las prolongaciones imaginarias de éste, del plano del objeto y del plano de la imagen, coinciden en un punto común (Figura 2.19-inferior).¹¹⁰ Este principio se aplica en oftalmología para conseguir una mayor profundidad de campo, y así conseguir una mayor región enfocada.¹¹⁰

Figura 2.19 Fotografía convencional (sup.) vs fotografía Scheimpflug (inf.). Adaptada de Cavas²¹

El principal problema de la fotografía estándar reside en que, si el sujeto no está situado

Respecto al sistema de imagen Scheimpflug actualmente existen en el mercado las siguientes tecnologías: Pentacam, Sirius y Galilei.

2.2.3.10.1 Pentacam

El equipo Pentacam (Oculus, Optikgeräte GmbH, Wetzlar, Alemania) es uno de los sistemas basados en imagen Scheimpflug más conocidos. En concreto, el sistema usa una cámara rotativa para obtener 50 imágenes Scheimpflug del segmento anterior en menos de dos segundos. Cada imagen tiene 500 puntos de elevación verdadera, lo que hace un total de 25,000 puntos sobre el total de la superficie corneal (Figura 2.20). Sus principales ventajas son:

- 1) Analiza en alta resolución la totalidad de la córnea, incluyendo la zona central.
- 2) Permite medir con precisión córneas con irregularidades marcadas, como el queratocono, lo que no es posible con la imagen Plácido.
- 3) Permite calcular la paquimetría de limbo a limbo.

Figura 2.20 Informe de equipo Pentacam. Extraída de internet¹¹¹

El equipo Pentacam permite estudiar ambas superficies corneales (anterior y posterior), proporcionando medidas más repetibles y reproducibles de la potencia corneal que la tecnología de escaneo de hendidura.¹¹²

2.2.3.10.2 Galilei

El Analizador Dual Scheimpflug Galilei (Ziemer Group, Port, Suiza) es un sistema óptico de alta precisión para la topografía corneal y el análisis tridimensional del segmento anterior del ojo, basado en una cámara Scheimpflug rotativa de doble canal y un disco de Plácido. Este equipo (Figura 2.21) combina las ventajas de dos tecnologías: la imagen Plácido proporciona datos de curvatura de alta precisión, y la imagen Scheimpflug se encarga de capturar datos de elevación precisos. Al igual que el Pentacam, el Galilei suministra medidas repetibles de la curvatura corneal y otros parámetros anatómicos del segmento anterior.¹¹³

Figura 2.21 Equipo Galilei. Extraída de internet¹¹⁴

2.2.3.10.3 Sirius

El tomógrafo corneal Sirius (Construzione Strumenti Oftalmici, Milán, Italia) (Figura 2.22) combina una cámara Scheimpflug rotatoria capaz de fotografiar 25 secciones del segmento anterior, con un disco de Plácido de 22 anillos, lo que permite su análisis en profundidad. Se obtienen datos de curvatura tanto sagital como tangencial de ambas superficies corneales (anterior y posterior), potencia refractiva corneal, mapa paquimétrico y una estimación de los parámetros biométricos característicos de otras estructuras del segmento anterior, tales como el diámetro de la pupila o la profundidad de la cámara anterior. Una segunda cámara comprueba que el alineamiento del ojo sea correcto durante la toma de medidas.³⁷

La doble tecnología Scheimpflug-Plácido permite la obtención de 35.632 puntos de la superficie anterior y 30.000 de la posterior, en algo menos de un segundo. Con estas “nubes de puntos”, el software asociado al sistema reconstruye el mapa paquimétrico, y lo muestra en pantalla (Figura 2.23).³⁷

El equipo Sirius ha mostrado medidas consistentes de las curvaturas corneales anterior y posterior, así como para las profundidades de la cámara anterior, para ojos sanos y con queratocono.^{115,116}

Figura 2.22 Tomógrafo Sirius. Extraído de CSO Italia¹¹⁷

Figura 2.23 Informe de equipo Sirius mostrando los mapas de espesores para el segmento anterior. Extraído de CSO Italia¹¹⁷

Los tres equipos Scheimpflug analizados ofrecen medidas repetibles de la morfología corneal, e incluso más precisas si se comparan con otras tecnologías. Sin embargo, no existe concordancia entre las medidas que proporcionan, por lo que no pueden considerarse intercambiables.^{113,116,118,119}

Dado que los tiempos necesarios por los equipos Pentacam y Galilei para la rotación y adquisición simultánea de los datos descriptivos de la morfología corneal son superiores a los del Sirius, y que por tanto la medida puede verse afectada por la pérdida de estabilidad de la película lagrimal durante el proceso de adquisición de medidas ³⁷, el equipo utilizado para las investigaciones que componen la presente tesis ha sido tomógrafo Sirius.

2.3. Reconstrucción de la estructura hemiesférica del segmento anterior

La reconstrucción de las superficies que forman la estructura hemiesférica del segmento anterior se realiza a partir de los datos que constituyen la matriz de elevaciones, por lo que el algoritmo de reconstrucción para el ajuste de la superficie puede ser fuente de errores. Este algoritmo de reconstrucción puede utilizar dos enfoques matemáticos distintos para la reconstrucción de superficies: los denominados métodos modales y los métodos zonales.

2.3.1 Métodos modales

Los métodos matemáticos modales intentan aproximar la superficie por medio de una serie de funciones básicas que quedan definidas de forma global en todo el dominio de los datos. Estas funciones pueden verse influenciadas por el número concreto de

parámetros y la cantidad mínima precisa para poder recuperar la información superficial relevante, intentándose en todo caso evitar sobreajustes en el error de medición de los mismos.¹²⁰

Los métodos modales habitualmente usados en oftalmología para reconstruir superficies partiendo de ficheros altimétricos normalizados se sustentan en los llamados polinomios de Zernike,¹²¹ pudiéndose asociar las aberraciones básicas o la degradación que se produce en las imágenes de los sistemas ópticos, con los coeficientes de expansión de dichos polinomios.¹²²

Sin embargo, este procedimiento adolece de una serie de problemas que han sido discutidos ampliamente en la literatura científica.¹²⁰ En particular, el método puede ser impreciso en los casos de tomografías complejas, que son las de mayor interés clínico, y el número de polinomios de Zernike a usar en la reconstrucción en escenarios complejos, requiere valores más elevados y en consecuencia conlleva un mayor coste computacional.¹²³ La solución a este problema pasa por utilizar técnicas de estimación objetiva de la cantidad de coeficientes de expansión necesarios para el polinomio de reconstrucción, aunque su complejidad computacional es elevada,¹²⁴ y aunque se han propuesto varias técnicas alternativas, todas ellas presentan los mismos problemas que la de los polinomios de Zernike, incluso añaden otros, como una elevada complejidad computacional en el manejo del error residual, o la presentación de resultados controvertidos.

2.3.2 Métodos zonales

En los métodos matemáticos zonales el dominio de los datos se divide en subdominios más elementales y la superficie se aproxima en cada subdominio definido con independencia del resto.^{120,121}

Este método de reconstrucción se caracteriza porque presenta flexibilidad y precisión en el ajuste al considerar datos dentro de una zona delimitada para el cálculo de un punto de la superficie. Esto significa que la representación es local, y por tanto, las irregularidades locales no afectan a la representación global de la superficie, en contraste con las funciones globales adoptadas en la reconstrucción modal, como superficies cuadráticas o polinomios de alto orden que carecen de la información a nivel local y por tanto, las irregularidades locales o defectos de la superficie no se pueden representar adecuadamente mediante estos enfoques.^{12,125}

La herramienta más común son las Splines,¹²⁶ en particular las B-Splines,^{12,127} que son funciones numéricamente estables, flexibles y presentan gran precisión en el ajuste.^{128,129}

Las funciones B-Spline han sido exitosamente utilizadas en campo de la oftalmología, en las siguientes aplicaciones:

- Caracterización de la superficie topográfica.^{12,125,130-132}
- Caracterización del globo ocular.¹³³
- Diseño de lentes ópticas para el tratamiento del queratocono.¹³⁴

- Diseño de una prótesis de superficie ocular para una patología corneal denominada queratoglobo.¹³⁵

En resumen, en función de la descripción de los modelos y finalidades realizadas anteriormente, y en base a la singularidad que presenta la morfología de la córnea, sería de gran interés y actualidad poder crear un modelo que combine las ventajas de los modelos personalizados con las ventajas que presenta la reconstrucción zonal mediante funciones B-Spline a nivel local para la caracterización real de la morfogeometría de la estructura hemiesférica del segmento anterior, y que dicho modelo pudiera a su vez ser utilizado para el diagnóstico de determinadas patologías relacionadas con la modificación de la morfología de la citada estructura.

2.3.3 Diseño geométrico asistido por ordenador (DGAO)

En los últimos años la generación de modelos virtuales ha experimentado un importante avance tecnológico gracias al desarrollo de nuevas herramientas computacionales para la adquisición y procesamiento de imágenes,¹³⁶ posibilitando así la generación de formas tridimensionales¹³⁷ y la formulación de modelos de comportamiento que reproduzcan con más fidelidad la geometría de una estructura sólida.¹³⁸

Una de estas herramientas es el Diseño Geométrico Asistido por Ordenador (DGAO), el cual surgió para tratar de resolver las necesidades tecnológicas de las empresas en los sectores de la automoción y la aeronáutica. El DGAO permite estudiar aspectos geométricos y computacionales de cualquier entidad física compleja, como superficies y volúmenes para generar modelos virtuales,¹³⁹ los cuales se diferencian de los modelos físicos por no suponer un proceso destructivo y reducir los costes en términos de producción y tiempo.¹⁴⁰

Concretamente en el campo de la Ingeniería Biomédica, el desarrollo de modelos virtuales a través del DGAO permite caracterizar estructuras biológicas, estableciendo nuevos procedimientos de experimentación en el ámbito de la medicina¹³⁸, con diferentes finalidades:

- Diagnóstico clínico y posterior tratamiento de la patología mediante técnicas invasivas o no.¹⁴¹
- Análisis del comportamiento en un escenario patológico mediante métodos numéricos.¹⁴²
- Fines educativos mediante la generación de modelos virtuales 3D¹⁴³ o mediante la obtención del modelo físico utilizando impresoras 3D.¹⁴⁴

En el campo de la óptica se han encontrado algunos modelos que proponen el uso del DGAO para la generación únicamente de la superficie de la córnea y su posterior análisis óptico. El análisis óptico se realiza a partir de los puntos espaciales obtenidos por los tomógrafos corneales para su posterior utilización mediante las funciones cónicas o bicónicas anteriormente descritas¹⁴⁵ o a partir de las imágenes de los cortes realizados a ojos de pollo ex vivo.¹⁴⁶ Sin embargo, en ambos casos el modelo generado de la córnea

no resulta completo, ya que para generar la nube de puntos (NURBS) constitutivos de la superficie, que posteriormente será reconstruida a partir del uso del DGAO, se realiza una interpolación de los datos y además solo reconstruye la superficie de la córnea con un interés óptico.

Por lo tanto, resulta de especial interés poder crear un modelo personalizado in vivo representativo de la estructura hemiesférica del segmento anterior en un entorno virtual. Para ello se utilizará la herramienta denominada Diseño Geométrico Asistido por Ordenador (DGAO), la cual se presenta como una solución válida y eficaz para resolver y caracterizar superficies geométricas complejas.

2.4. Ectasias corneales: el queratocono

El diccionario de la Real Academia Española de la Lengua define “ectasia” como el “estado de dilatación de un órgano hueco”, pudiéndose encontrar definiciones similares en otros idiomas si se consulta un diccionario médico.¹⁴⁷ Históricamente, los oftalmólogos y optometristas han hecho uso de este término de manera amplia, abarcando con él muchas condiciones clínicas asociadas a cambios en la forma de la córnea. A pesar de que la mayoría de estas condiciones oculares no cumplen estrictamente con la definición médica de ectasia, un grupo internacional de oftalmólogos expertos ha consensuado recientemente que deben englobarse bajo este término aquellos “desórdenes ectásicos” primarios que afecten a la forma corneal.¹⁰

Esta denominación incluye por tanto a las conocidas como patologías degenerativas o distróficas, que son aquellas en las que se produce un adelgazamiento progresivo de la córnea asociado con una modificación de su curvatura, generándose una protrusión de la misma en ausencia de un proceso inflamatorio. Existen varias patologías dentro de este grupo, como son la degeneración marginal pelúcida y el queratoglobo, que junto con el queratocono (Figura 2.24) pueden presentar variaciones en la expresión fenotípica del mismo mecanismo patogénico, con diferente localización de la ectasia en función de la zona adelgazada.

Las ectasias corneales pueden clasificarse:

Según su origen. Se dividen en naturales (queratocono, queratoglobo, degeneración marginal pelúcida) o iatrogénicas (ectasias tras una cirugía refractiva).¹⁴⁸

Según su configuración. En función de su configuración principal pueden ser:

- Axial (central o paracentral): queratocono, iatrogénica.
- Generalizada: queratoglobo.
- Periférica: degeneración marginal pelúcida.

Figura 2.24 Imagen que muestra los distintos tipos de patologías distróficas. Extraída de internet¹⁴⁹

La patología ectásica más frecuente es el queratocono (KC o KCN)¹⁵⁰, un trastorno bilateral no inflamatorio con una prevalencia de 54.5 por cada 100,000, que se caracteriza por un adelgazamiento estromal que produce en la córnea una protrusión de forma cónica, trayendo consigo un deterioro visual que puede ir desde leve hasta muy severo.²

La protrusión suele manifestarse más frecuentemente en la zona paracentral (72 % de los casos) y más raramente en la región central (25% de los casos). Por lo tanto, el 97 % de los casos con queratocono queda localizado para un radio desde $r = 0$ mm hasta $r = 4$ mm, comprendiendo las regiones central y paracentral de la córnea.¹⁵¹

La descompensación geométrica causante de la forma cónica, se localiza principalmente en el cuadrante inferior de la zona periférica media,¹⁵² y se debe a de la pérdida de tenacidad que sufre la estructura corneal por la reorientación de su anatomofisiología.¹⁵³

Además, esta descompensación morfológica produce un incremento en las aberraciones ópticas de alto orden,¹⁵⁴ presentando los pacientes altos valores de astigmatismo irregular, siendo su principal aspecto refractivo la imposibilidad de una compensación óptica completa de su ametropía con lentes esfero-cilíndricas. Consecuentemente, su agudeza visual se ve disminuida con respecto a los pacientes que no presentan esta patología.¹⁵⁵

El incremento de curvatura que el queratocono produce en la estructura hemiesférica del segmento anterior no afecta únicamente a su cara anterior, sin que también la superficie posterior puede verse afectada, incluso en queratoconos incipientes o tempranos.^{156,157} Por eso, lograr una completa caracterización del comportamiento geométrico de la superficie corneal posterior cuenta con enorme interés en el campo de la oftalmología para la detección precoz del queratocono.^{123,158,159}

Por otra parte, los pacientes con queratocono presentan un astigmatismo distinto con respecto a los pacientes sanos. Las córneas en un escenario sano adquieren una configuración geométrica en forma de pajarita bastante simétrica. Sin embargo, en un

escenario patológico, el astigmatismo adquiere una configuración geométrica en forma de pajarita asimétrica, con una angulación diagonal entre los hemi-meridianos inferior y superior que no existe en las córneas sanas (Figura 2.25).²

Figura 2.25 Patrones topográficos de pajarita simétrica (izqda.) y asimétrica (drcha.).
Extraída de internet¹⁶⁰

Por último, cabe señalar que la asfericidad es otro de los elementos diferenciadores de una córnea queratocónica. Cuando existe queratocono se produce una modificación de la asfericidad hacia valores negativos en ambas superficies anterior y posterior, es decir, las superficies de una córnea sana se comportan geoméricamente como elipses más prolatas.^{35,113} Consecuentemente, la morfogeometría de una córnea enferma de queratocono mostrará una mayor curvatura en la región central que en la periférica, y tenderán en su comportamiento más hacia una parábola que hacia una elipse prolata, y por todo ello aumentará el valor de la asfericidad para los grados más elevados de queratocono.^{21,37}

Para poder distinguir una córnea sana de una con queratocono, es preciso realizar una caracterización anatómico-fisiológica de la enfermedad, tanto a nivel macroscópico como microscópico.

2.4.1 Caracterización macroscópica

Existen varios signos que permiten distinguir el queratocono a simple vista:¹⁷

- Signo de Munson. Se corresponde con una angulación característica que se produce en el perfil horizontal del margen palpebral inferior cuando se pide al paciente que mire hacia abajo (Figura 2.26).²
- Signo de Rizzuti. Se corresponde con un reflejo de forma cónica que se produce sobre la superficie de la cara anterior de la córnea cuando se la ilumina con un haz de luz desde la región temporal (Figura 2.27).¹⁶¹
- Síndrome de los párpados flexibles. Se presenta a menudo en sujetos varones obesos como posible indicio de queratocono. Así, la placa tarsal del párpado se vuelve flexible, y el paciente suele presentar además ectropión nocturno, ptosis y conjuntivitis papilar (Figura 2.28).¹⁶²

Figura 2.26 Signo de Munson. Extraída de internet¹⁶³

Figura 2.27 Signo de Rizzuti. Extraída de internet¹⁶⁴

Figura 2.28 Síndrome de párpados flexibles. Extraída de internet¹⁶⁵

2.4.2 Caracterización microscópica

El queratocono también se manifiesta a nivel microscópico en cada una de las cinco capas que presenta la estructura hemiesférica del segmento anterior.

Es importante señalar que, a pesar de no ser una capa corneal propiamente dicha, la película lagrimal ha sido objeto de estudio, dado su fácil acceso y el hecho de que algunos pacientes presentan una mayor concentración de residuos procedentes de la degradación del colágeno si existe queratocono.^{17,166}

2.4.2.1 Epitelio

Cuando el queratocono está presente, las capas epiteliales muestran, estructuralmente hablando, cuantiosas irregularidades, así como una reducción de espesor en su morfogeometría, principalmente en las regiones corneal central o paracentral.¹⁶⁷ En estas regiones se advierte un alargamiento no solo de las células de la superficie sino también de las aladas.

Por otra parte, la morfología de las células basales se torna más irregular y fragmentada, apareciendo concentraciones considerables de ferrita a niveles intra y extracelulares.^{17,37,168} Las concentraciones de ferrita se muestran en las células situadas en la base de la protrusión, con un color pardo-amarillento, que hace que se las designe clínicamente como Anillo de Fleischer. Estas células se localizan a nivel del epitelio en la base de la protrusión de la córnea, mostrándose físicamente por un color pardo-amarillento que indica la existencia de ferrita. La concentración de este reservorio de hierro se manifiesta en forma de anillo, por ello se le conoce clínicamente con el nombre de Anillo de Fleischer.^{17,37,169}

2.4.2.2 Capa de Bowman

Los signos del queratocono no aparecen en la capa de Bowman hasta estadios más avanzados. En ellos, se puede observar como la capa se rompe y se vuelve más discontinua en las zonas más cercanas al ápice del cono, que es el lugar en el que suelen ubicarse las cicatrices corneales, surgidas del crecimiento del epitelio por la ruptura de la capa.¹⁷⁰⁻¹⁷² Este tejido cicatricial afecta a la transparencia de la capa, puesto que muestra una distribución discontinua de un colágeno anormal, generado por la conversión de queratocitos en fibroblastos.^{172,173}

2.4.2.3 Estroma

El estroma anterior afectado por el queratocono muestra un sensible adelgazamiento por la compactación y pérdida de organización de las fibrillas de colágeno, siendo este más notorio conforme se agrava la enfermedad.^{17,37,174,175}

Por otra parte, puede observarse mediante microscopía confocal que las etapas avanzadas de queratocono muestran en la zona del estroma inferior bandas oscuras de colágeno que se orientan verticalmente y varían en altura, presentando una conexión con los llamados pliegues o estrías de Vogt. Estas estrías aparecen por el estrés mecánico

al que son sometidas las láminas de colágeno como consecuencia de la deformación sufrida por la estructura de tejidos corneales por el queratocono.^{37,147}

2.4.2.4 Membrana de Descemet

La membrana de Descemet no muestra cambios morfológicos significativos en los estadios temprano del queratocono. Sin embargo, en los estadios moderados hacen su aparición pliegues o estrías de Vogt, que pueden desembocar en una ruptura de la membrana en los estados más avanzados.^{17,37} Esto se asocia con una hidratación masiva de la córnea por la penetración del humor acuoso en el estroma, lo que genera un edema agudo en la región afectada llamado hidropesía (*hydrops* en inglés).²

2.4.2.5 Endotelio

El endotelio puede mantener su aspecto normal hasta que el queratocono alcanza los estados más avanzados. En ellos, se observa un alargamiento celular en la dirección de la protrusión o del cono, y un debilitamiento de la monocapa celular. Esto puede conducir a un desprendimiento de la membrana de Descemet, del endotelio e incluso de la parte posterior del estroma.

En cuanto al recuento de células endoteliales y su forma, se observa que en los estados más avanzados el número de células se mantiene o desciende ligeramente¹⁷⁶, aumentando su tamaño (polimegatismo) y perdiendo su hexagonalidad (pleomorfismo).¹⁷⁷

2.5. Sistemas de diagnóstico y clasificación

La ectasia corneal más importante es el queratocono, se trata de un término clínico establecido por los expertos y definido en los epígrafes anteriores.¹⁰ A pesar de ello, existen otras condiciones diferenciadas, que es preciso definir desde el punto de vista de la nomenclatura:

Queratocono clínico o queratocono. Se denomina así a la condición en la que la córnea muestra una protrusión de forma cónica, como resultado de un adelgazamiento progresivo no inflamatorio, asociada con procesos de cicatrización corneal.^{2,10} Se diagnostica de forma clínica, en base a combinaciones de evidencias clínicas y datos cualitativos y cuantitativos que aportan los topógrafos corneales.

Queratocono frustre, temprano o subclínico. Se designa así a la situación inversa a la del queratocono clínico, es decir, se trata de condiciones en las que la córnea presenta un patrón topográfico anormal, pero no están presentes ninguno de los signos clínicos que caracterizan la enfermedad, ni se sospecha de otras causas (traumatismos, lentes de contacto, etc.) que expliquen ese patrón alterado.¹⁷⁸

Pseudoqueratocono. Se denomina así a la condición en la que alteraciones topográficas compatibles con el queratocono clínico o subclínico, pero que tienen un origen diferente

a los de la patología queratocónica. Podrían deberse a un moldeo por lentes de contacto, traumatismos, errores de captura topográfica, frotamiento ocular, queratopatía punteada, cirugía previa, adelgazamiento corneal inflamatorio y/o secreción meibomiana excesiva.³⁷ Este tipo de patología no se incluye en el alcance de la presente tesis doctoral.

El diagnóstico clínico y la clasificación del queratocono se realizan actualmente a partir de unos índices o descriptores topográficos corneales que utilizan complicadas fórmulas, basadas fundamentalmente en perfiles de grosor, mapas paquimétricos y mapas de curvatura.^{11,151,179-186} Ahora bien, estos índices o descriptores no son obtenidos directamente por los equipos, ya que están calculados por algoritmos internos de los propios topógrafos. Estos algoritmos, además, pueden ser fuente de errores asociados a posibles suposiciones o hipótesis implícitas para simplificar los cálculos de los índices propuestos.¹⁸⁷

Por tanto, aunque existen robustos modelos predictivos publicados en la literatura científica que permiten cuantificar la descompensación geométrica generada por la asimetría presente cuando avanza la enfermedad, no se ha llegado a alcanzar un acuerdo acerca de la importancia relativa de los índices y las tecnologías que es preciso usar para detectar qué pacientes podrían tener complicaciones post-quirúrgicas (ectasia iatrogénica progresiva) cuando se evalúa su idoneidad para la cirugía refractiva.

Otro de los principales problemas a los que se enfrentan los oftalmólogos actualmente es la falta de acuerdo entre los expertos acerca de cómo caracterizar la ectasia corneal temprana.^{150,188-193} Esto se debe a la ambigüedad que rodea la definición de la enfermedad en su etapa preclínica,^{190,194} el tamaño de las muestras usadas para estos estudios,¹⁹⁴ y el hecho de que la mayoría de los índices empleados para la detección de la enfermedad son específicos de cada tecnología, lo que los hace no intercambiables.^{194,195}

2.5.1 Clasificaciones del queratocono

Existen numerosos estudios en la literatura científica que han validado índices o descriptores topográficos corneales, a fin de definir valores de corte que permitan distinguir las corneas normales de las queratocónicas. Así, algunos evalúan un parámetro de forma aislada, como la queratometría,¹⁹⁶ o la paquimetría,^{197,198} pero su aplicación es muy limitada, dado que solo contemplan una característica de la enfermedad.

Por tanto, las clasificaciones más útiles desde un punto de vista clínico, son las multivariantes, ya que tienen en cuenta una combinación de distintas evidencias del queratocono. Estas pueden fundamentarse en aspectos morfológicos (aberraciones), queratométricos (curvatura y asfericidad), biomicroscópicos, o en el grado de agudeza visual, entre otras.^{11,155,199-205}

De entre todas las existentes, en la presente tesis se ha optado por estudiar el comportamiento de los nuevos parámetros morfogeométricos propuestos para la

detección y clasificación clínica del queratocono únicamente para tres clasificaciones: la de Amsler-Krumeich²⁰⁶, la denominada Amsler modificada por aberrometría o Alió-Shabayek²⁰⁷, y finalmente, la clasificación en función de la agudeza visual corregida o RETICS.^{155,208}

2.5.1.1 Clasificación de Amsler-Krumeich

Se trata de una de las clasificaciones más utilizadas en el campo de la oftalmología, siendo la más clásica de todas. Se basa principalmente en criterios queratométricos, pero también considera otros parámetros como la refracción y la paquimetría, entre otros signos clínicos observados durante la evaluación del paciente. Su principal inconveniente es que no tiene en cuenta que, dependiendo de su refracción manifiesta, los pacientes pueden mostrar importantes fluctuaciones refractivas causadas por la multifocalidad generada por la forma corneal.

La clasificación fija cuatro niveles (Tabla 2.2) que se corresponden con la severidad creciente de la enfermedad. Se puede dar casos en los que se solapen valores de los estadios de clasificación, optándose entonces por clasificar la patología en el grado que mayor número de criterios cumpla.

Tabla 2.2 Clasificación de acuerdo al criterio de Amsler-Krumeich. Adaptada de Cavas²¹

Estadio	Miopía y/o astigmatismo inducido (D)	Valores de queratometría central media (D)	Paquimetría mínima (μm)	Otros signos, cicatrices, encurvamiento
I	Hasta - 5 D	≤ 48 D		Ausencia de cicatrices y encurvamiento localizado excéntrico
II	Entre - 5 D y - 8 D	≤ 53 D	$> 400 \mu\text{m}$	Ausencia de cicatrices
III	Entre - 8 D y - 10 D	> 53 D	Entre $300 \mu\text{m}$ y 400	Ausencia de cicatrices
IV	Refracción no medible	> 55 D	$200 \mu\text{m}$	Cicatrices corneales centrales

2.5.1.2 Clasificación de Alió-Shabayek

Con el desarrollo tecnológico de la topografía corneal, los aparatos fueron capaces de proporcionar datos aberrométricos corneales, dando lugar a esta escala.²⁰⁷ Esta escala se adapta mejor a los métodos diagnósticos usados actualmente, incorporando a los factores antes expuestos, valores aberrométricos de la cara anterior de la córnea, con especial hincapié en las aberraciones tipo coma. El uso de las aberraciones tipo coma (y en general, las aberraciones de alto orden) se justifica por el hecho de que estas tienden a aumentar conforme aumenta la protrusión del cono, y por tanto, también lo hacen con el aumento de la enfermedad.

Esta escala establece los grados indicados en la Tabla 2.3.

Tabla 2.3 Clasificación de acuerdo al criterio de Alió-Shabayek. Adaptada de Alió²⁰⁷

Estadio	Valor RMS de la aberración en forma de coma (coma-like) (μm)	Valores de queratometría central media (D)	Paquimetría mínima (μm)	Otros signos, cicatrices, encurvamiento
I	De 1.5 a 2.5	≤ 48		Ausencia de cicatrices
II	> 2.5 y ≤ 3.5	> 48 y ≤ 53	$> 400 \mu\text{m}$	Ausencia de cicatrices
III	> 3.5 y ≤ 4.5	> 53 y ≤ 55	Entre $300 \mu\text{m}$ y 400	Ausencia de cicatrices
IV	> 4.5	> 55	$200 \mu\text{m}$	Cicatrices corneales centrales

2.5.1.3 Clasificación RETICS

Las clasificaciones utilizadas hasta la aparición de la clasificación RETICS tenían en cuenta la morfología topográfica de la enfermedad, pero no tenían en cuenta otras variables clínicas relacionadas con la calidad visual del paciente. Desde un punto de vista óptico, los pacientes aquejados de queratocono muestran una agudeza visual corregida lejana (CDVA) ciertamente deteriorada, en el sentido de que su rendimiento visual empeora con la progresión del grado de severidad de la enfermedad.

La clasificación RETICS, nacida de los estudios multicentro realizados en el seno de la Red Temática de Investigación Cooperativa en Salud, determina cinco grados para la enfermedad, basándose en un parámetro funcional (CDVA) y no puramente geométrico (Tabla 2.4).^{155,208}

Tabla 2.4 Clasificación grado de queratocono escala RETICS. Extraída de internet¹⁶⁰

GRADO	TOPO	CDVA	K	Astigmatismo Interno (D)	RMS coma-like (μm)	Q 8mm	Paquimetría (μm)
I		> 0.9	44.75 a 45.40D	1.59 a 2.14	1.16 a $1.52 \mu\text{m}$	-0.22 a -0.05	495 a $510 \mu\text{m}$
II		0.9 a 0.6	46.03 a 46.93D	2.18 a 2.79	1.82 a $2.31 \mu\text{m}$	-0.48 a -0.22	475 a $493 \mu\text{m}$
III		0.6 a 0.4	48.21 a 49.27D	3.04 a 4.17	2.65 a $3.32 \mu\text{m}$	-0.95 a -0.58	451 a $470 \mu\text{m}$
IV		0.4 a 0.2	51.42 a 53.12D	3.68 a 4.58	3.45 a $4.42 \mu\text{m}$	-1.21 a -0.83	433 a $454 \mu\text{m}$
IV-PLUS		< 0.2	$> 57\text{D}$	> 5.50	$> 5.50 \mu\text{m}$	> -1.50	360 a $420 \mu\text{m}$

Hipótesis y objetivos

3.1. Hipótesis y objetivos

El presente trabajo de investigación ha girado en torno a la siguiente hipótesis:

Es posible detectar (fase preclínica) y diagnosticar (fase clínica), desde un punto de vista óptico-geométrico, la progresión de la ectasia corneal, mediante la definición de patrones de comportamiento topográficos, optométricos y celulares.

Los objetivos de trabajo planteados para corroborar la hipótesis planteada, han sido los siguientes:

3.1.1 Objetivo Principal

- A. Definir y validar la capacidad de distintos parámetros morfogeométricos (lineales, superficiales y volumétricos) para la caracterización de la estructura hemiesférica del segmento anterior del ojo humano, tanto en ojos sanos como con queratocono, y analizar la variación de estos parámetros en diversos escenarios clínicos (incipiente, desarrollo, progresión, etc.) mediante técnicas de geometría computacional, a fin de poder determinar su potencial clínico.

3.1.2 Objetivos Secundarios

- B. Revisar los diferentes sistemas univariantes y multivariantes de diagnóstico y clasificación de las ectasias corneales basados en conjuntos de datos obtenidos mediante topógrafo Scheimpflug, incorporándoles un modelo corneal virtual creado mediante herramientas de geometría computacional, que a su vez, defina y valide parámetros morfogeométricos (1D, 2D y 3D, a nivel global y a nivel microscópico), ópticos (óptica-geométrica, óptica adaptativa, etc.) y tomográficos (espesor estructural global)
- C. Proponer un modelo predictivo integral de detección temprana de la patología corneal que establezca la probabilidad de haber clasificado correctamente cada caso, y validarlo frente al KC-Screening de los tomógrafos corneales.
- D. Validación del nuevo concepto en las diferentes clasificaciones clínicas de valoración de la progresión de la enfermedad (RETICS, Alió-Shabayek, Amsler-Krumeich).
- E. Proponer un nuevo concepto para mejorar la educación del paciente y la calidad asistencial, y validarlo en la práctica clínica mediante la impresión 3D de las córneas de los pacientes en materiales biodegradables.

En base a los objetivos enumerados, se relacionan las publicaciones que conforman la presente tesis doctoral y que cumplen cada uno de ellos:

Objetivo A:

Todos los artículos (1 a 12) y las patentes (A a C) contribuyen a lograr este objetivo.

Objetivo B:

Study of Morpho-Geometric Variables to Improve the Diagnosis in Keratoconus with Mild Visual Limitation. (Symmetry).

Assessment of the Association between In Vivo Corneal Morphogeometrical Changes and Keratoconus Eyes with Severe Visual Limitation. (J Ophthalmol.).

Automatic image processing applied to corneal endothelium cell count and shape characterization. (Dyna).

Efficacy of Morpho-Geometrical Analysis of the Corneal Surfaces in Keratoconus Disease According to Moderate Visual Limitation. (Lecture Notes in Mechanical Engineering, Springer).

Morphogeometric analysis for characterization of keratoconus considering the spatial localization and projection of apex and minimum corneal thickness point. (Journal of Advanced Research).

Software informático CoEnCell. (Número de solicitud: MU-164-2020).

Objetivo C:

Early keratoconus detection by patient-specific 3D modelling and geometric parameters analysis. (Dyna).

Detection of Subclinical Keratoconus Using Biometric Parameters. (Lecture Notes in Computer Science, Springer).

Subclinical keratoconus detection with three-dimensional (3-D) morphogeometric and volumetric analysis. (Acta Ophthalmologica).

A Machine-Learning Model Based on Morphogeometric Parameters for RETICS Disease Classification and GUI Development. (Applied Sciences).

EMKLAS: A New Automatic-Scoring System for Early and Mild Keratoconus Detection. (Translational Vision Science & Technology).

Software informático KERATOSCORE. (Número de solicitud: MU-170-2020).

Software informático EMKLAS. (Número de solicitud: MU-171-2020).

Objetivo D:

Comparison of Corneal Morphologic Parameters and High Order Aberrations in Keratoconus and Normal eyes. (Lecture Notes in Computer Science, Springer).

Objetivo E:

3D Printed Personalized Corneal Models as a Tool for Improving Patient's Knowledge of an Asymmetric Disease. (Symmetry).

Materiales y métodos

4.1. Pacientes

4.1.1 Selección

Los datos clínicos de pacientes utilizados en las publicaciones que componen la presente tesis, fueron seleccionados aleatoriamente de entre todos los disponibles en el Biobanco de datos “Iberia” (Universidad Miguel Hernández de Elche y adscrito al Comité Ético y Científico de la Red Valenciana de Biobancos) de datos oficial “Iberia”, creada para la Red Nacional de Investigación Clínica en Oftalmología RETICS-OFTARED. Se seleccionó un único ojo de cada sujeto, de acuerdo con una secuencia dicotómica de 0 y 1 creada por un software específico, a fin de evitar cualquier sesgo de correlación entre los dos ojos de un mismo individuo.³⁷

Los distintos estudios se supervisaron en la Unidad de Queratocono de Vissum Corporación S.L. en Alicante, España (un centro afiliado con la Universidad Miguel Hernández de Elche), y fueron respaldados por el Comité Ético de la institución, ciñéndose rigurosamente a los estándares de la Declaración de Helsinki (7ª revisión, octubre de 2013, Fortaleza, Brasil), por lo que los paciente fueron informados de los objetivos de los estudios antes de la toma de medidas, y firmaron un documento consintiendo su participación en ellos.

El número total de ojos seleccionados, fue posteriormente separado en dos grupos: por una parte ojos sanos o “control”, y por otra, ojos diagnosticados con queratocono o “KC”, de acuerdo a criterios clínicos estándar^{2,209}. Estos criterios se basan en los siguientes signos: patrón de topografía corneal anterior en forma de pajarita asimétrica, índice KISA ≥ 100 , y una o más evidencias biomicroscópicas de queratocono, tales como adelgazamiento corneal significativo, estrías de Vogt, anillo de Fleischer o protusión cónica alrededor del ápex corneal. Haber sido sometido a cirugías previas, tales como crosslinking del colágeno corneal o la inserción de anillos intraoculares, la presencia de opacidades y la evidencia de otras enfermedades oculares activas, tales como síndrome del ojo seco, glaucoma o queratitis herpética, fueron los criterios de exclusión considerados para el grupo KC.

El criterio de inclusión en el grupo de control fue no cumplir ninguno de los criterios específicos de exclusión: haber llevado lentes de contacto durante las 4 semanas previas a la revisión ocular, haberse sometido a alguna cirugía previa o presentar alguna otra comorbilidad ocular que pudiese afectar a los parámetros estudiados.

4.1.2 Protocolo de examen

Se realizó un examen clínico del ojo de todos y cada uno de los pacientes estudiados, que incluyó la medida de la agudeza visual sin corrección (UDVA), agudeza visual corregida (CDVA), anamnesis, refracción objetiva y subjetiva, microscopía confocal, biomicroscopía con lámpara de hendidura, tonometría de Goldman, biometría ocular (IOL-Master, Zeiss, Alemania) y análisis de la estructura hemiesférica mediante tomógrafo Sirius (Construzione Strumenti Oftalmici, Italia).

La versión del software utilizada para los estudios que nos ocupan ha sido la 1.0.5.72 (Phoenix, CSO, Florencia, Italia), aunque para los parámetros morfogeométricos, y a fin de evitar sesgos introducidos por el algoritmo interno del software, se ha trabajado con los ficheros de “datos en bruto” extraídos directamente del aparato como matrices de datos separados por comas (.csv).

Todas las medidas fueron realizadas por un examinador experimentado, llevándose a cabo un total de tres medidas consecutivas, seleccionándose la mejor (la topografía con la mayor calidad de adquisición en la imagen Scheimpflug y queratoscopia) como medida a usar en el estudio.

De acuerdo con el resultado de los exámenes previamente expuestos, y en función del estudio a realizar, cada caso de queratocono se clasificó en términos de severidad de acuerdo con las clasificaciones de Amsler-Krumeich^{152,206}, Alió-Shabayek^{152,207} o RETICS^{152,208}

Se registraron y evaluaron estadísticamente los parámetros demográficos, óptico-clínicos, y paquimétricos descritos en los siguientes subapartados.

4.1.2.1 Parámetros demográficos

- Edad: El rango de edad de los pacientes varió de los 7 a los 99 años.
- Género: En todos los estudios se procuró que la proporción de hombres / mujeres estuviese balanceada, para evitar sesgos por este motivo, no superándose en ningún caso la ratio 65 / 35 % ni 35 / 65 %.

4.1.2.2 Parámetros óptico-clínicos

Los principales parámetros óptico-clínicos utilizados en los estudios que componen esta tesis, se han descrito brevemente en la tabla siguiente (Tabla 5):

Tabla 4.1 Parámetros óptico-clínicos

Parámetro (Unidad)	Definición
Axis / Eje (°)	Es el meridiano de la lente que está a 90 grados del meridiano que contiene la potencia del cilindro. ²¹⁰
Sphere / Esfera (D)	Potencia de una lente, en dioptrías (D), para la corrección de miopía o hipermetropía. Significa que la corrección es 'esférica' o igual en todos los meridianos del ojo. ²¹⁰
Cylinder / Cilindro (D)	Potencia de la lente para la corrección del astigmatismo. Significa que la potencia adicionada para corregir el astigmatismo no es esférica, sino que está tallada de manera que a un meridiano no se le ha añadido curvatura y que el meridiano perpendicular a este, contiene la máxima potencia y la curvatura de la lente para la corrección. ²¹⁰

Spherical equivalent / Equivalente esférico (D)	Es la refracción esférica que conjuga la retina con el círculo de menor difusión del Conoide de Sturm. Indicaría la potencia esférica con la que el paciente con astigmatismo alcanzaría mejor agudeza visual. ²¹¹
J_0 (D)	Vector queratométrico de potencia, calculado en función de la toricidad corneal (AST) y la orientación del meridiano más plano (φ_1), de acuerdo a la ecuación: ²¹² $J_0 = (-AST / 2) \text{Coseno} (2 \varphi_1)$
J_{45} (D)	Vector queratométrico de potencia, calculado en función de la toricidad corneal (AST) y la orientación del meridiano más plano (φ_1), de acuerdo a la ecuación: ²¹² $J_{45} = (-AST / 2) \text{Seno} (2 \varphi_1)$
B (D)	Magnitud de curvatura, calculada en función de la toricidad corneal (AST), radio de curvatura del meridiano más plano (K_1) y los vectores J_0 y J_{45} , de acuerdo a las ecuaciones: ²¹² $M = K_1 + (AST / 2) ; B = (M^2 + J_0^2 + J_{45}^2)^{1/2}$
CDVA (LogMAR, Snellen)	Agudeza visual corregida. Da cuenta de la nitidez de la visión. Ésta se cuantifica mediante la capacidad del paciente para identificar letras o números en una tabla optométrica estandarizada, desde una distancia de visualización específica ²¹³
Q 4.5 mm anterior	Asfericidad. El índice Q toma como referencia una curvatura central de 3 a 4 mm de la córnea; y describe la tasa de cambio de la curvatura de la córnea desde el centro hasta la periferia ($Q = 0$ en córneas esféricas, $Q < 0$ en córneas prolatas y $Q > 0$ en córneas oblatas). En este caso, mide la asfericidad corneal a 4.5 mm del centro ³⁴
Q 8.0 mm anterior	Mide la asfericidad corneal a 8 mm del centro ³⁴
Total RMS (μm) ó HOA RMS (μm)	Aberraciones de alto orden. Son distorsiones adquiridas por el frente de onda de luz cuando pasa a través de un ojo con irregularidades en sus componentes refractivos (película lagrimal, córnea, humor acuoso, lente cristalina y humor vítreo), y se caracterizan mediante expresiones matemáticas basadas en los polinomios de Zernike. El orden de éstos hace referencia a la complejidad de la forma del frente de onda que emerge de la pupila (a mayor orden, mayor complejidad). Se mide su valor cuadrático medio, o RMS. ^{214,215}
Astigmatism RMS / Astigmatismo RMS	Valor RMS de la aberración correspondiente al término de segundo orden del polinomio de Zernike, $Z_2^{\pm 2}$. ²¹⁵

Coma RMS (μm)	Valor RMS de la aberración en coma, correspondiente al término de tercer orden del polinomio de Zernike, $Z_3^{\pm 1}$. ²¹⁵
SphericalAbZ40 / Spherical aberration / Aberración esférica (μm)	Valor de la aberración esférica, correspondiente al término de cuarto orden del polinomio de Zernike, Z_4^0 . ²¹⁵
Spherical-like RMS (μm)	Valor RMS de la aberración correspondiente a los términos de cuarto y sexto orden del polinomio de Zernike. ²¹⁵
Coma-like RMS (μm)	Valor RMS de la aberración correspondiente a los términos de tercero y quinto orden del polinomio de Zernike. ²¹⁵
IOP / PIO (mm Hg)	Presión intraocular. Es la presión que ejercen los líquidos intraoculares contra la pared del ojo, la cual es necesaria para que este órgano se mantenga distendido. ²¹⁶

4.1.2.3 Parámetros paquimétricos

Se han utilizado los siguientes parámetros para caracterizar el espesor corneal en la zona central (3 mm de diámetro) y paracentral (de los 3 a los 8 mm de diámetro)³⁷ de la córnea (Tabla 6):

Tabla 4.2 Variables paquimétricas

Parámetro (Unidad)	Definición
CCT (μm)	Espesor corneal central, definido como la distancia entre la cara anterior y posterior de la hemiesfera en la zona central.
MCT (μm)	Mínimo espesor corneal, definido como la mínima distancia entre la cara anterior y posterior de la hemiesfera.
Superior (μm)	Mínimo espesor corneal de los puntos en la zona superior.
Inferior (μm)	Mínimo espesor corneal de los puntos en la zona inferior.
Nasal (μm)	Mínimo espesor corneal de los puntos en la zona nasal.
Temporal (μm)	Mínimo espesor corneal de los puntos en la zona temporal.

4.2. Análisis morfogeométrico macroscópico

4.2.1 Caso general

El procedimiento de análisis morfogeométrico utilizado en la mayoría de los estudios que conforman esta tesis doctoral consta de las siguientes etapas (Figura 4.1):

Figura 4.1 Esquema del procedimiento de generación del modelo corneal virtual

1. Generación de la nube de puntos: El tomógrafo Sirius realiza un proceso de escaneo de las superficies corneales mediante dos cámaras estereoscópicas que comprenden una región de espacial de 180° (cubren la totalidad de la estructura hemisférica), en concreto el algoritmo de visión del equipo es capaz de escanear un conjunto de 256 puntos contenidos sobre cada anillo concéntrico para radios que van desde 0 hasta 6 mm y en pasos de 0.2 mm, estos anillos son los Discos de Plácido proyectados en la superficies corneales. Los datos espaciales escaneados pueden ser obtenidos del algoritmo de visión mediante un conjunto discreto y finito (matriz de datos) de puntos en coordenadas polares (radios y semi-meridianos), sin embargo durante el proceso de escaneo del algoritmo no puede leer todos los puntos de los anillos concéntricos debido a errores extrínsecos¹⁵², por lo que ese dato espacial lo interpreta el equipo en la matriz de datos como un dato -1000.

Respecto a la matriz de datos espaciales obtenidos del algoritmo de visión, cada columna representa un semi-meridiano (256 puntos por cada radio). Cada fila representa una muestra tomada siguiendo la trayectoria de un círculo de radio $i \cdot 0.2$ mm, siendo "i" el número de la fila, mientras que cada columna representa una muestra tomada siguiendo la trayectoria de un semi-meridiano en la dirección de $j \cdot 360/256u$, siendo "j" el número de la columna. Además, se generó otra matriz de datos $[i,j]$, en la que cada valor Z representaba el punto P ($i \cdot 0.2$, $j \cdot 360/256u$) en

coordenadas polares. Con esta organización, se definió una nube de puntos para la zona comprendida entre el vértex corneal normal (centro geométrico de la córnea, $r = 0$ mm) y la zona periférica media ($r = 4$ mm), sustentándose este criterio principalmente en motivos geométricos^{12,217} y clínicos¹⁵¹, ya que esta es la región de análisis que suele incluir la mayor parte de la información relativa a la morfología corneal, no solo para ojos sanos, sino también para los enfermos.

Una vez definidas las matrices, se procedió a programar un algoritmo en Matlab® V R2014 (Mathworks, Natick, EEUU) para

- i. Transformar las coordenadas expresadas en polares a formato Cartesiano.
 - ii. Eliminar los ficheros topográficos que contuvieran lecturas de datos erróneas en coordenadas polares (marcadas con el valor -1.000).
2. Reconstrucción geométrica de la superficie: Se realizó la importación de las nubes de puntos representativas de la arquitectura corneal al software de reconstrucción de superficies Rhinoceros® V 5.0 (MCNeel & Associates, Seattle, EEUU). Este software usa un modelo matemático para generar superficies basadas en B-splines racionales no uniformes (NURBS)¹²⁹, y su validez en el campo de la ingeniería biomédica²¹⁸⁻²²¹ y la oftalmología^{12,217,222-224} ha sido ampliamente demostrada, ya que estas funciones se basan en una distribución densa y uniforme de puntos de muestra escaneados, que confieren la fidelidad geométrica del modelo original a la nueva estructura generada. En los estudios que componen esta tesis, se utilizó la función “parche” de Rhinoceros para encontrar la superficie que mejor se ajustase a la nube de puntos, minimizando la separación nominal entre la nube de puntos tridimensional y la superficie generada. Esta desviación puede ser calculada posteriormente por el software, dando un valor medio del error de distancia para la superficie solución²²⁵. Los ajustes de configuración del programa usados para la función fueron los siguientes:

- Espaciado entre puntos de muestra (spacing): 256
- Planos de medida (span planes) de superficie en “u” y en “v”: 255
- Rigidez de la superficie solución (stiffness) 1

Con este software generamos las superficies anterior, posterior y perimetral, lo que nos permite obtener el modelo sólido completo de la córnea.

3. Modelado sólido: El sólido obtenido en el paso previo fue exportada al software de modelado sólido SolidWorks® V 2012 (Dassault Systèmes, Vélizy-Villacoublay, Francia). Usando este software, se analizó la geometría del modelo personalizado que representa la geometría corneal¹².
4. Cálculo y análisis de parámetros morfogeométricos: Tras obtener el modelo 3D personalizado de la estructura hemiesférica, este fue usado para definir un conjunto de variables morfogeométricas (angulares, lineales, superficiales y volumétricas) que

la caracterizan, tanto a nivel macroscópico como microscópico. La Tabla 7 siguiente resume las variables morfogeométricas utilizadas en los estudios que componen esta tesis doctoral.

Tabla 4.3 Variables morfogeométricas estudiadas en el modelo 3D personalizado

Variable morfogeométrica	Abreviatura	Descripción
Centro de masas X, Y, Z [mm]	$CM_x / CM_y / CM_z$ $COM_x / COM_y / COM_z$ $C_x / C_y / C_z$	Coordenadas X, Y, Z del centro de masas del sólido.
Desviación neta del centro de masas en el plano XY [mm]	Dev_{xy}	Módulo proyectivo XY del centro de masas del sólido.
Desviación del ápex anterior / posterior [mm]	$D_{antapex} / D_{postapex}$ $Dev_{aapex} / Dev_{papex}$ $D_{apexant} / D_{apexpost}$	Mínima distancia entre el punto de máxima curvatura anterior / posterior (ápex anterior / posterior) y el eje óptico que pasa por el centro geométrico de la superficie corneal anterior / posterior. (Figura 4.2 - B)
Diferencia de desviaciones del ápex anterior y posterior [mm]	$D_{apexant} - D_{apexpost}$	Diferencia media entre la distancia del ápex anterior al eje óptico y la del ápex posterior a este mismo eje.
Desviación del punto de mínimo espesor anterior / posterior [mm]	$D_{antmct} / D_{postmct}$ $Dev_{aminthk} / Dev_{pminthk}$ $D_{mctant} / D_{mctpost}$	Mínima distancia entre el punto de mínimo espesor anterior / posterior y el eje óptico que pasa por el centro geométrico de la superficie corneal anterior / posterior. (Figura 4.2 - C)
Diferencia de desviaciones de los puntos de mínimo espesor anterior y posterior [mm]	$D_{mctant} - D_{mctpost}$	Diferencia media entre la distancia del punto de mínimo espesor anterior al eje óptico y la del punto de mínimo espesor posterior a este mismo eje.
Ángulo eje geométrico-línea de ápex [°]	$GA-AP^\circ$	Ángulo mínimo entre el eje geométrico (eje óptico) y la línea definida por los ápex anterior y posterior de las superficies corneales que se cruzan en el espacio (Figura 4.4).
Ángulo eje geométrico-línea de mínimo espesor [°]	$GA-MCT^\circ$	Ángulo mínimo entre el eje geométrico (eje óptico) y la línea definida por los puntos de mínimo espesor anterior y posterior de las superficies corneales que se cruzan en el espacio (Figura 4.4).

Ángulo línea de ápex-línea de mínimo espesor [°]	AP-MCT °	Ángulo mínimo entre las líneas definidas por los ápex anterior y posterior y por los puntos de mínimo espesor anterior y posterior de las superficies corneales que se cruzan en el espacio (Figura 4.4).
Distancia entre ápex y punto de mínimo espesor de la cara anterior [mm]	Anterior AP-MCTd	Mínima distancia entre el ápex y el punto de mínima espesor de la superficie corneal anterior (Figura 4.4).
Distancia entre ápex y punto de mínimo espesor de la cara posterior [mm]	Posterior AP-MCTd	Mínima distancia entre el ápex y el punto de mínima espesor de la superficie cornea posterior (Figura 4.4).
Área de la superficie corneal anterior / posterior [mm ²]	A_{ant} / A_{post} $Corarea_{ant} / Corarea_{pos}$ $ACSA_{A-S} / PCSA_{A-S}$	Área de las superficies frontal/exterior y trasera/interior (Figura 4.2 - A).
Área total de la superficie corneal [mm ²]	A_{tot} $Corarea_{tot}$ $TCSA_{A-S}$	Suma de las áreas anterior, posterior y perimetral del modelo sólido generado. (Figura 4.2 - A)
Área en el plano sagital por el ápex anterior [mm ²]	$A_{apexant}$	Área de la córnea contenida en el plano sagital que pasa por el eje óptico y por el punto de mayor curvatura (ápex) de la superficie corneal anterior (Figura 4.2 - B).
Área en el plano sagital por el ápex posterior [mm ²]	$A_{postapex}$ $Splarea_{papex}$ $SPAP_{A-S}$ $A_{apexpost}$	Área de la córnea contenida en el plano sagital que pasa por el eje óptico y por el punto de mayor curvatura (ápex) de la superficie corneal posterior (Figura 4.2 - B).
Área en el plano sagital por el punto de mínimo espesor posterior [mm ²]	$A_{postmct}$ $Splarea_{minthk}$ $SPAMTP_{A-S}$ $A_{mctpost}$	Área de la córnea contenida en el plano sagital que, conteniendo al eje óptico, pasa por el punto de mínimo espesor de la superficie corneal posterior (Figura 4.2 - C)..

Volumen corneal total [mm ³]	CV Vol _{tot} TCV _{A-S}	Volumen comprendido entre las superficies frontal, trasera y periférica del modelo sólido generado.
Volumen corneal en el ápex anterior a radio R-x [mm ³]	CV _{A-S R-x} VOL _{Laap}	Volumen contenido en la intersección del modelo sólido de la córnea con un cilindro de revolución de radio “x” y eje definido por la línea recta perpendicular al plano tangente al ápex anterior. Se calcula para distintos radios, en incrementos de paso 0.1 mm, desde r = 0.1 hasta r = 1.5 mm (Figura 4.3).
Volumen corneal en el ápex posterior a radio R-x [mm ³]	VOL _{pap}	Volumen contenido en la intersección del modelo sólido de la córnea con un cilindro de revolución de radio “x” y eje definido por la línea recta perpendicular al plano tangente al ápex posterior. Se calcula para distintos radios, en incrementos de paso 0.1 mm, desde r = 0.1 hasta r = 1.5 mm (Figura 4.3).
Volumen corneal en los puntos de mínimo espesor a radio R-x [mm ³]	VOL _{mct}	Volumen contenido en la intersección del modelo sólido de la córnea con un cilindro de revolución de radio “x” y eje definido por los puntos de mínimo espesor anterior y posterior. Se calcula para distintos radios, en incrementos de paso 0.1 mm, desde r = 0.1 hasta r = 1.5 mm (Figura 4.3).
Número de células endoteliales [n]	n	Conteo de células endoteliales por unidad de superficie, generalmente por mm ² .
Porcentaje de hexagonalidad [%]	% H	Se define como la aproximación de la relación entre el área/perímetro ² en cada una de las celdas, a la ideal de un hexágono regular, que toma el valor 0.07216875, medida en %.

Figura 4.2 Las variables morfogeométricas relacionadas con: A) áreas, B) puntos ápex, C) puntos de mínimo espesor. Adaptada de Cavas F.²¹

Figura 4.3 Procedimiento para el cálculo del volumen cilíndrico corneal R-x centrado en: A) ápex anterior, B) ápex posterior y C) eje que une los puntos de mínimo espesor anterior y posterior.

Figura 4.4 Variables angulares medidas sobre un ojo sano y un ojo queratocónico

4.2.2 Caso particular: impresión 3D de modelos personalizados

El objetivo principal de este estudio (artículo 7) no consistió en caracterizar geométricamente la córnea para diagnosticar o clasificar la enfermedad del queratocono, como ocurre en el resto de estudios que componen esta tesis, sino que se centró en proponer un nuevo concepto de información al paciente basado en el modelo morfogeométrico macroscópico impreso en 3D, que permita mejorar la estrategia de comunicación entre oftalmólogo y paciente en la práctica clínica. Esto facilita la comprensión, por parte del paciente, de su enfermedad y su tratamiento posterior, evitando la situación en la que estos desconocen la verdadera dimensión de la condición sufrida, que puede llevar a frustración y malos resultados.

Por tanto, aunque la metodología planteada muestre elementos en común con la del resto de artículos constitutivos de esta tesis, como puede ser el uso del tomógrafo Sirius para obtener archivos de nube de puntos representativos de las superficies corneales; o el uso de la misma base de datos de pacientes "Iberia", es preciso señalar las particularidades que la definen y la diferencian del resto dado que se utilizó software de código abierto.

4.2.2.1 Metodología

El proceso de reconstrucción del modelo impreso a medida constó de las siguientes etapas sucesivas (Figura 4.5): I) generación de la superficie y modelo 3D, II) preparación del modelo imprimible en 3D, III) impresión del modelo en la clínica.

Figura 4.5 Metodología usada para la impresión del modelo 3D personalizado

- I. Generación de la superficie y el modelo 3D: Esta tarea se puede llevar a cabo mediante distintas aplicaciones software. En este estudio, se utilizó el software de código abierto CloudCompare 2.9.1 para generar el modelo 3D, usando su opción “Delaunay 2.5D (mejor plano de ajuste)” para crear una rejilla a partir de la nube de puntos de cada superficie. A continuación, se creó la superficie perimetral y, mediante operaciones Booleanas, se fusionó con las superficies corneales anterior y posterior para modelizar el volumen final, que fue entonces cortado con un plano sagital pasante por el eje óptico y los puntos de mínimo espesor (anterior y posterior) de las superficies. Las entidades de CloudCompare se guardaron en formato .BIN,

formato que es altamente compatible con la mayoría del software de código abierto para gestión de gráficos en 3D, de modo que pudiera ser usado de forma fácil en cualquier red de investigación colaborativa.

- II. Preparación del modelo imprimible en 3D: El modelo de impresión en 3D precisa definir las superficies del modelo sólido como una malla de triángulos poligonal. Sin embargo, incluso haciendo esto, el modelo 3D virtual está aún inacabado y los bordes tienen que ser desbastados. Otras mejoras superficiales son también posibles, como la inspección y modificación de superficies superpuestas, y el simplificado del fichero de imagen para mejorar la eficiencia de la impresión. Para ello, se utilizó el software Cura 2.5 (Ultimaker, Holanda). Así, los ficheros generados en CloudCompare fueron exportados a formato .STL (Stereolithography, Standard Triangle Language or Standard Tessellation Language),²²⁶ que es un formato muy versátil y altamente compatible con todas las impresoras 3D. A continuación, se fijaron los parámetros de impresión en Cura, y el fichero que contenía toda la información de impresión (puntos, trayectorias, velocidad, llenado, etc.) se generó como archivo .GCODE, que fue finalmente cargado a la impresora 3D por medio de un pendrive USB.

- III. Impresión 3D: La impresora 3D seleccionada para este proyecto fue un modelo de tecnología FDM (deposición de material fundido) diseñada por la organización UPCT-Makers, llamada “3D Printer ETSII –UPCT”.²²⁷ Esta impresora 3D forma parte del proyecto RepRap,²²⁸ por lo que sus planos y datos técnicos son abiertos y están disponibles en internet, permitiendo su construcción por cualquier usuario. Estaba dotada de un controlador Arduino MEGA, RAMPS 1.4 y controladores V. 88.25, y fue programada mediante el software Marlin. Se la podría considerar una impresora de bajo coste, ya que tiene un coste aproximado inferior a los 120 €, con una vida media esperada de 2000 horas de servicio.

Tabla 4.4 Ajustes de impresión

Parámetro	Valores / Ajuste
Material	PLA
Calidad: altura de capa	0.2 – 0.3 mm
Densidad del material fusible	1.25 g/cm ³
Punto de fusión del material	160° C
Temperatura de impresión	225° C
Diámetro de la tobera	1 mm
Ratio de flujo	100%
Velocidad de impresión	500 mm/s
Velocidad de desplazamiento	130 mm/s
Área de impresión	22x23x20 cm

El material usado para la impresión 3D fue ácido poliláctico (PLA), ya que es un polímero rígido biodegradable²²⁹, que es estable a la luz ultravioleta, tiene baja inflamabilidad y sus características son similares al tereftalato de polietileno (PET). Sus propiedades, así como los principales parámetros de impresión, se muestran en la Tabla 8.

4.3. Análisis morfogeométrico microscópico

El estudio microscópico de la morfogeométrica de la córnea puede ser de gran utilidad. En concreto, el estudio de las células del endotelio corneal puede ayudar a la detección, diagnóstico y control de algunas patologías, tales como retinopatías²³⁰, glaucoma²³¹ o queratocono⁹¹.

El artículo 5 y el registro del software CoEnCell de la presente tesis doctoral, muestran un procedimiento para el preprocesado, segmentación y análisis automático de imágenes obtenidas por microscopio confocal. Para aplicarlo, se ha usado la transformada Watershed, y una interfaz gráfica de usuario (GUI) creada con Matlab®, que componen conjuntamente una forma más cómoda y eficiente de contar las células endoteliales, así como de medir su porcentaje de hexagonalidad.

Estas imágenes se seleccionaron aleatoriamente de la base de datos de fotos de endotelios de pacientes tomadas con microscopio confocal Konan NSP-9900 (Konan Medical, Hyogo, Japón). Las fotos fueron tomadas por un técnico experto, con el software propio del microscopio (CellCheck®), y fueron exportadas en formato .JPG para su importación a una GUI diseñada al efecto (Figura 4.6).

Figura 4.6 GUI mostrando el resultado de la transformada de Watershed, el número de células, el porcentaje de hexagonalidad y un histograma de dicho porcentaje

El entorno de programación para los algoritmos de filtrado de imagen y detección de células, así como para la creación de la GUI, fue el software comercial Matlab® R2017b (MathWorks®, Natick, EEUU). Matlab® es una poderosa herramienta para el tratamiento de imágenes, ya que puede descomponerlas y tratarlas como matrices. El diagrama de flujo del proceso puede observarse en la Figura 4.7.

Figura 4.7 Diagrama de flujo del procedimiento

4.4. Análisis estadístico

Se diferenciaron tres grupos con enfoques estadísticos distintos, en función del tipo de investigación a realizar: por una parte, los estudios encaminados a definir y validar la capacidad de distintos parámetros morfogeométricos para la caracterización de la estructura hemiesférica (artículos 1 a 4, 6 y 9 a 11), por otra, los destinados a diagnosticar y clasificar los casos de queratocono en función de esos parámetros (artículos 8 y 12); y finalmente, los estudios de aplicación clínica del modelo (artículos 5 y 7).

4.4.1 Estudios para definición y validación de parámetros

El análisis estadístico se llevó a cabo con los programas SPSS versiones 15.0, 17.0, 19.0, 23.0 y 24.0 (IBM Corp., Armonk, NY, EEUU) y Graphpad Prism versiones 6 y 7

(GraphPad Software, La Jolla, EEUU) dependiendo del estudio, incluyendo estadística descriptiva tanto para el grupo “control” como para el grupo “KC”, a fin de demostrar la distribución de las variables con un mayor detalle. Los datos categóricos (género) se analizaron mediante el test χ^2 . Para las variables cuantitativas, se comprobó la normalidad mediante el test de Kolomgorov-Smirnov. Cuando el análisis paramétrico fue posible, se utilizaron el t-test de Student para datos no pareados o el análisis de la varianza (ANOVA) como métodos de comparación entre grupos. Si la condición de normalidad se cumplía, los grupos se compararon mediante este t-test, y en el resto de situaciones, se utilizaron test no paramétricos, como el U-Mann-Whitney-Wilcoxon, o el de Kruskal-Wallis. Para el análisis comparativo post-hoc de ANOVA, se seleccionó el test de Bonferroni para varianzas homogéneas y el test T2 de Tamhane en caso de que estas no mostraran homogeneidad. Se fijó un p-valor inferior a 0,05 como significativo en todos los test estadísticos.

En los artículos en los que se llevó a cabo estudio de correlación entre parámetros, esta se comprobó mediante los coeficientes de Pearson (para datos normalmente distribuidos) o Spearman (en caso de no normalidad). Cuando se deseó comprobar la potencia de la correlación entre grupos, se llevó a cabo una regresión lineal.

Para la construcción de un modelo predictivo de la presencia de queratocono en función de la influencia de cada variable, se llevó a cabo una regresión logística binaria, construyéndose un modelo multivariante basado en los valores de Wald.

Para todas las métricas se aplicaron curvas de operador-receptor características (curvas ROC) para determinar la precisión predictiva, representando la sensibilidad frente a 1-especificidad y calculando el área bajo la curva (AUC) como medida de precisión, fijándose los valores de corte óptimos en cada caso para cada una de las variables estudiadas mediante el índice J de Youden^{232,233}.

4.4.2 Estudios para diagnóstico y clasificación de queratocono

El análisis estadístico para estos estudios se llevó a cabo mediante el paquete R Statistics v3.6.1 (R Foundation for Statistical Computing, Viena, Austria)²³⁴, mientras que el desarrollo y despliegue de las aplicaciones web, así como la identificación de usuario, fueron realizados con los paquetes Shiny (RStudio Inc., Boston, EEUU)²³⁵ y ShinyAuthr (Paul Campbell, Paris, Francia)²³⁶ respectivamente. Ambos estudios comparten un enfoque general similar, por lo que sus características son coincidentes en muchos aspectos.

En concreto, en ambos casos las variables cuantitativas fueron resumidas usando la mediana $\pm$ rango intercuantílico (IQR) y la media $\pm$ desviación estándar (SD), mientras que las cualitativas lo fueron por conteo y porcentaje. Se comprobó la normalidad mediante el test de Shapiro-Wilks y la colinealidad se midió con el coeficiente de correlación de Pearson. El t-test de Student se usó para comparar entre dos grupos de variables normalmente distribuidas, mientras que, en el caso de existir tres o más grupos a comparar, se optó por el método ANOVA. Para las variables con distribución no

normal, se usaron los test de Mann-Whitney y de Kruskal-Wallis respectivamente. Las diferencias en las variables cualitativas entre grupos independientes fueron comparadas mediante el test χ^2 . Los p-valores inferiores a 0.05 fueron considerados como estadísticamente significativos.

Para ambos estudios, se realizó un análisis del poder estadístico por simulación, usando el test de Wald para estimar el poder de cada covariable con respecto al tamaño muestral, como se describe en la literatura^{237,238}.

No obstante, a partir de este punto los objetivos perseguidos, y consecuentemente también las metodologías utilizadas en ambos estudios, difieren, contando cada uno con particularidades que es preciso señalar.

4.4.2.1 Modelo para el diagnóstico y la clasificación del queratocono de acuerdo a la escala RETICS.

El modelo de puntuación predictiva para la detección de queratocono incipiente fue definido por regresión logística multivariante con los grupos “control” y RETICS grado I, seleccionándose 17 variables a incluir en él. La eficacia discriminativa del modelo fue evaluada mediante curvas características receptor-operador (ROC), en las que el área bajo la curva (AUC), la sensibilidad y la especificidad fueron tomadas como indicadores de rendimiento.

Se realizó una validación interna del modelo por agregación de *bootstrap* (empaquetado)²³⁹, cuyo funcionamiento es el siguiente: primero se genera un nuevo conjunto de datos de igual tamaño por muestreo con reemplazo del conjunto de datos original. A continuación, el modelo es entrenado con esos datos, siendo finalmente usado para hacer predicciones en aquellos casos no usados para el entrenamiento. Este proceso se repitió 100 veces para obtener un conjunto de datos de calidad que pudieran promediarse, y en los que calcular intervalos de confianza. De media, se usaron el 63.2% de los datos del set original en estas 100 etapas de entrenamiento, mientras que el 36.8% restante se usaron para validación.

Para la determinación del grado RETICS, se recurrió a la regresión logística mutivariante ordinal con las mismas variables predictivas. En este caso, se hizo uso de la matriz de confusión para estimar el rendimiento del modelo por medio de la sensibilidad, especificidad y la precisión balanceada por grupo.

Los paquetes del software R utilizados fueron: “tidyr”, “dplyr”, “dlookr” y “smbinning” para la carga, exploración y transformación de datos; “corrplot”, “yarr” y “FactoMiner” para la visualización de datos; y “pROC”, “ROCR” y “Epi” para el análisis y representación de las curvas ROC.

El modelo de regresión logística fue entrenado con la función “glm” del paquete base, mientras que el de regresión logística ordinal lo fue con la función “polr” del paquete “MASS”. Las matrices de confusión fueron analizadas con el paquete “caret” y los

cálculos del tamaño muestral óptimo se llevaron a cabo con los paquetes “rcompanion” y “pmsamplesize”.

4.4.2.2 Modelo para determinar la probabilidad de sufrir queratocono incipiente o suave.

En este caso, se utilizó la técnica de regresión logística ordinal para modelizar la relación multivariante entre los parámetros disponibles y el grado:

$$\log \frac{P(Y \leq j)}{P(Y > j)} = \beta_{j0} - \beta_1 x_1 - \dots - \beta_p x_p \quad (1)$$

donde Y es un resultado ordinal con J categorías, $P(Y \leq j)$ es la probabilidad acumulada de que Y sea menor o igual a una categoría específica $j = 1, \dots, J - 1$, β_{j0} es la intersección para la categoría j , y $\beta_1, \beta_2, \dots, \beta_p$ son los coeficientes para cada predictor p .²³⁹ Se considera que las intersecciones son diferentes para cada categoría, pero las pendientes son constantes a lo largo de las categorías (modelo de probabilidad proporcional). Se realizó un proceso de eliminación hacia atrás (*backwards stepwise regression*) con criterio de información de Akaike (AIC) para obtener el mínimo conjunto de variables que contuvieran la máxima cantidad de información posible. Inicialmente, se construyó el modelo completo (con todos los parámetros disponibles). A continuación, se fueron eliminando los parámetros de uno en uno y se construyó un nuevo modelo. Se calcularon los valores de AIC para todos estos modelos usando la expresión siguiente:²⁴⁰

$$AIC = -2 \cdot \log\text{-verosimilitud maximizada} + 2 \cdot \text{número de parámetros}$$

El parámetro causante de la reducción más marcada en el AIC era definitivamente eliminado y el proceso fue repetido hasta que no existieron reducciones en el AIC. La hipótesis de modelo de probabilidad proporcional se comprobó mediante el test de razón de verosimilitud de Venables-Ripley y el test de Brant.

El modelo fue evaluado por los valores de precisión, sensibilidad y especificidad derivados de la correspondiente matriz de confusión. Se llevó a cabo una validación cruzada interna por medio de agregación de *bootstrap* (empaquetado)²³⁹, similar al descrito en el epígrafe anterior, pero en este caso se realizó además una validación externa del modelo con una muestra de datos independientes.

Los paquetes del software R utilizados para el preprocesado, análisis y representación, así como para el cálculo y validación fueron: “dplyr”, “corrplot”, “nnet”, “MASS”, “generalhoslem”, “pscl”, “brant”, “effects”, “grid”, “caret”, “yarr” y “ROCR”.

El modelo de regresión logística ordinal fue entrenado con la función “polr” del paquete “MASS”.

4.4.3 Estudios de aplicación clínica del modelo

Este epígrafe lo componen dos estudios cuyo enfoque difiere en gran medida de aquél del resto de estudios expuestos en epígrafes anteriores, por lo que se mostrará el enfoque estadístico de cada uno de manera individualizada.

4.4.3.1 Estadística descriptiva en el conteo de células endoteliales y caracterización de su porcentaje de hexagonalidad.

En este caso, el único estudio estadístico realizado se limitó a la estimación del error de medida cometido. Para estimar el error cometido durante el conteo, se consideró la medida manual como el valor exacto, y a continuación se contabilizó la desviación respecto a ella con el conteo automático, con la siguiente ecuación:

$$E_i = \frac{C_a \cdot 100}{C_m}$$

Donde E_i es el error en cada medida, C_m es el total de células medidas manualmente, y C_a es el total de células medidas de forma automática.

Para determinar el error medido en el porcentaje de hexagonalidad, se procedió de forma similar, considerando la medida manual como referencia, y comparándola con la automática:

$$H_i = \frac{P_a \cdot 100}{P_m}$$

Donde H_i es el error en la hexagonalidad en cada medida, P_m es el porcentaje de hexagonalidad medido manualmente y P_a es el porcentaje de hexagonalidad medido automáticamente.

4.4.3.2 Estadística descriptiva en aplicación de modelos 3D personalizados para la educación del paciente.

A fin de evaluar la utilidad del modelo impreso en 3D, se pasó un cuestionario a cada paciente. Si este sufría de queratocono, su modelo personalizado impreso en 3D se comparaba con una córnea típicamente sana, y se les explicaba a continuación su condición, rellenando cada paciente el cuestionario justo después de finalizar la explicación.

Las preguntas realizadas se recogen en la Tabla 9. Cuando se seleccionó la escala para cada cuestión, para las preguntas Q1, Q2 y Q5 se usaron 10 niveles Likert en lugar de los cinco más comunes, para minimizar el sesgo de tendencia central, mientras que para las cuestiones Q3 y Q4 se optó por una escala absoluta (Si/No/Neutro).

Tabla 4.5 Cuestiones planteadas a los pacientes

Número	Aspecto testado	Posible respuesta
Q1	¿Qué utilidad atribuye a este modelo 3D personalizado?	De 1 = totalmente inútil a 10 = extremadamente útil
Q2	¿Cuánto cree que el modelo 3D personalizado le ha ayudado a entender mejor su condición?	De 1 = nada en absoluto a 10 = en gran medida
Q3	¿Querría llevarse el modelo 3D personalizado a casa tras la consulta?	Si / No / Neutro
Q4	¿Considera que usar este modelo 3D personalizado mejora la calidad de nuestro servicio clínico?	Si / No / Neutro
Q5	¿Cuánto cree que podría beneficiar a los pacientes el uso de estos modelos 3D personalizados en las consultas?	De 1 = nada en absoluto a 10 = en gran medida

Resultados y discusión

5.1. Artículo 1

Estudio de variables morfogeométricas para mejorar el diagnóstico del queratocono con limitación visual leve. [Cavas-Martínez F, Fernández-Pacheco DG, Cañavate FJF, Velázquez-Blázquez JS, Bolarín JM, Alió JL. Study of Morpho-Geometric Variables to Improve the Diagnosis in Keratoconus with Mild Visual Limitation. *Symmetry*. 2018;10(8):306. DOI: [10.3390/sym10080306](https://doi.org/10.3390/sym10080306)]

5.1.1 Resumen

La validación de nuevos métodos diagnósticos para casos incipientes de queratocono con limitación visual leve es de gran interés en el campo de la oftalmología. Los actuales índices diagnósticos no recogen la descompensación geométrica de la curvatura corneal ni la variación del perfil espacial que tiene lugar en los puntos singulares de la córnea durante la progresión asimétrica de la enfermedad.

Este trabajo ahonda en la caracterización estructural de la asimetría de la enfermedad mediante el uso de parámetros morfogeométricos en ojos sanos y queratocónicos con limitación visual suave, aplicando para ello modelos virtuales personalizados creados mediante herramientas de diseño asistido por ordenador (CAD). Este estudio comparativo incluyó un total de 202 ojos de 202 pacientes, comprendiendo el grupo “KC” 80 ojos de 80 pacientes diagnosticados con queratocono grado II (con limitación visual suave) en escala RETICS [29 mujeres (36.2%) y 51 hombres (63.8%) con una edad media de 41.8 ± 13.1 años, comprendida desde los 16 hasta los 72 años]. El grupo “control” se compuso de 122 ojos normales de 122 pacientes [54 mujeres (44.2%) y 68 hombres (55.8%)] con edad media de 34.89 ± 7.8 años, comprendida entre los 19 y los 64 años.

5.1.2 Resultados y conclusiones

Los principales hallazgos y consideraciones sobre los resultados obtenidos se exponen a continuación.

1. Al comparar el grupo “KC” con el grupo “control, se encontraron diferencias estadísticamente significativas para la mayoría de las métricas corneales generales, lo que incluye el volumen total (CV) ($p < 0.001$), área de la superficie anterior (A_{ant}) ($p < 0.001$), desviación del ápex anterior (D_{antapex}) ($p < 0.001$), desviación del punto de mínimo espesor anterior (D_{antmct}) ($p < 0.001$), área de la superficie posterior (A_{post}) ($p < 0.001$), área del plano sagital por el ápex posterior (A_{postapex}) ($p < 0.001$), área del plano sagital por el punto de mínimo espesor (A_{postmct}) ($p < 0.001$), desviación del ápex posterior (D_{postapex}) ($p < 0.001$), desviación del punto de mínimo espesor posterior (D_{postmct}) ($p < 0.001$), coordenada del centro de masas en Y (CM_y) ($p < 0.001$), y coordenada del centro de masas en Z (CM_z) ($p = 0.006$). Las únicas variables modeladas que no mostraron capacidad de discriminación entre grupos fueron la coordenada del centro de masas en X (CM_x) ($p = 0.073$) y la superficie corneal total (A_{tot}) ($p = 0.205$). Por lo tanto, las variables obtenidas desde los datos en bruto del

tomógrafo Sirius en forma de nube de puntos 3D, permiten generar un sólido confiable y con propiedades de supresión de ruido, con vistas a la comparación de ojos sanos y ojos con queratocono con limitación visual leve.

2. En el análisis ROC, las variables que obtuvieron un AUC superior a 0.7 fueron desviación del ápex posterior (área: 0.904, sensibilidad: 88.8%, especificidad: 81.1%, corte: ≥ 0.0846 mm, $p = 0.000$), desviación del ápex anterior (área: 0.866, sensibilidad: 76.3%, especificidad: 95.9%, corte: ≥ 0.001 mm, $p = 0.000$), y área de la superficie corneal posterior (área: 0.761, sensibilidad: 76.3%, especificidad: 64.8%, corte: ≥ 43.16 mm², $p = 0.000$) (Figura 5.1). La desviación del ápex posterior obtuvo el mejor coeficiente de discriminación porque el ápex es el punto de máxima curvatura de la superficie corneal, y de acuerdo con publicaciones anteriores¹⁵⁸, la curvatura posterior puede influir en el rendimiento visual, lo hace pensar que la medida de la desviación del ápex posterior es la mejor forma de caracterizar el perfil geométrico del KC en la etapa en la que comienza a aparecer la disminución de la agudeza visual. Además, la desviación del ápex anterior también muestra una capacidad de discriminación aceptable, aunque su sensibilidad es menor en esta investigación, lo que está en línea con los hallazgos de otros autores, que han reportado que los índices topográficos y los valores de elevación posteriores del equipo Galilei están significativamente correlacionados con la función visual²⁴¹.

Figura 5.1 Curvas ROC de los parámetros con mayor precisión predictiva para el queratocono con limitación visual leve²⁴²

- El análisis de las correlaciones entre variables, mostró que las más fuertemente correlacionadas, para el grupo “KC” y el grupo “control”, fueron, respectivamente, las reflejadas en la Tabla 10 y la Tabla 11 siguientes:

Tabla 5.1 Valores significativos de coeficientes de correlación para las variables del grupo “KC”

Grupo de KC con limitación visual leve (n = 80)		
Correlación medida	Coeficiente de correlación	P valor
Apostapex / CV	0.969	0.000
Aant/Apost	0.853	0.000
CV / A _{tot}	0.699	0.000
Aant / CM _z	0.627	0.000
Apost / CM _z	0.766	0.000
A _{tot} / CM _z	0.816	0.000
Apostapex / A _{postmct}	0.989	0.000
CV / A _{postmct}	0.978	0.000
Dantmct/D _{postmct}	0.996	0.000

Tabla 5.2 Valores significativos de coeficientes de correlación para las variables del grupo “control”

Grupo normal (n = 122)		
Correlación medida	Coeficiente de correlación	P valor
Apostapex / CV (mm ³)	0.987	0.000
Apostapex / A _{tot}	0.814	0.000
A _{tot} / CM _z	0.723	0.000
Aant / A _{post}	0.774	0.000
A _{post} / A _{tot}	0.649	0.000
A _{post} / CM _z	0.719	0.000
CV / A _{tot}	0.858	0.000
CV / CM _z	0.768	0.000
A _{tot} / CM _z	0.943	0.000
Apostapex / CM _z	0.723	0.000
A _{postmct} / A _{postapex}	0.996	0.000
CV / A _{postmct}	0.987	0.000
A _{tot} / A _{postmct}	0.813	0.000
CM _z / A _{postmct}	0.730	0.000
Dantmct/D _{postmct}	0.988	0.000

Estos resultados permiten dar cuenta de la fuerte relación entre el patrón geométrico de las superficies corneales anterior y posterior. Es más, para ojos con KC, la correlación más fuerte encontrada fue la existente entre los puntos de mínimo espesor anterior y posterior ($R^2 = 0.997$, $p = 0.000$), lo que confirma la robusta interrelación entre la desviación del ápex y la variación del índice paquimétrico, tal y como han propuesto otros autores.²⁴³

4. El análisis de regresión reveló, para ambos grupos, correlaciones fuertes y significativas entre las variables morfogeométricas, permitiendo establecer las siguientes expresiones para el grupo “KC”:

$$D_{\text{postmct}} = 0.944 \times D_{\text{antmct}} + 0.236 \quad (R^2 = 0.997)$$

$$A_{\text{postmct}} = 1.05 \times A_{\text{postapex}} + 0.018 \quad (R^2 = 0.958)$$

$$CV = 5.757 \times A_{\text{postapex}} + 1.197 \quad (R^2 = 0.953)$$

$$A_{\text{postmct}} = 0.16 \times CV + 0.136 \quad (R^2 = 0.955)$$

Abreviaturas: D_{postmct} = Desviación de punto de mínimo espesor posterior; D_{antmct} = Desviación de punto de mínimo espesor anterior; A_{postmct} = Área en el plano sagital pasando por el punto de mínimo espesor posterior; A_{postapex} = Área en el plano sagital pasando por el ápex posterior; CV: Volumen corneal;

Y también para el grupo “control”:

$$CM_z = 0.0195 \times A_{\text{tot}} - 1.255 \quad (R^2 = 0.907)$$

$$A_{\text{postapex}} = 1.005 \times A_{\text{postmct}} - 0.031 \quad (R^2 = 0.994)$$

$$CV = 5.829 \times A_{\text{postapex}} + 0.633 \quad (R^2 = 0.978)$$

$$A_{\text{postmct}} = 0.166 \times CV + 0.034 \quad (R^2 = 0.978)$$

Abreviaturas: CM_z = Coordenada Z del centro de masas; A_{tot} = Área total de la superficie corneal; A_{postmct} = Área en el plano sagital pasando por el punto de mínimo espesor posterior; A_{postapex} = Área en el plano sagital pasando por el ápex posterior; CV: Volumen corneal

Por lo tanto, este enfoque computacional personalizado determina eficientemente el perfil de caracterización de modelado para ojos que sufren queratocono con limitación visual leve.

5.2. Artículo 2

Detección del queratocono temprano mediante modelado 3D personalizado y análisis de sus parámetros geométricos. [Cavas-Martínez F, Fernández-Pacheco DG, Canavate FJF, Velázquez-Blázquez JS, Bolarín J, Tiveron M, Alió J. Early keratoconus detection by patient-specific 3D modelling and geometric parameters analysis. *Dyna*. 2019. 94(2). DOI: [10.6036/8895](https://doi.org/10.6036/8895)]

5.2.1 Resumen

En este estudio se ha evaluado si el análisis del modelado geométrico de la córnea podría ser útil para la detección del queratocono (KC) temprano con agudeza visual normal (grado I de escala RETICS) por discriminación con respecto a los casos sanos normales. Se llevó a cabo una reconstrucción a partir de los datos en crudo de la tomografía corneal Scheimpflug-Placido Sirius, así como un posterior análisis del modelo personalizado virtual en 3D. Las variables morfogeométricas extraídas del modelo corneal fueron analizadas estadísticamente para ambos grupos de estudio. Por último, se establecieron curvas características de receptor-operador (ROC) a fin de determinar sus valores predictivos y parámetros de precisión. El estudio incluyó un total de 286 sujetos (149 ojos con KC temprano asociados a visión normal, con edad promedio de 36.14 ± 10.28 años y 137 ojos normales con una media de edad de 34.38 ± 7.02 años).

5.2.2 Resultados y conclusiones

Los principales hallazgos y consideraciones sobre los resultados obtenidos se exponen a continuación.

1. Se observaron diferencias estadísticamente significativas entre los grupos de estudio en la mayoría de las variables analizadas ($P < 0.05$) (Tabla 5.3). Los valores descriptivos y diferencias entre ojos normales y ojos con KC temprano se muestran por medio de las catorce variables modeladas. En este sentido, la variable centro de masa Z fue la única que no mostró diferencia estadística alguna entre los grupos ($P = 0.425$). Por lo tanto, las variables analizadas permiten la caracterización y discriminación fiable de córneas normales de aquellas con KC temprano.

Tabla 5.3 Valores descriptivos y diferencias en las variables morfogeométricas modeladas entre los grupos normal y KC temprano. DT: desviación típica. P: test estadístico, Z: Z-score

Medición	Grupo normal (n = 137)				Grupo KC temprano (n = 149)				Z	P
	Media	DT	Min	Máx.	Media	DT	Min	Máx.		
Volumen corneal total (mm ³)	25.79	1.47	22.99	29.50	24.10	1.57	19.74	28,96	-8.44	0.00
Superficie corneal anterior (mm ²)	43.08	0.14	42.73	43,39	43.24	0.19	42.82	43.75	-6.98	0.00
Superficie corneal posterior (mm ²)	44.25	0.28	43.49	44.90	44.49	0.34	43.57	45.46	-5.79	0.00
Superficie corneal total (mm ²)	103.96	1.15	100.73	106.15	103.50	1.25	100.75	107.32	-3.19	0.00

Área del plano sagital por el ápex (mm ²)	4.33	0.25	3.84	5.00	4.01	0.27	3.24	4.90	-9.11	0.00
Área del plano sagital por el punto de mínimo espesor (mm ²)	4.31	0.25	3.85	5.01	4.01	0.27	3.22	4.89	-9.03	0.00
Desviación del ápex anterior (mm)	0.00	0.00	0.00	0.01	0.00	0.01	0.00	0.04	-6.28	0.00
Desviación del ápex posterior (mm)	0.07	0.05	0.02	0.65	0.16	0.09	0.02	0.46	-10.42	0.00
Centro de masa X (mm)	0.02	0.04	-0,08	0.09	0.00	0.05	-0,08	0.10	-4.14	0.00
Centro de masa Y (mm)	0.03	0.02	-0,01	0.10	0.02	0.03	-0,09	0.09	-3.46	0.00
Desviación neta del centro de masa XY (mm)	0.04	0.03	0.00	0.11	0.01	0.02	0.00	0.11	-7.68	0.00
Centro de masa Z (mm)	0.77	0.02	0.71	0.81	0.77	0.03	0.71	0.85	-0.80	0.43
Desviación del punto de mínimo espesor anterior (mm)	0.86	0.23	0.44	1.66	1.04	0.32	0.32	2.04	-4.68	0.00
Desviación del punto de mínimo espesor posterior (mm)	0.79	0.21	0.38	1.53	0.96	0.30	0.27	1.92	-4.91	0.00

2. Se realizó un análisis ROC para determinar el valor predictivo de las variables morfogeométricas analizadas. De las catorce variables modeladas, la desviación del ápex posterior alcanzó la mayor área bajo la curva ROC (AUROC) con una puntuación de 0,856 (Figura 5.2).

Figura 5.2 Curvas ROC de los parámetros con mayor precisión predictiva para el queratocono temprano

Este hallazgo está en sintonía con el anterior informe de Cavas-Martinez *et al.*,¹² que encontró la misma variable prominente en relación con el diagnóstico del KC (AUROC de 0.891). Estos resultados podrían explicarse por la inestabilidad estructural con las consiguientes líneas de estrés detectada en el estroma posterior de córneas con KC temprano²⁴⁴, lo que sugiere que las alteraciones en la geometría afectan a la disposición del estrés en el tejido corneal.⁵

3. La presente investigación arrojó sensibilidades de 79,3%, 74,2%, 75,1% y 79,8% en las variables relacionadas con la desviación del ápex posterior, área del plano sagital por el ápex, área del plano sagital por el punto de mínimo espesor y desviación neta del centro de masas XY, respectivamente (todas ellas con un AUROC > 0.7). En cuanto a la especificidad analizada en todos los parámetros mencionados anteriormente, la desviación del ápex posterior mostró una especificidad similar a la del área del plano sagital por el ápex, ambas considerando como referencia la cara posterior, sin embargo, cuando se comparan las áreas de las superficies corneales anterior y posterior, la superficie anterior es el predictor más específico para la detección, lo que se alinea con los hallazgos de algunos investigadores²⁴⁵. De hecho, la elevación posterior generalmente precede a alteraciones en la superficie anterior, pero en algunos casos preclínicos no surge necesariamente antes que los cambios en la anterior^{90,200}. Se concluye por tanto, que existen varios parámetros que pueden ser utilizados para detectar deformaciones corneales, y no se considera pues que las anormalidades de elevación posterior sean obligatorias para la detección del KC, según lo declarado por otros investigadores,¹⁰ dado que se han encontrado robustas variables alternativas para la detección de evidencias sutiles en sus primeros estadios.

5.3. Artículo 3

Detección del queratocono subclínico usando parámetros biométricos. [Velázquez-Blázquez JS, Cavas-Martínez F, Alió del Barrio J, Fernandez-Pacheco DG, Cañavate FJF, Parras-Burgos D, Alió J. Detection of Subclinical Keratoconus Using Biometric Parameters. In: Rojas I, Valenzuela O., Rojas F., Ortuño F. (eds) Bioinformatics and Biomedical Engineering. IWBBIO 2019. Lecture Notes in Computer Science, vol 11466. Springer, Cham. DOI: [10.1007/978-3-030-17935-9_44](https://doi.org/10.1007/978-3-030-17935-9_44)]

5.3.1 Resumen

Hasta ahora, el diagnóstico del queratocono subclínico se ha realizado combinando varios criterios clínicos que han permitido el establecimiento de índices y árboles de decisión, que han probado su valía como herramientas diagnósticas. Sin embargo, es preciso realizar mejoras que permitan reducir el riesgo de ectasia en pacientes que se someten a cirugías refractivas. Este trabajo muestra un nuevo método de detección de queratocono subclínico basado en el análisis de ciertos parámetros biométricos extraídos de un modelo 3D personalizado. En este estudio retrospectivo se incluyeron dos grupos: el primero compuesto de 67 pacientes con ojos sanos y visión normal, y el segundo compuesto de 24 pacientes también con visión normal, pero con queratocono subclínico de acuerdo al criterio de Amsler-Krumeich. Se propuso un método de detección que usa herramientas de diseño gráfico asistido por ordenador (CAGD) y datos de las superficies corneales suministrados por un tomógrafo corneal. Se definieron parámetros bio-geométricos derivados del modelo, y se analizaron estadísticamente para detectar cualquier mínima deformación corneal.

5.3.2 Resultados y conclusiones

Los principales hallazgos y consideraciones sobre los resultados obtenidos se exponen a continuación.

1. La mayor parte de los parámetros modelados mostraron diferencias estadísticamente significativas en la comparación de corneas con KC subclínico y corneas normales, con la única excepción de las variables centro de masa X ($p = 0.28$) centro de masa Y ($p = 0.14$) y centro de masa Z ($p = 0.08$), como se muestra en la Tabla 5.4 siguiente:

Tabla 5.4 Valores descriptivos y diferencias en los parámetros biométricos modelados entre los grupos normal y KC subclínico. DT: desviación típica. P: test estadístico, Z: Z-score

Parámetros Biométricos	Grupo Normal (n = 67)				Grupo KC subclínico (n = 24)					
	Media	DT	Min	Max	Media	DT	Min	Max	z	P
Volumen corneal total (mm ³)	25.80	1.57	21.29	29.39	24.09	1.69	19.79	28.21	-8.39	0.00

Superficie corneal anterior (mm ²)	43.10	0.16	42.69	43.40	43.18	0.16	43.01	43.48	-6.88	0.00
Superficie corneal posterior (mm ²)	44.19	0.31	43.38	44.91	44.31	0.34	43.57	44.79	-5.80	0.00
Superficie corneal total (mm ²)	103.94	1.25	100.80	106.09	103.50	1.20	101.31	105.49	-3.17	0.00
Área del plano sagital por el ápex (mm ²)	4.29	0.25	3.60	4.99	4.02	0.31	3.24	4.86	-9.02	0.00
Área del plano sagital por el punto de mínimo espesor (mm ²)	4.30	0.49	0.00	5.01	3.99	0.30	3.22	4.81	-9.01	0.00
Desviación del ápex anterior (mm)	0.00	0.00	0.00	0.01	0.00	0.01	0.00	0.21	-6.01	0.00
Desviación del ápex posterior (mm)	0.07	0.02	0.02	0.15	0.14	0.07	0.05	0.40	-10.42	0.00
Desviación del punto de mínimo espesor anterior (mm)	0.84	0.3	0.42	2.21	1.2	0.29	0.61	1.79	-4.72	0.00
Desviación del punto de mínimo espesor posterior (mm)	0.79	0.26	0.46	2.01	1.1	0.29	0.49	1.69	-4.89	0.00
Desviación neta del centro de masa XY (mm)	0.05	0.03	0.01	0.09	0.08	0.04	0.00	0.12	-4.20	0.00
Centro de masa X (mm)	0.05	0.03	0.01	0.10	0.04	0.03	0.00	0.08	-3.46	0.28
Centro de masa Y (mm)	0.04	0.03	0.00	0.11	0.01	0.02	0.00	0.10	-7.70	0.14
Centro de masa Z (mm)	0.81	0.02	0.72	0.83	0.78	0.03	0.70	0.81	-0.82	0.08
Volumen del cilindro corneal (mm ³) de radio 0.5 mm	0.47	0.29	0.34	3.21	0.4	0.03	0.29	0.48	-1.02	0.00
Volumen del cilindro corneal (mm ³) de radio 1.0 mm	1.69	0.13	1.39	1.99	1.49	0.15	1.19	1.9	-1.58	0.00
Volumen del cilindro corneal (mm ³) de radio 1.5 mm	3.89	0.44	3.31	7.29	3.6	0.3	2.9	4.3	-1.9	0.00
Volumen del cilindro corneal (mm ³) de radio 2.0 mm	7.11	0.45	5.94	8.3	6.55	0.5	5.25	7.8	-2.3	0.00

Por tanto, es posible distinguir los ojos sanos de aquellos con KC subclínico utilizando estos parámetros.

2. Los valores volumétricos estudiados y el volumen de los cilindros corneales analizados mostraron una reducción de volumen estadísticamente significativa en el grupo subclínico. El proceso degenerativo del queratocono se caracteriza por una reducción significativa del volumen corneal total en la comparación con ojos sanos, que se activa por una alteración de las fibras de colágeno corneales que provoca adelgazamiento estromal y roturas en la membrana de Bowman.² Esta reducción de volumen observada en nuestro estudio lo ha sido también en otros, siendo considerada como parámetro característico en la diferenciación de ojos subclínicos.^{35,192,246} La protrusión presente en los ojos KC, que conlleva a un incremento de la curvatura corneal, acarrea también un incremento en las distancias de los ápices y los puntos de mínimo espesor, tanto en la superficie anterior como en la posterior, lo que ha sido observado en estudios previos, para los casos en los que la enfermedad ya está claramente establecida.²
3. Los ojos con queratocono subclínico mostraron diferencias estadísticamente significativas en las áreas de las superficies anterior y posterior, en comparación con los ojos sanos. Éstas fueron mayores en el grupo KC, debido a que el debilitamiento estructural provoca un pronunciamiento local que reduce el radio de curvatura, incrementándose por tanto la superficie corneal.^{2,32}
4. Sin embargo, el área corneal total, que incluye el área de la zona periférica, fue mayor en los ojos sanos, debido a su espesor más constante comparado con el adelgazamiento detectado en el grupo patológico, motivado por la influencia de la presión intraocular en la estructura debilitada.
5. El valor predictivo de los parámetros modelados se estableció mediante un análisis ROC. Se encontraron seis parámetros biométricos con áreas bajo la curva ROC (AUROC) superiores a 0.7 (Figura 5.3).

Figura 5.3 Curvas para los parámetros modelados en la detección de KC subclínico con AUROC superior a 0.7

6. La casi inexistencia de una inestabilidad estructural en los casos de queratocono subclínico explica por qué la desviación del ápex posterior muestra los mejores resultados discriminativos (ROC área: 0.891, $p < 0.000$, error estándar: 0.039, IC 95%: 0.799-0.959). La superficie corneal posterior es más susceptible de sufrir variaciones dadas las fuerzas ejercidas sobre el tejido²⁴⁷, es por esto que la desviación del ápex posterior es una de las variables que mejor representa los cambios tempranos sufridos por los pacientes en las primeras etapas de la enfermedad. Varios estudios han corroborado la importancia y el interés de la superficie corneal posterior²⁴⁸, y la utilidad de su análisis en la identificación del KC subclínico.¹⁹²
7. El método propuesto en este estudio se basa en un análisis de parámetros biométricos no finitos de la córnea humana, y no depende de ningún algoritmo comercial restringido, por lo que podría ser implementado en cualquier topógrafo, permitiendo la comparación de datos de distintos aparatos.

5.4. Artículo 4

Evaluación de la relación entre los cambios morfogeométricos *in vivo* de la córnea y los ojos con queratocono con limitación visual severa. [Velázquez JS, Cavas F, Alió Del Barrio J, Fernández-Pacheco DG, Alió J. Assessment of the Association between In Vivo Corneal Morphogeometrical Changes and Keratoconus Eyes with Severe Visual Limitation. *J Ophthalmol.* 2019;2019:8731626-8731626. DOI: [10.1155/2019/8731626](https://doi.org/10.1155/2019/8731626)]

5.4.1 Resumen

La evaluación de los cambios sufridos por la córnea durante la progresión del queratocono se ha comprobado vital para el diagnóstico y el tratamiento de esta enfermedad. Este estudio de serie de casos observacional determina el perfil biométrico de los ojos considerados como queratocónicos con limitación visual severa, evaluando nuevos índices objetivos. Para ello, se seleccionaron 50 córneas sanas y 30 córneas con KC grado IV RETICS, siguiendo un protocolo validado creado por nuestro grupo de investigación, que había sido previamente usado para el diagnóstico y caracterización de ojos asintomáticos (preclínicos, grado I RETICS) y con limitación visual leve (grado II RETICS). Se estudió el poder discriminativo de los índices y su correlación, y se usaron curvas ROC para determinar la sensibilidad y especificidad de los índices seleccionados.

5.4.2 Resultados y conclusiones

Los principales hallazgos y consideraciones sobre los resultados obtenidos se exponen a continuación.

1. La mayor parte de los parámetros morfo-biométricos mostraron diferencias estadísticamente significativas en la comparación de corneas con KC severo y corneas normales, con la única excepción de las variables desviación del punto de mínimo espesor anterior ($p = 0.27$) y desviación del punto de mínimo espesor posterior ($p = 0.23$), como se muestra en la Tabla 5.5 siguiente:

Tabla 5.5 Valores descriptivos y diferencias en los índices morfo-biométricos modelados entre los grupos normal y KC severo. SD: desviación standard. P: test estadístico, Z: z-score

Índices	Grupo Normal (n = 50)				Grupo KC severo (n = 30)				z	P
	Media	SD	Min	Max	Media	SD	Min	Max		
<i>morfo-biométricos</i>										
Vol _{tot} (mm ³)	25.72	1.53	23.23	29.07	23.74	1.85	20.17	28.40	5.18	≤0.01
Corarea _{ant} (mm ²)	43.08	0.14	42.77	43.33	43.80	0.59	42.66	45.11	-6.56	≤0.01
Corarea _{pos} (mm ²)	44.24	0.26	43.53	44.71	45.44	0.95	43.78	47.97	-6.78	≤0.01
Corarea _{tot} (mm ²)	103.89	1.12	100.73	105.66	105.20	2.13	102.35	112.68	-3.14	≤0.01
Splarea _{papex} (mm ²)	4.32	0.26	3.93	4.87	3.86	0.40	2.96	5.02	6.33	≤0.01

Splareaminthk (mm ²)	4.31	0.26	3.92	4.86	3.84	0.40	2.97	5.03	6.41	≤0.01
Dev _{aa} pex (mm)	0.00	0.00	0.00	0.00	0.03	0.02	0.00	0.06	-8.26	≤0.01
Dev _{pa} pex (mm)	0.07	0.02	0.04	0.09	0.26	0.12	0.05	0.59	-6.68	≤0.01
COM _x (mm)	0.04	0.02	0.01	0.09	-0.01	0.06	-0.20	0.12	4.23	≤0.01
COM _y (mm)	0.03	0.02	0.00	0.08	-0.01	0.09	-0.13	0.33	2.57	0.02
COM _z (mm)	0.77	0.02	0.71	0.81	0.85	0.08	0.70	1.06	-5.56	≤0.01
Dev _{va} minthk (mm)	0.83	0.21	0.44	1.27	0.91	0.36	0.16	1.68	-1.12	0.27
Dev _{pm} minthk (mm)	0.76	0.20	0.38	1.24	0.85	0.34	0.10	1.60	-1.23	0.23

- El valor predictivo de los parámetros modelados se estableció mediante un análisis ROC (Figura 5.4).

Figura 5.4 Curvas para los parámetros modelados en la detección de KC severo

Se encontraron cinco parámetros morfo-biométricos con áreas bajo la curva ROC (AUROC) superiores a 0.85: la desviación del ápex anterior alcanzó la mayor área bajo la curva (AUC, 0.977), con muy alta sensibilidad (96.7%) y especificidad (94.0%), debido al hecho de que el ápex es el punto de máxima curvatura de la superficie corneal. Es más, la desviación del ápex posterior mostró también una alta capacidad discriminativa (AUC, 0.948) con muy buena sensibilidad (90%) y excelente especificidad (99.9%). Las superficies corneales anterior y posterior, y las coordenadas del centro de masas, mostraron una alta AUC, pero, aunque su especificidad fue alta, su sensibilidad no fue tan buena como la relativa a la desviación de los ápices.

- Se realizó un estudio de las correlaciones existentes entre los parámetros biométricos modelados para el grupo de KC severo, obviándose el mismo para el grupo normal por ya haber sido realizado en un estudio previo²⁴⁹. La Tabla 5.6 resume las correlaciones más significativas encontradas.

Tabla 5.6 Correlaciones significativas para las variables modeladas en el grupo KC severo

<i>Correlaciones medidas</i>	<i>Grupo KC severo (n = 30)</i>	
	<i>Coefficiente de correlación</i>	<i>P valor</i>
Splarea _{papex} / Vol _{tot}	0.919	≤0.001
Corarea _{ant} / Corarea _{pos}	0.917	≤0.001
Corarea _{ant} / Corarea _{tot}	0.835	≤0.001
Corarea _{pos} / Corarea _{tot}	0.899	≤0.001
Vol _{tot} / Corarea _{tot}	0.439	0.015
COM _Y / Splarea _{papex}	0.448	0.013
COM _Z / Dev _{aapex}	0.366	0.046
COM _Z / Corarea _{ant}	0.925	≤0.001
COM _Z / Corarea _{pos}	0.874	≤0.001
COM _Z / Corarea _{tot}	0.873	≤0.001
Dev _{aminthk} / Dev _{papex}	0.597	≤0.001
Dev _{pminthk} / Dev _{papex}	0.611	≤0.001
Splarea _{aminthk} / Splarea _{papex}	0.989	≤0.001
Vol _{tot} / Splarea _{aminthk}	0.931	≤0.001
COM _X / COM _Y	-0.375	0.041
COM _X / Dev _{aminthk}	-0.429	0.018
COM _X / Dev _{pminthk}	-0.476	0.008
COM _Y / Splarea _{aminthk}	-0.403	0.027
Dev _{aapex} / Dev _{papex}	0.995	≤0.001

- Los índices morfo-biométricos volumétricos mostraron una reducción del volumen total corneal estadísticamente significativa en el grupo de KC severo en comparación con el grupo de sanos, lo que está en línea con el adelgazamiento corneal descrito por algunos autores con el progreso de la enfermedad^{35,250,251} a causa de la pérdida de tenacidad de la estructura corneal,^{252,253} y los resultados de estudios similares.^{185,254} Además, se encontraron correlaciones significativas positivas del volumen corneal con el área en el plano sagital por el ápex posterior ($R^2 = 0.919$, $p \leq 0.001$) y con el área en el plano sagital por el punto de mínimo espesor ($R^2 = 0.931$, $p \leq 0.001$) de modo que cuando el volumen disminuye por la pérdida de resistencia estructural que tiene lugar durante la progresión de la enfermedad, las áreas de los planos sagitales también disminuyen, aumentando la curvatura corneal. Esto concuerda con los hallazgos de volúmenes significativamente menores asociados con reducciones paquimétricas en ojos con KC grado II y superior.³⁵
- Los índices relativos a las áreas de las superficies anterior y posterior mostraron un aumento significativo, siendo mayor el área de la superficie posterior a la de la anterior, lo que puede explicarse por la tendencia de la córnea a mantener una arquitectura cónica en las etapas más avanzadas de la enfermedad, en las que la relación entre ambas superficies cambia a causa del debilitamiento biomecánico que manifiesta la córnea por la reorientación de su anatomofisiología.⁵

Las áreas anterior, posterior y total mostraron una fuerte correlación positiva entre ellas, incrementándose sus valores en el grupo KC severo, lo que se puede explicar por el debilitamiento estructural causado por una menor presencia de fibras de colágeno en cada lamela que aboca a una protrusión local severa que incrementa la superficie corneal¹⁵² por la acción de la presión intraocular sobre una arquitectura biológica estructuralmente debilitada. Estos resultados coinciden con los presentados en otros estudios.^{250,251,255}

6. Las desviaciones de los puntos de mínimo espesor mostraron la correlación más fuerte ($R^2 = 0.995$, $p \leq 0.001$), aunque estos fueron los únicos parámetros que no mostraron evidencia estadística de su capacidad para discriminar entre grupos. Esto da cuenta de relación ya conocida entre las curvaturas de las dos superficies corneales en los ojos con KC,^{250,255} pero en el caso de limitación visual severa, esta desviación varía de manera tal entre individuos, que la discriminación es imposible.
7. Las desviaciones de los ápices anterior y posterior se incrementaron para el grupo de KC severo. Este desplazamiento del eje óptico ha sido descrito como uno de los signos de las etapas más tardías del KC.² Además, la desviación del ápex posterior muestra una importante variabilidad con respecto al anterior, lo que está motivado por la tendencia del perfil asférico a reproducir el prolatismo fisiológico de la córnea en las etapas más avanzadas de la enfermedad.^{250,255} Esta variabilidad ha sido descrita en estudios previos,^{245,256,257} siendo esta la primera vez que la asimetría de la superficie posterior es cuantificada para ojos queratocónicos con limitación visual severa.
8. Los resultados mostraron una fuerte correlación entre el centro de masas Z y las áreas corneales anterior, posterior y total ($R^2 = 0.925$, $p \leq 0.001$; $R^2 = 0.874$, $p \leq 0.001$; $R^2 = 0.873$, $p \leq 0.001$; respectivamente), así como un desplazamiento del centro de masas a lo largo del eje de las Z positivas, lo que es lógico, ya que la pérdida de volumen corneal que curva las superficies, debe también forzar al centro de masas a moverse hacia la protrusión, como consecuencia del correspondiente desplazamiento de ambos ápices en la coordenada Z. Esto está en línea con lo hallado por otros autores, que encontraron que el valor medio de las elevaciones corneales anteriores y posteriores era mayor en ojos con KC subclínico o clínico.

5.5. Artículo 5

Procesado automático de imagen aplicado al conteo y caracterización de la forma de células endoteliales corneales. [Velázquez-Blázquez JS, Cavas-Martínez F, Campuzano VA, Alió del Barrio J, Cañavate FJF, Alió J. Automatic image processing applied to corneal endothelium cell count and shape characterization. *Dyna*. 2020;95(2). DOI: [10.6036/9275](https://doi.org/10.6036/9275)]

5.5.1 Resumen

El conteo de células del endotelio corneal, así como la caracterización de su porcentaje de hexagonalidad, cuentan con gran importancia en la actualidad para la detección de anomalías y patologías del ojo humano, tales como el glaucoma. El conteo automático de células realizado por el software integrado en los microscopios es bastante inconsistente, por lo que muchos laboratorios optan por usar el conteo manual como alternativa más fiable. Este conteo manual es una tarea ardua y tediosa, que puede dar lugar a errores humanos, por lo que se han realizado diversas propuestas para automatizar el proceso. Este artículo presenta un procedimiento para el pre-procesado, segmentación y análisis automático de las imágenes obtenidas por el microscopio confocal Konan NSP-9900 (Konan Medical, Hyogo, Japón), mediante la transformada watershed y el interfaz gráfico de usuario (GUI) creado con Matlab® a tal efecto. Se analizaron 30 imágenes del endotelio corneal (11 hombres / 19 mujeres, con edades comprendidas entre los 21 y los 52 años) seleccionadas de forma aleatoria de la base de datos de fotos con un número de células de entre 90 y 170, a fin de realizar su recuento y medir su porcentaje de hexagonalidad, comparando el resultado obtenido con el del conteo automático del software del microscopio, y cuantificando el error.

5.5.2 Resultados y conclusiones

Los principales hallazgos y consideraciones sobre los resultados obtenidos se exponen a continuación.

1. Se ha usado la transformada Watershed, y una interfaz gráfica de usuario (GUI) creada con Matlab®, para crear conjuntamente una forma más cómoda y eficiente de contar las células endoteliales, así como de medir su porcentaje de hexagonalidad.
2. Los resultados obtenidos sugieren que en cada caso es indispensable la adquisición de una región de interés (ROI) de la imagen, ya que suelen existir habitualmente diferencias de contraste, regiones en las que las células no son homogéneas o en las que sus bordes se mezclan, entre otras imperfecciones. La Figura 5.5 muestra la imagen original, la ROI seleccionada y el resultado final del proceso.

Figura 5.5 Imagen de partida (izq.), ROI seleccionada (centro) y resultado del proceso (drcha.)

3. El método para la detección de las regiones máximas funciona correctamente, aunque sus resultados dependen en gran manera de la segmentación previa y de la calidad de la imagen original.
4. Aunque se ensayaron muchos otros algoritmos de detección de bordes, tales como “sobel”, “prewitt” o “canny”, se optó finalmente por usar la transformada Watershed con distancia Cuasi-Euclídea, ya que proporciona resultados que recuerdan mucho a una forma hexagonal, que es la forma ideal de las células endoteliales corneales.
5. El error medio obtenido entre el procedimiento automático y el manual (considerado como “exacto”) para el conteo de células fue del 4.3 % (desviación estándar: ± 2.9 %), que puede considerarse un resultado razonablemente bueno (Figura 5.6). Los casos en los que el error fue superior al 10% correspondieron siempre a casos en los que la calidad de imagen era mala y/o existía alta variabilidad en el tamaño/forma de las células.

Figura 5.6 Error del conteo de células en modo automático

6. El error medio obtenido entre el procedimiento automático y el manual (considerado como “exacto”) para el porcentaje de hexagonalidad fue superior al 16 % (desviación estándar: ± 8.8 %), por lo que es preciso un estudio posterior para su reducción (Figura 5.7).

Figura 5.7 Error del conteo de porcentaje de hexagonalidad en modo automático

5.6. Artículo 6

Eficacia del análisis morfogeométrico de las superficies corneales en el queratocono con limitación visual moderada. [Velázquez-Blázquez JS, Fernández-Pacheco DG, Alió del Barrio J, Alió JL, Cavas-Martínez F. Efficacy of Morpho-Geometrical Analysis of the Corneal Surfaces in Keratoconus Disease According to Moderate Visual Limitation. In: Cavas-Martínez F., Sanz-Adan F., Morer Camo P., Lostado Lorza R., Santamaría Peña J. (eds) *Advances in Design Engineering. INGEGRAF 2019. Lecture Notes in Mechanical Engineering*. Springer, Cham. [10.1007/978-3-030-41200-5_29](https://doi.org/10.1007/978-3-030-41200-5_29)]

5.6.1 Resumen

En la enfermedad del queratocono tiene lugar una pérdida de tenacidad en las fibras de colágeno encargadas de proporcionarle a la estructura hemiesférica corneal una geometría estable y homogénea. provocándole un cambio de su curvatura, y, por consiguiente, dando lugar a una pérdida de calidad visual en los pacientes. La caracterización geométrica de la estructura hemiesférica por medio de parámetros biométricos es una técnica de diagnóstico muy sólida, basada en modelos virtuales en 3D, que ha sido ya validada para diversos grados de la patología queratocónica, aplicándose en el presente estudio para caracterizar la patología en ojos con una limitación visual moderada, equivalente a un grado III en la escala RETICS. ($0.4 < \text{CDVA} \leq 0.6$ en escala decimal, o $6/15 < \text{CDVA} \leq 6/9.5$ en Snellen). En este estudio prospectivo comparativo, se modelaron geoméricamente 93 corneas de 93 pacientes (seleccionadas aleatoriamente para evitar sesgos) estructuradas en dos grupos: un grupo “normal” (con corneas sanas), que incluyó 50 sujetos sin patologías oculares (36.80 ± 15.67 años); y un segundo grupo, compuesto de 43 diagnosticados con KC moderado (46.67 ± 24.99 años).

5.6.2 Resultados y conclusiones

Los principales hallazgos y consideraciones sobre los resultados obtenidos se exponen a continuación.

1. La mayor parte de los parámetros morfo-biométricos mostraron diferencias estadísticamente significativas en la comparación de corneas con KC moderado y corneas normales, con la única excepción de las variables desviación del punto de mínimo espesor anterior ($p = 0.713$) y desviación del punto de mínimo espesor posterior ($p = 0.570$), como se muestra en la Tabla 5.7 siguiente:

Tabla 5.7 Valores descriptivos y diferencias en los parámetros biométricos modelados entre los grupos normal y KC moderado SD: desviación standard. P: test estadístico, Z: z-score.

Parámetros	Grupo Normal (n = 50)				Grupo KC moderado (n = 43)				z	P
	Media	SD	Min	Max	Media	SD	Min	Max		
Vol _{tot} (mm ³)	25.71	1.53	23.23	29.07	23.97	1.52	21.06	28.74	-5.16	0.000

Corarea _{ant} (mm ²)	43.08	0.14	42.77	43.33	43.67	0.47	42.79	45.09	-7.37	0.000
Corarea _{pos} (mm ²)	44.24	0.26	43.53	44.71	45.22	0.80	44.17	47.53	-7.24	0.000
Corarea _{tot} (mm ²)	103.87	1.12	100.73	105.66	104.91	1.70	101.91	109.95	-3.47	0.001
Splarea _{papex} (mm ²)	4.32	0.26	3.93	4.87	3.93	0.29	3.19	4.83	6.72	0.000
Splarea _{aminthk} (mm ²)	4.31	0.26	3.92	4.86	3.92	0.29	3.19	4.82	6.61	0.000
Dev _{aapex} (mm)	0.00	0.00	0.00	0.01	0.02	0.00	0.00	0.07	-7.57	0.000
Dev _{papex} (mm)	0.07	0.02	0.04	0.09	0.21	0.08	0.03	0.34	-7.37	0.000
COM _x (mm)	0.04	0.02	0.01	0.09	0.02	0.05	-0.15	0.20	3.39	0.001
COM _y (mm)	0.03	0.02	0.00	0.08	0.00	0.05	-0.14	0.16	-5.14	0.000
COM _z (mm)	0.77	0.02	0.71	0.81	0.83	0.06	0.72	1.00	-6.26	0.000
Dev _{aminthk} (mm)	0.83	0.21	0.44	1.27	0.81	0.09	0.35	1.81	0.37	0.713
Dev _{pminthk} (mm)	0.76	0.20	0.38	1.24	0.74	0.26	0.30	1.31	0.57	0.570

Estos resultados concuerdan con los obtenidos en otros estudios previos que han evaluado algunos de estos parámetros anatómicos con equipos basados en la tecnología Scheimpflug²⁵⁵

- El valor predictivo de los parámetros modelados se estableció mediante un análisis ROC (Figura 5.8).

Figura 5.8 Curvas para los parámetros modelados en la detección de KC severo

Como puede observarse, se encontraron cuatro parámetros con valores de discriminación muy altos (AUROC > 0.9). Dos parámetros, que fueron las áreas de las superficies corneales anterior y posterior, mostraron valores de 0.937 y 0.945, motivado por el hecho de que en un escenario patológico tiene lugar un debilitamiento causado por la pérdida de tenacidad de la estructura hemiesférica y consecuentemente, se produce un incremento de la curvatura corneal. Esta tendencia

está en línea con algunos estudios previos en los que se ha realizado estudios de ratios entre las áreas de las superficies anterior y posterior par los distintos grados de severidad de la enfermedad.²⁵⁵ Los otros dos parámetros con alto poder de discriminación fueron la desviación del ápex anterior (AUROC, 0.910), y la desviación del ápex posterior (AUROC, 0.945), debido a que el ápex es el punto de máxima curvatura y por tanto, de acuerdo con otros autores¹⁵⁸, la desviación del ápex es un parámetro que puede afectar al rendimiento visual de los pacientes.

3. Se realizó un estudio de las correlaciones existentes entre los parámetros biométricos modelados para el grupo de KC moderado, obviándose el mismo para el grupo normal por ya haber sido realizado en un estudio previo²⁴⁹. La Tabla 5.8 resume las correlaciones más significativas encontradas.

Tabla 5.8 Correlaciones significativas para las variables modeladas en el grupo KC moderado

<i>Correlaciones medidas</i>	<i>Grupo KC moderado (n = 43)</i>	
	<i>Coefficiente de correlación</i>	<i>P valor</i>
Splareapapex / Voltot	0.965	0.000
Corareaant / Devpapex	0.313	0.041
Corareapos / Devpapex	0.361	0.017
Corareaant / Corareapos	0.941	0.000
Corareaant / Corareatot	0.778	0.000
Corareapos / Corareatot	0.864	0.000
Voltot / Corareatot	0.354	0.020
COMx / Corareaant	-0.340	0.025
COMx / Corareapos	-0.317	0.038
COMx / Corareatot	-0.361	0.017
COMx / COMz	-0.369	0.015
COMz / Corareaant	0.938	0.000
COMz / Corareapos	0.882	0.000
COMz / Corareatot	0.844	0.000
Devaminthk / Devpapex	0.440	0.003
Devpminthk / Devpapex	0.532	0.000
Devaminthk / Devpminthk	0.979	0.000
Splareaminthk / Splareapapex	0.997	0.000
Voltot / Splareaminthk	0.963	0.000
Devapapex / Devpapex	0.403	0.007

4. Así, los parámetros relativos a las áreas mostraron una fuerte correlación positiva, concretamente entre las áreas de las superficies anterior y posterior ($R^2= 0.941$, $p = 0.000$), la superficie anterior y la superficie corneal total ($R^2= 0.778$, $p = 0.000$), y las superficies posterior y corneal total ($R^2= 0.864$, $p = 0.000$), por el hecho de que las superficies corneales tienden a comportarse proporcionalmente durante la evolución de la enfermedad. Estos resultados son consistentes con los obtenidos para la curvatura corneal en ojos con queratocono, con el debilitamiento biomecánico de la córnea, y con el posible efecto de la presión intraocular sobre la estructura debilitada.^{5,35}
5. Con respecto a las desviaciones entre ambos ápices ($R^2= 0.832$, $p = 0.000$) y entre los puntos de mínimo espesor ($R^2= 0.997$, $p = 0.000$), se ha observado una fuerte correlación positiva, que se alinea con los resultados reportados por otros autores,²⁵⁵ que han demostrado una robusta correlación entre la desviación de los ápices y los puntos de mínimo espesor, y la progresión paquimétrica del espesor corneal.
6. En este trabajo se ha comprobado que los parámetros con mejor poder predictivo para el queratocono con limitación visual moderada son: el área de la superficie corneal anterior y la desviación del ápex posterior. Por lo tanto, este nuevo enfoque basado en el diagnóstico personalizado por modelos computacionales puede conducir a un mejor entendimiento de la enfermedad para este nivel de limitación óptica.

5.7. Artículo 7

Modelos personalizados impresos en 3D como herramienta para la mejora del conocimiento del paciente de una enfermedad asimétrica. [Velázquez JS, Cavas F, Bolarín JM, Alió JL. 3D Printed Personalized Corneal Models as a Tool for Improving Patient's Knowledge of an Asymmetric Disease. *Symmetry*. 2020;12(1):151. [10.3390/sym12010151](https://doi.org/10.3390/sym12010151)]

5.7.1 Resumen

La fabricación aditiva es una tecnología de vanguardia que se está usando actualmente en diversos campos de la medicina. Este estudio trata de evaluar la viabilidad, en la práctica clínica, de un modelo personalizado en 3D que permita mejorar las estrategias de asistencia doctor-paciente. Los datos obtenidos del tomógrafo corneal se utilizaron para hacer un modelo virtual en 3D con software CAD, para después imprimir este modelo mediante tecnología FDM y conseguir en consulta una réplica exacta a escala de la córnea de cada paciente. El software CAD y de impresión utilizado fue de código abierto, y el material de impresión seleccionado fue biodegradable y de coste bajo. Los usuarios de la clínica aportaron su retroalimentación por medio de una encuesta acerca de sus sensaciones al percibir con sus sentidos su propia córnea impresa.

5.7.2 Resultados y conclusiones

Los principales hallazgos y consideraciones sobre los resultados obtenidos se exponen a continuación.

1. En este estudio, se generaron dos modelos virtuales para cada paciente, uno de una córnea completa, y otro de una córnea con un corte sagital definido por los puntos de mínimo espesor.
2. Desde estos modelos virtuales, y usando software de código abierto, así como hardware de fabricación de bajo coste y acceso libre, se fabricaron modelos físicos. Para este trabajo, se testaron diferentes velocidades, espesores de lámina y tamaños de tobera, y se pudo observar que una mayor velocidad generalmente implicó mayores espesores de capa, y consecuentemente, peor acabado superficial del modelo, lo que concuerda con los hallazgos de otros autores ²⁵⁸
3. Se optó por la velocidad, espesor y tamaño de tobera indicados en la Tabla X, a fin de conseguir un acabado superficial aceptable con tiempos de impresión inferiores a 30 minutos, que es el tiempo medio que los pacientes esperan tras los test clínicos para entrar en la consulta del doctor a que les informe de su diagnóstico.
4. Con estos parámetros, la impresión es ligeramente más barata que en otros casos, ²⁵⁹ y otorga a la córnea impresa un aspecto “escalonado”, aunque con precisión suficiente para mostrar, de forma evidente, las diferencias entre una córnea normal y una con su espesor localmente disminuido.
5. El coste de fabricación del modelo impreso en 3D, dada su simplicidad y el bajo coste del PLA, fue de 1.10 € por unidad, lo que queda muy por debajo de los 490 € que

pueden costar modelos más complejos de órganos, tales como riñones, fabricados en material fotopolimérico.²⁶⁰

6. Los resultados del cuestionario planteado en clínica se muestran en la Tabla 5.9.

Tabla 5.9 Resultados del cuestionario

Pregunta realizada	Posible respuesta	Porcentaje	Media	Desviación estándar
Q1- ¿Qué utilidad atribuye a este modelo 3D personalizado?	De 1 = totalmente inútil a 10 = extremadamente útil	-	9.67	0.53
Q2- ¿Cuánto cree que el modelo 3D personalizado le ha ayudado a entender mejor su condición?	De 1 = nada en absoluto a 10 = en gran medida	-	9.74	0.45
Q3- ¿Querría llevarse el modelo 3D personalizado a casa tras la consulta?	Si	100.0		
	No	0.0		
	Neutro	0.0		
Q4- ¿Considera que usar este modelo 3D personalizado mejora la calidad de nuestro servicio clínico?	Si	95.2		
	No	0.0		
	Neutro	4.8		
Q5- ¿Cuánto cree que podría beneficiar a los pacientes el uso de estos modelos 3D personalizados en las consultas?	De 1 = nada en absoluto a 10 = en gran medida	-	8.62	0.58

7. Los resultados de la pregunta Q1 están en línea con los obtenidos en otras investigaciones similares.²⁶¹
8. Igual ocurre con los resultados de la cuestión Q2, que se alinean con lo observado en investigaciones previas, en las que se han usado modelos 3D para explicar a los pacientes su condición o la cirugía a la que se van a someter.^{260,262}
9. En relación con la cuestión Q3, su resultado contrasta con los resultados de otros estudios, en los cuales el 39% de pacientes expresaron que no estarían interesados en comprar el modelo²⁵⁹, lo que puede explicarse por el hecho de que el bajo coste de fabricación del modelo permite a la clínica ofrecer este servicio sin cargo adicional al paciente, integrando su coste en el de la propia consulta, facilitando que el paciente se lo quiera llevar consigo.
10. Los resultados de la cuestión Q4 están en línea con los presentados por otros autores, los cuales demuestran la utilidad de la impresión 3D para mejorar la práctica clínica,²⁶³ concretamente el 95.8% de los encuestados consideraron útiles los modelos 3D.
11. Los resultados de la cuestión Q5 van en línea con los valores obtenidos en otros estudios (9,4/10) cuando los pacientes eran preguntados acerca del nivel de satisfacción con los servicios médicos tras el uso de los modelos 3D para su educación.²⁶⁰

12. Las principales limitaciones del estudio son la limitada extensión de la cohorte de pacientes, dada la baja prevalencia de esta degeneración corneal, y que el estudio se limita a un único hospital.
13. En conclusión, la impresión 3D ha permitido la creación de modelos físicos precisos que reflejan las modificaciones asimétricas asociadas al queratocono. La percepción visual y táctil de estos modelos ha permitido a los pacientes comprender mejor, y por ende gestionar de mejor manera, las perspectivas de tratamiento de su enfermedad, haciendo el trabajo de los especialistas más eficiente, y por tanto mejorando la percepción de calidad el servicio prestado.

5.8. Artículo 8

Un modelo de aprendizaje automático basado en parámetros morfogeométricos para la clasificación de enfermedad RETICS y desarrollo de GUI. [Bolarín JM, Cavas F, Velázquez JS, Alió JL. A Machine-Learning Model Based on Morphogeometric Parameters for RETICS Disease Classification and GUI Development. *Applied Sciences*. 2020;10(5):1874. [10.3390/app10051874](https://doi.org/10.3390/app10051874)]

5.8.1 Resumen

Este estudio desarrolla y valida una interfaz gráfica de usuario (GUI) que combina dos modelos de aprendizaje automático basados en un conjunto de variables independientes con un doble objetivo: definir un nuevo concepto de probabilidad de riesgo asociado a estar aquejado de queratocono incipiente, y clasificar la severidad de la enfermedad de acuerdo a la escala RETICS (Red Temática para la Investigación Cooperativa en Salud), para asistir a los profesionales de la oftalmología en la gestión de la enfermedad. Para ello, se reclutaron 169 ojos de 169 individuos, 62 sanos (48.4% hombres y 51.6% mujeres) con edades comprendidas entre los 7 y los 60 años, y 107 con queratocono (63.2% hombres y 36.8% mujeres), con edades entre los 15 y los 98. Estos fueron clasificados de nuevo en 5 subgrupos, de acuerdo a la escala RETICS: 44 grado I; 18 grado II; 15 grado III; 15 grado IV y 15 grado V. Se midieron diferentes parámetros demográficos, ópticos, paquimétricos y geométricos, y se utilizaron los datos obtenidos para entrenar dos modelos de aprendizaje automático (*machine-learning*): un modelo de regresión logística multivariante para la detección del queratocono incipiente, y un modelo de regresión logística ordinal para la comprobación del grado RETICS.

5.8.2 Resultados y conclusiones

Los principales hallazgos y consideraciones sobre los resultados obtenidos se exponen a continuación.

1. No se encontraron diferencias estadísticamente significativas en términos de edad o género entre ninguno de los grupos.
2. El análisis descriptivo indicó que la mayoría de las variables no seguían una distribución normal. Se encontraron p-valores estadísticamente significativos para todas las variables entre el grupo control (Ctrl) y el grupo RETICS grado I, excepto para la edad ($p = 0.665$). Al testar las diferencias entre todos los grupos, (Ctrl y RETICS grados I a V), todos los p-valores fueron significativos de nuevo, menos la edad ($p = 0.344$).
3. Los resultados del modelo de regresión logística multivariante para los pacientes del grupo Ctrl vs RETICS I, mostraron que las variables con la contribución estadísticamente más significativa fueron: género, coma-like, espesor central, alto-orden y temporal.
4. La curva ROC de la Figura 5.9 muestra el punto de corte óptimo a 0.475, con un AUC de entrenamiento de 0.990, sensibilidad de 0.977 y especificidad de 0.919,

correspondiente a 59 verdaderos negativos, 41 verdaderos positivos, 3 falsos positivos y 3 falsos negativos.

Figura 5.9 Curva ROC del modelo de regresión logística en el que se indican el punto de corte óptimo y los parámetros de la validación por *bootstrapping*

- La Figura 5.10 muestra la distribución de las puntuaciones calculadas para ambos grupos, donde puede observarse que la gran mayoría de los casos control puntuaron entre 0 y 0.1, y los casos RETICS I lo hicieron entre 0.9 y 1.0.

Figura 5.10 Distribución de las puntuaciones de la regresión logística entre los pacientes del grupo Ctrl y RETICS I, y punto de corte óptimo

- Los parámetros del modelo de regresión logística ordinal que aportaron una contribución estadísticamente más significativa fueron: agudeza visual corregida a distancia, espesor central y temporal, mostrando la matriz de confusión una precisión global de 0,698 en un intervalo de confianza al 95% entre 0.623 y 0.766. Los valores de sensibilidad, especificidad y precisión balanceada entre grupos pueden verse en la Tabla 5.10.

Tabla 5.10 Matriz de confusión mostrando la sensibilidad, especificidad y precisión balanceada para cada grupo

True value	Predicted value					
	Ctrl	I	II	III	IV	V
Ctrl	55	7	0	0	0	0
I	12	26	4	2	0	0
II	2	9	6	3	1	0
III	0	3	3	6	3	0
IV	0	1	0	1	12	1
V	0	0	0	1	1	13

Sensitivity	0.887	0.591	0.333	0.400	0.800	0.867
Specificity	0.869	0.840	0.954	0.955	0.968	0.994
Balanced accuracy	0.878	0.715	0.643	0.677	0.884	0.930

7. Este es el primer clasificador de casos de queratocono que se basa en la agudeza visual de los pacientes. Los indicadores de rendimiento entre grupos son relativamente bajos, particularmente entre los grupos I, II y III, con precisiones que varían entre 0,623 y 0,766 respectivamente. Esto puede deberse a un bajo tamaño muestral, además de a falta de homogeneidad en la misma (hay muchos más pacientes en el grupo Ctrl y I que en los II a V).

Figura 5.11 Capturas de: (a) un individuo sano correctamente clasificado (verdadero negativo); (b) un individuo sano incorrectamente clasificado (falso positivo); (c) un KC grado I correctamente clasificado (verdadero positivo); (d) un KC grado I incorrectamente clasificado (falso negativo)

8. Se creó una interfaz gráfica de usuario para la aplicación de los modelos de aprendizaje automático, y se observó que la puntuación (*score*) se incrementaba rápidamente al pasar del grupo Ctrl al de grado I, manteniéndose en el 100% para el resto de gradaciones RETICS, lo que es consistente con la sensibilidad y especificidad del modelo. Durante el proceso de ajuste, el modelo trata de encontrar generalizaciones que agrupen predictores y predicción con la mayor eficacia posible, pero algunas muestras pueden no encajar en esta generalización dada la naturaleza subjetiva de los datos. Por tanto, es razonable esperar una cierta falta de precisión, lo que no implica necesariamente un fallo de la capacidad de ajuste del modelo. La Figura 5.11 muestra el aspecto general de la GUI, para cuatro casos incorrectamente clasificados, de acuerdo a criterios médicos.
9. El modelo confirmó cuantitativamente la dificultad de discernir entre los grupos de control y grado I ya que 17 de los 106 casos (16%) obtuvieron una puntuación entre 0.1 y 0.9.
10. Varios estudios han reportado resultados similares a los de este, usando modelos basados en métricas Scheimpflug^{150,189,190,264}, y aunque existen otros estudios que muestran resultados de sensibilidad y especificidad superiores a los de este,^{88,89,194,265-267}, bien definen un concepto de queratocono distinto al expuesto en el presente trabajo, o bien se basan en tecnologías distintas, lo que hace imposible su comparación directa.
11. Sería conveniente repetir el estudio con una muestra mayor y más homogénea, para comprobar si la precisión en el modelo de regresión logística ordinal aumenta, dado que el tamaño muestral óptimo de 374 individuos no pudo alcanzarse por el limitado tamaño del biobanco de datos.

5.9. Artículo 9

Comparación de parámetros morfológicos corneales y aberraciones de alto orden en ojos con queratocono y normales. [Velázquez JS, Cavas F, Bolarín JM, Alió JL. Comparison of Corneal Morphologic Parameters and High Order Aberrations in Keratoconus and Normal eyes. In: Rojas I, Valenzuela O., Rojas F., Ortuño F. (eds) Bioinformatics and Biomedical Engineering. IWBBIO 2020. Lecture Notes in Computer Science, vol 12108. Springer, Cham. DOI: [10.1007/978-3-030-45385-5_8](https://doi.org/10.1007/978-3-030-45385-5_8)]

5.9.1 Resumen

Este estudio se centra en evaluar la influencia de la geometría corneal en las aberraciones del sistema óptico, y su utilidad como criterio diagnóstico para el queratocono. Se incluyeron 451 ojos de 451 individuos con edades comprendidas entre los 16 y los 75 años, dividiéndose en dos grupos: el primero no presentaba patologías oculares y consistió en 159 ojos sanos de 159 pacientes (89 hombres / 70 mujeres, edad media 37.8 ± 11.6), mientras que el segundo correspondió a ojos enfermos, diagnosticados como con queratonoco de acuerdo a la escala de Alió-Shabayek, y con presencia de aberraciones de alto orden (HOA) de grado 3, tomándose 292 de 292 pacientes (162 hombres / 130 mujeres, edad media 42.2 ± 17.6). Todos los ojos fueron sometidos a un minucioso examen oftalmológico, se creó un modelo 3D de cada ojo por medio de software CAD y se midieron distintos parámetros anatómicos relacionados con la superficie y el volumen. Finalmente, se realizó un análisis de curvas ROC para determinar los parámetros que mejor caracterizan las córneas enfermas.

5.9.2 Resultados y conclusiones

Los principales hallazgos y consideraciones sobre los resultados obtenidos se exponen a continuación.

1. El análisis descriptivo de las variables y sus diferencias en la comparación de los grupos de ojos sanos y queratocónicos (Tabla 5.11), evidenció que todas las variables tienen buena capacidad de discriminación entre grupos ($p < 0.05$), sin excepción

Tabla 5.11 Valores descriptivos y diferencias enteras las variables geométricas modeladas entre los grupos normal y queratocono. SD: desviación estándar, P: test estadístico

Medidas	Grupo Normal (n = 159)				Grupo Queratocono (n = 292)				z	P
	Media	SD	Min	Max	Media	SD	Min	Max		
TCV _{A-S} (mm ³)	25.55	1.58	25.51	25.61	23.91	1.89	23.85	23.96	25.08	<0.001
ACSA _{A-S} (mm ²)	43.10	0.15	43.07	43.14	43.45	0.54	43.32	43.64	175.59	<0.001
PCSA _{A-S} (mm ²)	44.27	0.30	44.22	44.32	44.82	0.87	44.69	44.99	151.62	<0.001
TCSA _{A-S} (mm ²)	103.87	1.18	103.81	103.91	104.07	1.99	104.01	104.16	36.16	<0.001
SPAP _{A-S} (mm ²)	4.28	0.26	4.22	4.34	3.96	0.33	3.91	4.00	34.46	<0.001
SPAMTP _{A-S} (mm ²)	4.27	0.27	4.22	4.33	3.94	0.33	3.89	3.97	36.38	<0.001
CV _{A-S} R-0.5 (mm ³)	0.41	0.03	0.35	0.45	0.36	0.05	0.23	0.40	221.38	<0.001
CV _{A-S} R-1 (mm ³)	1.69	0.11	1.63	2.01	1.47	0.08	1.38	1.50	221.20	<0.001

CV _{A-S} R-1.5 (mm ³)	3.86	0.25	3.80	3.91	3.43	0.37	3.36	3.46	73.39	<0.001
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- De los parámetros volumétricos, el volumen total corneal (TCV_{A-S}) mostró diferencias significativas entre los grupos de estudio, aunque estas no fueron señalables, no coincidiendo este resultado con los de otros estudios previos,^{12,35,116} lo que puede ser explicado por el hecho de que el grupo de KC incluye una importante cantidad de ojos con KC avanzado. Además, esto se alinea con la existencia de diferencias significativas en los volúmenes medidos a R = 0.5, R = 1 y R = 1.5, pues la tendencia de la estructura corneal es ser más irregular u oblata (más curvada) en la zona central que en la periférica, en la que es más regular o prolata.
- En cuanto a los parámetros superficiales, todas las variables presentaron diferencias estadísticamente significativas entre grupos, siendo estas especialmente remarcables para las áreas de las superficies anterior y posterior. Este hallazgo está en línea con los de otros estudios que han usado la misma tecnología Sirius^{35,268}. Una posible explicación al hallazgo de nuestro estudio de que la superficie posterior se curva más que la anterior, puede ser por la relación de debilidad mecánica que presentan los tejidos corneales en el queratocono²⁶⁹
- El análisis de sensibilidad de las variables medidas reveló que algunas variables tenían valores de AUROC > 0.7, en concreto TCV_{A-S} AUC, ACSA_{A-S}, PCSA_{A-S}, SPAP_{A-S}, SPAMTP_{A-S}, CV_{A-S} R-0.5, CV_{A-S} R-1 and CV_{A-S} R-1.5 (Figura 5.12). Consecuentemente, estas variables pueden ser usadas para el diagnóstico del KC.

Figura 5.12 Curvas ROC de los parámetros modelados para la detección de KC

5.10. Artículo 10

Detección de queratocono subclínico mediante análisis morfogeométrico y volumétrico tridimensional (3-D). [Toprak I, Cavas F, Velázquez JS, Alió del Barrio JL, Alió JL. Subclinical keratoconus detection with three-dimensional (3-D) morphogeometric and volumetric analysis. *Acta Ophthalmologica*. (in press). [10.1111/aos.14433](https://doi.org/10.1111/aos.14433)]

5.10.1 Resumen

En este estudio se verificó la eficacia de la caracterización morfogeométrica y volumétrica de la córnea basada en modelado 3D para el diagnóstico del queratocono subclínico. Consistió en un estudio transversal para el que fueron seleccionados 93 ojos con queratocono subclínico y agudeza visual corregida lejana $\geq 20/20$ (grado 0 en la clasificación RETICS) y 109 ojos control. Se generó un modelo de la morfogeometría corneal 3D por ordenador usando los datos topográficos sin procesar. Se establecieron parámetros de distancia lineal, superficiales y volumétricos para el análisis estadístico. Posteriormente, se realizó un análisis de regresión mediante curvas ROC, para establecer la capacidad diagnóstica de cada variable. Finalmente, se llevó a cabo un análisis de regresión logística binario, y se desarrolló un modelo multifactorial para discriminar los casos sanos de los queratocónicos.

5.10.2 Resultados y conclusiones

Los principales hallazgos y consideraciones sobre los resultados obtenidos se exponen a continuación.

1. Los grupos de KC subclínico y control se mostraron estadísticamente similares para las variables edad, género y valor esférico ($p > 0.05$). Los valores de cilindro y equivalente esférico fueron significativamente superiores para el grupo de KC subclínico, así como los de presión intraocular (IOP), espesor corneal central (CCT) y mínimo espesor (MCT) fueron significativamente menores ($p > 0.05$).
2. Las variables $D_{apexant}$, $D_{apexpost}$, D_{mctant} , $D_{mctpost}$, mostraron valores significativamente más altos que los observados en el grupo control ($p < 0.05$). Estos resultados verifican un desplazamiento muy significativo (desde el vértex) de los ápices y puntos de mínimo espesor anterior y posterior en los ojos con KC subclínico, con respecto a los sanos. Es más, el desplazamiento apical posterior fue superior al anterior en ambos grupos.
3. Las variables A_{ant} , A_{post} y $A_{apexant}$ también mostraron valores significativamente más altos que los observados en el grupo control ($p < 0.05$). Estos resultados sugieren la presencia de elevaciones focales en las superficies corneales anterior y posterior, lo que incrementa el área en los ojos con KC subclínico.
4. Por otra parte, los valores de A_{total} , $A_{apexpost}$, $A_{mctpost}$, C_x , C_y y C_z fueron más bajos que los del grupo control. La reducción de A_{total} se debe a que equivale a la suma de A_{ant} , A_{post} y la superficie perimetral (correlacionada con el espesor corneal), por lo que un menor espesor corneal reduce el A_{total} por afectación de la superficie lateral.^{217,242,270}

De igual forma, el menor valor de $A_{apexpost}$ indica que el ápex posterior se localiza en la zona en la que la córnea circundante es más fina en ojos con KC subclínico (quizá debido al adelgazamiento estromal observado en el KC o a una elevación aislada del foco posterior), porque una córnea más fina disminuye el valor del área sagital. Esta explicación es razonable también para el menor valor de $A_{mctpost}$.^{217,242,270}

5. La diferencia en valor absoluto $D_{apexant}-D_{apexpost}$ fue significativamente más alta en el grupo KC que en el control ($p < 0.001$), mientras que para los puntos de mínimo espesor $D_{mctant}-D_{mctpost}$ no mostró capacidad de discriminación entre grupos ($p = 0.535$).
6. Tanto V_{total} como VOL_{mct} , VOL_{aap} y VOL_{pap} (para cada paso de radio 0.05 mm, entre los diámetros 0.1 y 1.5 mm) fueron significativamente menores en el grupo KC subclínico, en comparación con el control ($p < 0.001$). La reducción del volumen corneal en ojos con KC subclínico (Figura 5.13) se debe probablemente al adelgazamiento corneal, que fue confirmado por las medidas topográficas de espesor realizadas en el estudio. Por otra parte, la distensión de la matriz de colágeno puede quizás también contribuir a la pérdida de volumen en ojos con KC subclínico.²⁷¹

Figura 5.13 Evolución del volumen corneal alrededor del ápex anterior. Se observa que los ojos con KC subclínico presentan una reducción significativa para cada incremento de radio de 0.05 mm. Similar comportamiento se observó para el ápex posterior y los puntos de mínimo espesor

7. El análisis ROC mostró que $D_{apexpost}$ ($AUC= 0.890$, $p<0.0001$), MCT ($AUC= 0.888$, $p<0.0001$), la diferencia $D_{apexant}-D_{apexpost}$ ($AUC= 0.887$, $p<0.0001$), CCT ($AUC= 0.844$, $p<0.001$), VOL_{mct} , VOL_{aap} y VOL_{pap} ($AUC=$ comprendida de 0.828 a 0.866, $p<0.001$ para todos) y $A_{mctpost}$ ($AUC= 0.800$, $p<0.0001$) mostraron el rendimiento individual más alto para distinguir los ojos con KC subclínico de los sanos.

8. El análisis de regresión logística binaria desarrolló un modelo capaz de clasificar correctamente el 95% de los ojos (en normales y con KC subclínico) al 95% de confianza. Dicho modelo se expresó mediante la fórmula:

$$\text{Fórmula diagnóstica} = 35.470 \text{ (constante)} - (55.928 * [\text{diferencia } D_{\text{apexant}} - D_{\text{apexpos}}]) - (12.712 * \text{VOL}_{\text{aap}} 1.0 \text{ mm}) - (52.021 * C_x) - (0.028 * \text{CCT}) - (0.951 * \text{cilindro}) - (0.349 * \text{IOP})$$

Dicha fórmula aportó una sensibilidad del 96.8% y una especificidad del 95.4% en la discriminación de KC subclínico del normal cuando el valor de corte se fijaba a 1.07 AUC= 0.984, $p < 0.0001$, IC al 95%= 0.970-0.999, Figura 5.14)

Figura 5.14 Curvas ROC para la fórmula de discriminación de ojos normales de ojos con KC subclínico

9. Estos valores de sensibilidad y especificidad son superiores a los del algoritmo de monitoreo estándar del tomógrafo Sirius (44.1% sensibilidad y 96.3% especificidad) y a los previamente reportados en la detección de KC subclínico.^{35,86,256,272,273.}
10. El análisis corneal en 3D realizado en este estudio demuestra que, para ojos con KC subclínico existe un desplazamiento altamente asimétrico entre los ápices corneales anterior y posterior, y un notable descenso del volumen corneal comparado con el de ojos sanos.

5.11. Artículo 11

Análisis morfogeométrico para la caracterización del queratocono considerando la localización espacial y la proyección del ápex y el punto de mínimo espesor. [Velázquez JS, Cavas F, Piñero DP, Cañavate FJF, Alió del Barrio J, Alió JL. Morphogeometric analysis for characterization of keratoconus considering the spatial localization and projection of apex and minimum corneal thickness point. *Journal of Advanced Research*. (in press). DOI: [10.1016/j.jare.2020.03.012](https://doi.org/10.1016/j.jare.2020.03.012)]

5.11.1 Resumen

Este trabajo evaluó los cambios que experimentan en el queratocono varios nuevos índices morfogeométricos desarrollados, que consideran la posición de los ápices corneales anterior y posterior y los puntos de mínimo espesor, tanto entre ellos como entre cada uno de ellos y el eje geométrico. Este estudio prospectivo comparativo incluyó 440 ojos de 440 pacientes: 124 ojos de 124 sujetos para el grupo control (28.2%) y 316 ojos de 316 sujetos (71.8%) para el grupo KC, con una edad media de 38.4 años (SD:15.6; mediana: 36.0, rango: 7-99). Los pacientes del grupo KC fueron clasificados de acuerdo a la escala Amsler-Krumeich en 223 ojos grado I (70.6%), 57 grado II (18.1%) 9 grado III (2.8%) y 27 grado IV (8.5%) La información tomográfica (Sirius®, Costruzione Strumenti Oftalmici, Italia) fue tratada con el software SolidWorks v2013, definiéndose los siguientes nuevos parámetros morfogeométricos: ángulo eje geométrico-línea de ápex (GA-AP), ángulo eje geométrico-línea de mínimo espesor (GA-MCT), ángulo línea de ápex-línea de mínimo espesor (AP-MCT), y las distancias entre le ápex y el punto de mínimo espesor anterior (AP-MCTd) y posterior (posterior AP-MCTd). Se realizó un análisis estadístico de los parámetros, estudiando su correlación y se estudió su capacidad de detección del queratocono mediante curvas ROC, seleccionándose en este caso la mitad de individuos para el estudio, y la otra mitad para su validación.

5.11.2 Resultados y conclusiones

Los principales hallazgos y consideraciones sobre los resultados obtenidos se exponen a continuación.

1. Se hallaron diferencias estadísticamente significativas entre los grupos control y KC para todos los parámetros salvo J_{45} . Por tanto, las variables seleccionadas permiten detectar la presencia de KC.
2. Se analizó la repetibilidad interobservador de las variables paquimétricas, no encontrándose diferencias significativas del valor de S_w asociados a los valores de espesor corneal central o mínimo ($p = 0.470$). Por tanto, la variabilidad de las medidas no puede achacarse al aparato ni al observador, sino a diferencias motivadas por la presencia de la enfermedad.
3. El análisis morfogeométrico mostró valores significativamente más altos de A_{ant} y A_{post} para el grupo KC al comparar con el control ($p < 0.001$). Este dato es consistente con los resultados de estudios previos,^{12,217} y confirma que el encurvamiento local

- que tiene lugar en las superficies corneales anterior y posterior en el KC, lleva a un incremento del área que ocupa cada superficie.^{254,274-279}
4. Los nuevos parámetros morfogeométricos GA-AP, GA-MCT, AP-MCT y anterior AP-MCTd mostraron diferencias estadísticamente significativas entre los grupos ($p < 0.001$). Se observaron valores significativamente más altos de GA-AP, GA-MCT y AP-MCT en el grupo KC, lo que confirma la pérdida de simetría de revolución en la córnea cuando existe KC, con una mayor discrepancia del eje óptico (la línea que une el centro geométrico de ambas superficies corneales) con respecto a la línea que une los ápices de ambas superficies y la línea que une los puntos de mínimo espesor. Esto está en línea con los resultados de estudios previos.^{254,276,280}
La pequeña (en magnitud) pero estadísticamente significativa diferencia entre los grupos control y KC para anterior AP-MCTd confirma que la diferencia entre ápex y punto de MCT en cada superficie es menos crítico que la proyección de estas posiciones sobre la propia superficie, y prueba que la correlación entre las geometrías de ambas caras corneales está alterada en el KC.⁸⁷
 5. En el grupo control, se encontraron correlaciones muy débiles entre los nuevos parámetros morfogeométricos y otros parámetros clínicos. Por el contrario, se encontraron varias correlaciones significativas en el grupo KC (Tabla 5.12).

Tabla 5.12 Resumen de las distintas correlaciones estadísticamente significativas encontradas entre los parámetros corneales definidos y obtenidos por análisis morfogeométrico y los parámetros clínicos para el grupo KC

Parámetro morfogeométrico	Correlación con	Coefficiente de correlación	p-valor
GA-AP °	CDVA	0.428	<0.001
	HOA RMS	0.753	<0.001
	Coma RMS	0.750	<0.001
	Coma-like RMS	0.749	<0.001
	Spherical-like RMS	0.655	<0.001
	Q 8 mm anterior	-0.487	<0.001
	Grado de severidad del KC	0.418	<0.001
	MCT	-0.618	<0.001
	CCT	-0.486	<0.001
GA-MCT °	Grado de severidad del KC	0.155	0.006
AP-MCT °	HO RMS	0.667	<0.001
	Coma RMS	0.664	<0.001
	Coma-like RMS	0.662	<0.001
	Spherical-like RMS	0.587	<0.001
	Grado de severidad del KC	0.367	<0.001
	MCT	-0.550	<0.001
	CCT	-0.414	<0.001

Anterior AP-MCTd (mm)	Q 4.5 mm anterior	0.600	<0.001
	Q 8 mm anterior	0.430	<0.001
	Grado de severidad del KC	-0.180	0.001
Posterior AP-MCTd (mm)	Q 4.5 mm anterior	0.650	<0.001
	Q 8 mm anterior	0.550	<0.001
	Grado de severidad del KC	-0.225	<0.001

Se observa cómo la correlación del grado de severidad del KC con los nuevos parámetros morfogeométricos es bastante limitada.

Se hallaron correlaciones significativas moderadas entre las aberraciones corneales (≥ 0.587 , $p < 0.001$), especialmente el coma-RMS (Figura 5.15) y los parámetros de espesor corneal ($r \leq -0.414$, $p < 0.001$) con GA-AP y AP-MCT.

Figura 5.15 Diagrama de dispersión que muestra la relación entre coma-RMS y: GA-AP (sup.) y AP-MCT (inf.)

La Q anterior para las áreas de 4.5 mm y 8 mm se encontró significativamente correlacionada con anterior AP-MCTd ($r \geq 0.430$, $p < 0.001$) y posterior AP-MCTd ($r \geq 0.550$, $p < 0.001$) (Figura 5.16).

Figura 5.16 Diagrama de dispersión que muestra la relación entre Q 4.5 mm y; anterior AP-MCTd (sup.) y posterior AP-MCTd (inf.)

6. Se encontraron valores de CDVA más bajos y un mayor nivel de aberraciones corneales tipo coma-like y spherical-like, así como valores más negativos de asfericidad y menores espesores central y mínimo, en los ojos con mayores valores de GA-AP y AP-MCT. Esto confirma la capacidad de estos dos parámetros para caracterizar los cambios estructurales que tienen lugar en el KC con un nivel creciente de severidad.
7. De igual manera, se encontraron correlaciones significativas entre las asfericidades corneales anterior y posterior y posterior AP-MCTd, concretamente, valores más altos de estos parámetros se observaron en ojos con valores menos negativos de asfericidad. Por tanto, el punto de mínimo espesor y el ápex se aproximan en

aquellos ojos con superficies corneales anterior y posterior más prolatas, lo que se asocia a las etapas más avanzadas del KC.^{277-279,281,282}

8. Respecto al análisis ROC, con la mitad de población evaluada los parámetros GA-AP y AP-MCT mostraron la mejor habilidad diagnóstica para la detección de KC, con áreas bajo la curva (AUC) de 0.908 y 0.891 respectivamente ($p < 0.001$). Los valores de corte óptimos para estos parámetros fueron 9.61° (sensibilidad 85.5%, especificidad 80.3%) y 18.08° (sensibilidad 80.5%, especificidad 78.7%), respectivamente. Cuando el punto de corte obtenido se aplicó al resto de la muestra, las tasas de falsos positivos (FP) y falsos negativos fueron del 9.7% y 15.2% respectivamente, por lo que el valor predictivo resultante para los casos positivos (PPV) fue del 95.8%, y de los negativos (NPV) del 71.8%, respectivamente.
9. Se concluye que, aunque los cambios ocurren de forma separada en cada superficie corneal, existe una alteración significativa de la configuración 3D de la estructura corneal durante el KC, que debe ser considerada en las evaluaciones y decisiones clínicas.

5.12. Artículo 12

EMKLAS: un nuevo sistema automático de puntuación para la detección de los queratoconos incipiente y leve. [Velázquez-Blázquez JS, Bolarín JM, Cavas-Martínez F, Alió JL. EMKLAS: A New Automatic-Scoring System for Early and Mild Keratoconus Detection. *Translational Vision Science & Technology*. (in press)]

5.12.1 Resumen

Este trabajo tuvo por objeto la creación de un modelo predictivo basado en un conjunto de variables demográficas, ópticas y geométricas, con un doble fin: clasificar el queratocono en sus primeras etapas de manifestación clínica, y establecer la probabilidad de haber clasificado correctamente cada caso. Para ello, se seleccionaron 178 ojos de 178 pacientes (115 hombres, 64.6%; 63 mujeres, 35.4%; rango edad: 15-76 años), de los cuales, 74 fueron sujetos control “sanos”, y 104 padecían de queratocono de acuerdo con el sistema de gradación RETICS (Red Temática para la Investigación Cooperativa en Salud), siendo este subdividido a su vez en 61 paciente con grado I (KC incipiente) y 43 con grado II (KC leve). Se seleccionó únicamente un ojo de cada paciente, y se estudiaron 27 parámetros en total (demográficos, clínicos, paquimétricos y geométricos). Se realizó un estudio de correlación, y se seleccionaron finalmente 5 variables clave. Los datos obtenidos se utilizaron para entrenar un modelo de regresión logística ordinal programado en forma de aplicación web, capaz de usar los datos de nuevos pacientes para predicciones en tiempo real. Un segundo juego de 41 ojos (19 sanos, 14 grado I y 8 grado II) obtenidos 4 meses después se usó para la validación independiente del modelo.

5.12.2 Resultados y conclusiones

Los principales hallazgos y consideraciones sobre los resultados obtenidos se exponen a continuación.

1. Tras usar los test de Kruskal-Wallis para las variables cuantitativas y χ^2 para la variable cualitativa “genero”, se observó que todas las variables cuantitativas, salvo la edad, eje y aberración esférica, mostraron relaciones significativas, mientras que la variable cualitativa “genero” no lo hizo. Se utilizó un test no paramétrico porque la mayor parte de las variables cuantitativas no pasaron el test de normalidad.
2. El estudio de correlación reveló que todas las variables salvo edad, esfera, eje, aberración esférica y desviaciones de los puntos de mínimo espesor anterior y posterior estaban fuertemente correlacionadas, y por tanto aportaban poca información (Figura 5.17). Esto sugirió que un modelo simple con un número limitado de variables sería el deseable para aplicar la técnica de regresión logística.

Figura 5.17 Diagrama de correlaciones para las variables cuantitativas. El color indica correlación positiva o negativa

- Se seleccionaron de entre todas las variables edad, género, CDVA, Q8mm y desviación del MTP posterior, aunque como se ve en la Figura 5.18, la contribución de la edad y el género al modelo fueron muy pequeñas.

Figura 5.18 Gráficos de efecto de las variables incluidas en el modelo de regresión logística ordinal

- En la distribución de puntuaciones para cada grupo, pudo observarse que la predicción de puntuación para el grupo Ctrl sigue una distribución marcadamente diferente para los verdaderos Ctrl vs los verdaderos KC incipiente y KC leve (Figura 5.19). Un comportamiento similar se observó para la predicción de KC leve para los verdaderos KC ligeros vs los verdaderos control y KC incipiente. Sin embargo, la puntuación de predicción de los KC incipiente para los verdaderos KC incipiente frente a los verdaderos Ctrl y KC leve no muestra esas diferencias tan marcadas, lo que indica que los pacientes con KC incipiente se encuentran en algún punto de una zona intermedia entre los otros dos grupos.

Figura 5.19 Distribución de las puntuaciones generadas por el modelo de regresión logística ordinal para todos los sujetos del conjunto de entrenamiento. Cada gráfico corresponde a la puntuación predicha para el grupo, mientras que cada “judía” en los gráficos corresponde al grupo de referencia. Las “judías” muestran la distribución aproximada, y las cajas marcan la mediana y los cuartiles 25° y 75°. Cada punto representa un paciente

- La matriz de confusión mostró que solamente un paciente con KC leve se predijo como Ctrl, y de nuevo, sólo un verdadero paciente Ctrl se predijo como KC leve. Un mayor grado de incorrección en la clasificación pudo ser observado entre los grupos adyacentes (Ctrl vs KC incipiente, o KC incipiente vs KC leve), con 47 pacientes (26.4%) incorrectamente clasificados entre falsos positivos y falsos negativos. La precisión balanceada del modelo de entrenamiento para cada grupo se muestra en la Tabla 5.13, siendo la precisión global de 0.73 (IC 95%: 0.65 – 0.79).

Tabla 5.13 Resultados de sensibilidad, especificidad y precisión balanceada para el modelo de regresión logística ordinal entrenado

	Ctrl	KC incipiente	KC leve
Sensibilidad	0.85	0.57	0.72
Especificidad	0.82	0.82	0.93
Precisión balanceada	0.83	0.70	0.83

6. El área bajo la curva ROC, la sensibilidad y la especificidad alcanzada tras el proceso de validación interna del modelo de detección ordinal, sugieren una alta eficacia, con valores de AUC de 0.87, 0.89 y 0.94 para los grupos Ctrl, KC incipiente y KC leve respectivamente.
7. La validación independiente del modelo de regresión logística ordinal mostró una precisión global de 0.71 (IC 95%: 0.55 – 0.84), lo que sugiere que, aunque los valores fueron ligeramente inferiores a los de entrenamiento (precisión de 0.79, 0.69 y 0.80 para los grupos Ctrl, KC incipiente y KC leve, respectivamente), los resultados en general van en línea con los obtenidos en la validación interna por *bootstrapping*.
8. Se creó una aplicación web que contenía el modelo pre-entrenado para permitir al usuario estimar de forma instantánea la probabilidad de que un paciente pertenezca a cada grupo modelado. Tras pulsar el botón “GET SCORE”, la aplicación devuelve una predicción en forma de porcentaje (llamada “EMKLAS”), mostrando una córnea típica con los principales parámetros usados en la predicción (Figura 5.20).

Figura 5.20 Captura de pantalla de un sujeto con KC incipiente (RETICS) y la representación típica del modelo 3D virtual

9. Debe tenerse en cuenta que este clasificador ha sido entrenado tomando el diagnóstico de los oftalmólogos profesionales como “estándar de oro”, lo que inevitablemente implica un cierto grado de subjetividad en la información que se toma como cierta. Durante el proceso de ajuste, el modelo trata de encontrar una generalización que enlace los predictores con la predicción, maximizando el rendimiento. Sin embargo, algunos casos implican ciertas muestras que no encajan en ninguna de las generalizaciones (Figura 5.21), dada la naturaleza subjetiva del modelo de entrenamiento, lo que hace difícil establecer fronteras bien definidas entre los grupos.

Figura 5.21 Captura de pantalla representando todas las posibles clases del modelo. La fila superior corresponde a verdaderos individuos sanos, pronosticados como sano (A), KC incipiente (B) y KC leve. La fila intermedia corresponde a individuos con verdadero KC incipiente, diagnosticados como sano (D), con KC incipiente (E) y con KC leve (F). La fila inferior corresponde a individuos con verdadero KC leve, diagnosticados como sano (G), KC incipiente (H) y KC leve (I)

10. Los resultados obtenidos van en línea con los de otros estudios basados en la misma tecnología,^{150,190,264} lo que sugiere que la eficacia validada del modelo es bastante buena, aunque la toma de decisiones basada en el modelo de regresión logística ordinal debe hacerse con cautela, siendo recomendable repetir el entrenamiento del modelo con una muestra independiente más grande para corroborar los resultados.

6

Conclusiones y prospección

6.1. Conclusiones

De acuerdo al objetivo principal y los objetivos secundarios establecidos para la presente tesis, se han podido extraer las siguientes conclusiones:

- ❖ Se han utilizado con éxito herramientas de Diseño Asistido por Ordenador (CAD) para la creación de modelos personalizados que representan la estructura hemisférica del segmento anterior del ojo humano a nivel macroscópico, y se han utilizado para validar parámetros morfogeométricos ya existentes (lineales, superficiales y volumétricos) y comprobar la utilidad clínica de otros nuevos (angulares y de alineamiento axial) para distintos grados de evolución del queratocono.
- ❖ Se ha estudiado a nivel microscópico la morfogeometría de las células endoteliales corneales, y se ha logrado diseñar y programar tanto una GUI como varios algoritmos de detección de células, que reducen el tiempo de análisis y evitan los errores humanos cuando se usa el software del microscopio confocal. Sin embargo, se ha detectado que la calidad y las características de las imágenes originales afectan considerablemente el nivel de error
- ❖ Se han revisado los distintos sistemas univariantes y multivariantes de diagnóstico y clasificación del queratocono por medio de tecnología Scheimpflug, y se ha demostrado que los parámetros morfogeométricos propuestos permiten tanto la detección, como el diagnóstico y la clasificación exitosos del queratocono (tanto subclínico como clínico) en las escalas RETICS, Amsler-Krumeich y Alió-Shabayek.
- ❖ Las aplicaciones web EMKLAS y KERATOSCORE conforman un modelo predictivo basado en un sistema de aprendizaje automático que permite la detección temprana y clasificación de todos los grados de queratocono en escala RETICS, indicando la probabilidad de haber clasificado correctamente cada caso, y si bien es cierto que las herramientas no son infalibles, y que sería conveniente reentrenar sus modelos predictivos con una muestra de pacientes mayor, es innegable que mejoran sustancialmente los resultados del KC-screening del tomógrafo corneal Sirius, y suponen una valiosa herramienta para la toma de decisiones del oftalmólogo.
- ❖ Se ha aplicado el modelo solido personalizado impreso en 3D a la educación del paciente, comprobándose que la percepción visual y táctil del modelo permite a los pacientes entender mucho mejor su enfermedad y el tratamiento indicado para ella, haciendo por tanto el trabajo de los profesionales de la salud más sencillo, y mejorando la percepción de calidad del servicio asistencial prestado por ellos.

Por lo tanto, podemos concluir que se debe aceptar la hipótesis de partida, y consecuentemente, se pueden utilizar patrones de comportamiento topográficos, optométricos y celulares para la detección, diagnóstico y caracterización de las ectasias corneales, desde un punto de vista óptico-geométrico.

6.2. Prospección

Los estudios que conforman la presente tesis sientan las bases para el desarrollo de futuras líneas de investigación de creciente interés, como las que se detallan a continuación:

- ❖ Utilización del modelo personalizado y las variables morfogeométricas propuestas para la caracterización de ojos sanos y ojos con otras patologías ectasias corneales, como son el queratoglobos o la degeneración marginal pelúcida.
- ❖ Utilización del modelo 3D personalizado para el estudio de la morfogeometría corneal y que sea compatible con las métricas obtenidas de otros topógrafos Scheimpflug, tales como Pentacam (Oculus, Alemania) y Galilei (Ziemer Ophthalmology, Alemania), todos ellos basados en el principio de proyección de una hendidura de luz.
- ❖ Caracterizar desde el punto de vista morfológico el efecto de tratamientos como el crosslinking o los anillos intracorneales, en la geometría y comportamiento biomecánico de la córnea, estudiando los parámetros de agudeza visual y relacionándolos con los cambios estructurales experimentados por la estructura hemiesférica del segmento anterior.
- ❖ Diseño de sistemas de aprendizaje automático basados en parámetros morfogeométricos para evaluar la progresión de la enfermedad tras la aplicación de tratamientos invasivos (crosslinking o por anillos intracorneales), con el fin de evaluar la eficiencia de estos tratamientos.
- ❖ Utilizar el modelo 3D personalizado para la impresión 3D con otros materiales, tales como polímeros transparentes, que puedan utilizarse para la educación al paciente y la mejora de la calidad asistencial en clínicas, o la educación en centros universitarios.

Otras contribuciones e indicios de calidad

7.1. Otras contribuciones e indicios de calidad

7.1.1 Congresos internacionales

L. Bataille, F. Cavas-Martínez, D. Fernández Pacheco, J. Velázquez, J. Bolarín, J. Alió. *“Evaluation of the diagnostic ability of geometrical parameters characterizing the morphology and regularity of the cornea in keratoconus”*. 36th Congress of the ESCRS, Vienna, 2018.

L. Bataille, F. Cavas-Martínez, D. Fernández Pacheco, J. Velázquez, J. Bolarín, J. Alió. *“Comparison of corneal surface measurements in normal and keratoconic eyes, a comprehensive model for disease detection”*. 9th Eucornea Congress, Viena, Austria. 2018.

L. Bataille, F. Cavas-Martínez, D. Fernández Pacheco, J. Velázquez, J. Bolarín, J. Alió. *“Optical and volumetrical characterization of the corneal asymmetry in keratoconus and application in its detection”*. 9th Eucornea Congress, Viena, Austria. 2018.

Cavas-Martínez F, Fernández-Pacheco DG, Cañavate FJF, Velázquez-Blázquez JS, Bolarín JM, Alió JL. *“Study of Morpho-Geometric Variables to Improve the Diagnosis in Keratoconus with Mild Visual Limitation”*. 9th International Joint Conference on Mechanics, Design Engineering and Advanced Manufacturing (JCM2018), Cartagena, España. 2018.

Cavas-Martínez F, Fernández-Pacheco DG, Canavate FJF, et al. *“Early keratoconus detection by patient-specific 3D modelling and geometric parameters analysis”*. 9th International Joint Conference on Mechanics, Design Engineering and Advanced Manufacturing (JCM2018), Cartagena, España. 2018.

Velázquez-Blázquez JS, Cavas-Martínez F, Alió del Barrio J, et al. *“Detection of Subclinical Keratoconus Using Biometric Parameters”*. 7th International Work-Conference on Bioinformatics and Biomedical Engineering (IWBBIO2019). Granada, España. 2019.

Velázquez-Blázquez JS, Fernández-Pacheco DG, Alió del Barrio J, Alió JL, Cavas-Martínez F. *“Efficacy of Morpho-Geometrical Analysis of the Corneal Surfaces in Keratoconus Disease According to Moderate Visual Limitation”*. 29^o Congreso Internacional de Ingeniería Gráfica (INGEGRAF2019), Logroño, España. 2019.

7.1.2 Premios de investigación

Premio a la mejor comunicación en la categoría de “Bioingeniería Gráfica” en la International Joint Conference on Mechanics, Design Engineering and Advanced Manufacturing (JCM2018) por *“Study of Morpho-Geometric Variables to Improve the Diagnosis in Keratoconus with Mild Visual Limitation”*. Cartagena, España. 2018.

Premio a la mejor comunicación en la categoría de “Bioingeniería Gráfica” el 29^o Congreso Internacional de Ingeniería Gráfica (INGEGRAF2019) por *“Efficacy of Morpho-Geometrical Analysis of the Corneal Surfaces in Keratoconus Disease According to Moderate Visual Limitation”*. Logroño, España. 2019

7.1.3 Registros de software

De la presente investigación se han derivado tres conjuntos de programas informáticos, cuya propiedad intelectual se ha solicitado registrar:

- A. Cavas F, Velázquez JS, Campuzano VM, Cañavate FJF. CoEnCell. Número de solicitud: MU-164-2020. Fecha de Registro: 28/02/2020. Entidad titular de los derechos: Universidad Politécnica de Cartagena.
- B. Cavas F, Velázquez JS, Bolarín JM. KERATOSCORE. Número de solicitud: MU-170-2020. Fecha de Registro: 02/03/2020. Entidad titular de los derechos: Universidad Politécnica de Cartagena.
- C. Cavas F, Velázquez JS, Bolarín JM. EMKLAS. Número de solicitud: MU-171-2020. Fecha de Registro: 02/03/2020. Entidad titular de los derechos: Universidad Politécnica de Cartagena.

Se han incluido en el apéndice final las memorias descriptivas de cada programa.

9

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APÉNDICE

Article

Study of Morpho-Geometric Variables to Improve the Diagnosis in Keratoconus with Mild Visual Limitation

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Abstract: The validation of new methods for the diagnosis of incipient cases of Keratoconus (KC) with mild visual limitation is of great interest in the field of ophthalmology. During the asymmetric progression of the disease, the current diagnostic indexes do not record the geometric decompensation of the corneal curvature nor the variation of the spatial profile that occurs in singular points of the cornea. The purpose of this work is to determine the structural characterization of the asymmetry of the disease by using morpho-geometric parameters in KC eyes with mild visual limitation including using an analysis of a patient-specific virtual model with the aid of computer-aided design (CAD) tools. This comparative study included 80 eyes of patients classified as mild KC according to the degree of visual limitation and a control group of 122 eyes of normal patients. The metric with the highest area under the receiver operating characteristic (ROC) curve was the posterior apex deviation. The most prominent correlation was found between the anterior and posterior deviations of the thinnest point for the mild keratoconic cases. This new custom computational approach provides the clinician with a three-dimensional view of the corneal architecture when the visual loss starts to impair.

Keywords: geometric model; asymmetric evolution; computer-aided design; corneal topographer

1. Introduction

The human eye has four refractive surfaces, five refractive indexes, and four thicknesses [1]. The variation of any of these parameters affects the refractive state of the eye. Among all of them, the cornea is the most important parameter from a refractive point of view.

A perfect optical system would be completely symmetrical and would be free of distortion and transverse chromatic aberration. However, the cornea is not a perfect biological structure because its surfaces do not present symmetry of revolution in a healthy scenario, which entails the existence of deformations, misalignments, and decentralizations between its anterior and posterior surfaces and between its singular points (apex, vertex, and minimum thickness point) [2]. However, in a pathological scenario, the progression of the asymmetry in the corneal architecture contributes to a decrease in its optical capacity, which causes a loss of the patients' visual quality [3]. This decrease in optical functionality may have its origin in a physio-pathological mechanism derived from a pathology called keratoconus. Keratoconus (KC) has an estimated prevalence of approximately 50–230 individuals

per 100,000 people in the general population [4]. This asymmetrical ectatic disorder is geometrically characterized by [5] the details below.

- a geometric decompensation or progressive distortion of the corneal curvature from a singular point denominated the corneal apex.
- a decompensation of the spatial profile of pachymetry, which is described as an annular increase/decrease of its thickness from a singular point called the minimum thickness point.

Both characterizations involve a local geometric alteration in the cornea during keratoconus. Depending on the level of corneal deformation, it leads to a gradual deterioration of visual performance [6–8].

Several reports had the task to assess the different stages of KC and their corneal deformations by using different devices and analyses [9,10]. Most of the studies performed have only taken into consideration the morphological features to discriminate the different stages of the disease without considering other important clinical aspects directly correlated to the corneal visual disability [11].

As recently reported, the corneal geometric modeling has been proposed for the study of ectasia characterization [12]. Nevertheless, to the author's knowledge, this new tool has not been considered for the study of KC eyes with mild impaired visual function as graded along the evolution of the disease. Patient-specific 3D modeling may help to better recognize the changes that happen in the cornea when KC is developed and it correlates with vision decay as the disease evolves [11] (Figure 1). There is an important threshold between normality and, when the disease starts to clinically affect the patient, a better understanding of these cases could help the management of ectasia in the clinical practice.

The purpose of the current study was to determine the geometrical profile and novel correlations of the corneal deformation for KC eyes with mild visual limitation compared to normal corneas by using the morphogeometric custom modeling analysis. Our aim was to understand the modeled changes observed in the keratoconic cornea with a mild visual loss and also attempt to find a morpho-geometrical correlation.

Figure 1. Use of a predictive patient-specific model for the diagnosis of keratoconus with mild visual limitation.

2. Patients and Methods

2.1. Patients

The study included a total of 202 eyes of 202 patients (122 normal and 80 keratoconic cases) enrolled at Vissum Instituto Oftalmológico Alicante, Spain (Vissum) who were adequately informed

about the clinical study and voluntarily signed their consent to participate. The study was ratified by the clinic's Institutional Review Board in compliance with the ethical restrictions established in the Declaration of Helsinki (Seventh revision, October 2013, Fortaleza, Brasil).

All patients were selected, according to the Cooperative Research Thematic Network (RETICS) grading [8,11] based on the limitation of spectacle corrected distance visual acuity (CDVA) and also taking into account corneal aberrations, internal astigmatism, and corneal biomechanical properties. Inclusion criteria were patients diagnosed as KC eyes with mild visual impairment ($0.6 < \text{CDVA} \leq 0.9$ in decimal scale, or $20/33 < \text{CDVA} \leq 20/22$ Snellen), normal visual acuity achieved by fitting a rigid gas permeable contact lens, corneal topography revealing a localized steepening, and/or an asymmetric bowtie pattern with or without skewed radial axis. The exclusion criteria were the following. Any previous ocular surgery, ocular surface inflammation, moderate to severe dry eye or other active ocular comorbidity, or use of contact lenses within the four weeks prior to the first visit.

The control group comprised 122 normal eyes of 122 patients. This group was selected at random by subjects assessed in the refractive surgery department. Exclusion criteria for this range were the following: participants with any ocular disease, topographic irregularities or abnormal aberrometry, familial history of KC, contact lens wearing within four weeks, or those whose eyes had undergone any previous surgery.

2.2. Ophthalmological Examination

A detailed and uniform ophthalmologic examination was performed in all cases, according to the clinical standards [3]. Testing sessions consisted of a minimum of three corneal topographies for each cornea made with Sirius Tomographer (CSO, Florence, Italy), which was always carried out by the same experienced examiner. Only the best topographies with the highest acquisition quality for the Scheimpflug images were selected for providing data.

2.3. Morpho-Geometric Reconstruction of the Cornea

This analysis defined by the authors was conducted on all participants. The corneal morpho-geometric reconstruction procedure consists of the following successive stages (Figure 2): (i) obtaining the point clouds of both corneal surfaces, (ii) geometrically reconstructing the corneal surfaces, and (iii) generating a representative solid model of the cornea.

Figure 2. Scheme of the morpho-geometric reconstruction of the cornea.

2.3.1. Acquisition of the Point Clouds

The point clouds that represent the geometry of the corneal surfaces were generated from the data provided by a Sirius corneal topographer (CSO, Florence, Italy). This topographer offers an Excel file that includes information regarding both corneal surfaces for each patient. Within this information, the most reliable information to perform geometric modeling is the raw altimetry data of the anterior and posterior elevations (radii of Placido's disc rings), which have not been manipulated by any software process inside the topographer [13].

2.3.2. Geometric Reconstruction of Corneal Surfaces

The point clouds representative of corneal geometry are later imported by the surface reconstruction software Rhinoceros v5.0 (MCNeel & Associates, Seattle, WA, USA). This software uses a mathematical model to generate surfaces based on non-uniform rational B-splines (NURBS) [14] and its validity in the Biomedical Engineering [15–18] and Ophthalmology [19–22] fields has been widely demonstrated. For this study, the “patch” surface generation function was used to reconstruct both corneal surfaces. These surfaces were then connected by their vertex in relation to the optical axis and the perimetral surface was obtained.

2.3.3. Generation of the Solid Model of the Cornea

The reconstructed surfaces of each case by Rhinoceros were later imported into the solid modeling software SolidWorks (Dassault Systèmes, Vélizy-Villacoublay, France), which permitted to generate a solid model representative of the real and customized geometry of the cornea.

2.4. Characterization of the Cornea

After obtaining the 3D patient-specific model of the cornea in SolidWorks, it can be used to calculate certain morpho-geometric variables, which will characterize the analyzed cornea (Figure 3). Table 1 shows a detailed description of the geometrical variables analyzed for the KC group during the present study.

Figure 3. Scheme of the Characterization of the Cornea.

Table 1. Corneal morpho-geometric variables analyzed in the study.

Morpho-Geometric Variable	Acronym	Description
Corneal volume (mm ³)	CV	Volume defined by the solid model generated
Anterior/Posterior corneal surface area (mm ²)	A _{ant} /A _{post}	Area of the exterior/interior surface
Corneal surface area (mm ²)	A _{tot}	Total area defined by the solid model generated
Posterior sagittal plane apex area (mm ²)	A _{postapex}	Area of the cornea within the sagittal plane passing through the optical axis and the apex of the posterior corneal surface
Anterior/Posterior apex deviation (mm)	D _{antapex} /D _{postapex}	Distance from the optical axis to the apex of the anterior/posterior corneal surfaces
Sagittal plane area at minimum thickness point (mm ²)	A _{postmct}	Area of the cornea within the sagittal plane passing through the optical axis and the minimum thickness point of the posterior corneal surface
Anterior/Posterior minimum thickness point deviation (mm)	D _{antmct} /D _{postmct}	Distance in the XY plane from the optical axis to the minimum thickness points of the anterior/posterior corneal surfaces
Center of mass X, Y, Z (mm)	CM _x /CM _y /CM _z	Center of mass coordinates X, Y, Z of the solid

The main outcome measure of this study was to define the model that the keratoconic cornea follows when mild visual loss is associated with corneal deformation. The second outcome was the correlation coefficients, sensitivity, and specificity of this new KC detection method.

2.5. Statistical Analysis

All data were analyzed using IBM SPSS 19.0 software (IBM Corp., Armonk, NY, USA). The statistical analysis included descriptive statistics for both normal and KC groups to demonstrate the distribution of the thirteen morpho-geometric variables in more detail. Normality was checked using the Kolmogorov-Smirnov test. When parametric analysis was possible, the Student *t*-test for unpaired data was used as a comparison between groups. When the normality condition was met, groups were compared using a Student *t*-test for unpaired data. For all other situations, a Mann-Whitney test was used. A *p*-value lower than 0.05 was considered significant in all statistical tests. Correlation between parameters was assessed using Pearson coefficients (for normally distributed data) or Spearman coefficients (not normally distributed). With the aim of quantifying the strength of the correlation between the two groups, a linear regression was executed.

For all metrics, we applied receiver operating characteristic (ROC) curves to determine the overall predictive accuracy by plotting sensitivity versus 1-specificity.

3. Results

From a total of 202 eyes of 202 patients, the KC group comprised 80 eyes of 80 patients [29 women (36.2%) and 51 men (63.8%) with a mean age of 41.8 years $\pm$ 13.1 ranging from 16 to 72 years]. The control group was composed of 122 normal eyes of 122 patients (54 women (44.2%) and 68 men (55.8%)) with a mean age of 34.89 $\pm$ 7.8 years ranging from 19 to 64 years. There was no statistical difference regarding the age between groups (*p* > 0.05).

Regarding the KC group, the mean value of the posterior apex deviation (0.19 $\pm$ 0.10 mm) was higher than the anterior apex deviation (0.01 $\pm$ 0.02 mm) while the mean deviation at the minimum thickness point of the anterior and posterior curvatures was 1.11 $\pm$ 0.48 mm and 1.04 $\pm$ 0.45 mm, respectively. From the metrics of the center of mass coordinates X, Y, and Z, the value in Z reached the largest one with 0.78 $\pm$ 0.04 mm. The total corneal volume resulted in an average of 23.60 $\pm$ 2.28 mm³.

For metrics from the total corneal surface, the anterior surface, and the posterior surface, the average achieved areas were $103.61 \pm 1.62 \text{ mm}^2$, $43.39 \pm 0.35 \text{ mm}^2$, and $44.70 \pm 0.56 \text{ mm}^2$, respectively. For the measurement of the sagittal plane area, the mean values reached were $3.91 \pm 0.37 \text{ mm}^2$ (posterior surface) and $3.89 \pm 0.39 \text{ mm}^2$ (at the minimum thickness point of the posterior surface). The descriptive values of the thirteen corneal morpho-geometric variables and their distribution in more detail are summarized in Table 2 for both keratoconic and control groups.

Table 2. Summary of the modeled morpho-geometric variables in control and keratoconus with mild visual limitation groups. SD (standard deviation).

Measurement	Normal Group $n = 122$	Keratoconus Group with Mild Visual Limitation $n = 80$	p Value
	Mean (SD) Median (Range)	Mean (SD) Median (Range)	
CV (mm^3)	25.70 (1.49) 25.70 (22.99 to 29.50)	23.60 (2.28) 23.31 (16.95 to 27.74)	<0.001
A_{ant} (mm^2)	43.08 (0.14) 43.08 (43.06 to 43.11)	43.39 (0.35) 43.26 (42.85 to 44.36)	<0.001
A_{post} (mm^2)	44.24 (0.27) 44.25 (44.19 to 44.28)	44.70 (0.56) 44.57 (43.64 to 46.36)	<0.001
A_{tot} (mm^2)	103.87 (1.14) 103.78 (100.73 to 106.01)	103.61 (1.62) 103.70 (99.97 to 106.51)	0.205
A_{postapex} (mm^2)	4.31 (0.25) 4.30 (4.27 to 4.36)	3.91 (0.37) 3.82 (3.00 to 4.66)	<0.001
A_{postmct} (mm^2)	4.30 (0.25) 4.29 (4.26 to 4.35)	3.89 (0.39) 3.81 (3.80 to 3.98)	<0.001
D_{antapex} (mm)	0.00 (0.00) 0.00 (0.00 to 0.00)	0.01 (0.02) 0.00 (0.00 to 0.07)	<0.001
D_{postapex} (mm)	0.06 (0.02) 0.06 (0.06 to 0.07)	0.19 (0.10) 0.18 (0.02 to 0.45)	<0.001
CM_x (mm)	0.02 (0.04) 0.03 (0.02 to 0.04)	0.01 (0.05) 0.02 (−0.09 to 0.12)	0.073
CM_y (mm)	0.03 (0.01) 0.03 (0.00 to 0.08)	0.02 (0.04) 0.02 (−0.09 to 0.28)	<0.001
CM_z (mm)	0.77 (0.02) 0.77 (0.76 to 0.78)	0.78 (0.04) 0.78 (0.71 to 0.90)	0.006
D_{antmct} (mm)	0.84 (0.23) 0.83 (0.80 to 0.88)	1.11 (0.48) 1.05 (0.33 to 3.11)	< 0.001
D_{postmct} (mm)	0.77 (0.21) 0.76 (0.73 to 0.81)	1.04 (0.45) 0.99 (0.28 to 2.94)	<0.001

In comparison to the control group, the differences between groups were statistically significant for overall corneal metrics, which includes total volume ($p < 0.001$), anterior surface area ($p < 0.001$), anterior apex deviation ($p < 0.001$), anterior minimum thickness point deviation ($p < 0.001$), posterior surface area ($p < 0.001$), posterior sagittal plane apex area ($p < 0.001$), sagittal plane area at minimum thickness point ($p < 0.001$), posterior apex deviation ($p < 0.001$), posterior minimum thickness point deviation ($p < 0.001$), center of mass Y ($p < 0.001$), and center of mass Z ($p = 0.006$). In this regard, the modeled variables with no statistical difference for groups discrimination were the center of mass X ($p = 0.073$) and the total corneal surface area ($p = 0.205$).

When applying the ROC analysis, the highest area under the curve (AUC) was reached by the corneal posterior apex deviation. Considering an AUC greater than 0.7, the variables found were a

posterior apex deviation (area: 0.904, sensitivity: 88.8%, specificity: 81.1%, cutoff: ≥ 0.0846 mm, $p = 0.000$), an anterior apex deviation (area: 0.866, sensitivity: 76.3%, specificity: 95.9%, cutoff: ≥ 0.001 mm, $p = 0.000$), and a posterior corneal surface area (area: 0.761, sensitivity: 76.3%, specificity: 64.8%, cutoff: ≥ 43.16 mm², $p = 0.000$). The curves derived from these significant AUC values are demonstrated in Figure 4.

Figure 4. Combined receiver operating characteristic (ROC) curves for the modeled parameters with the highest predictive accuracy diagnosing keratoconus with mild visual limitation (plotted only variables with the area under the curve over 0.7).

Table 3 summarizes the statistically significant correlations between all the modeled morpho-geometric variables for the KC group. Table 4 also shows the significant correlations for the normal group.

Table 3. The significant correlation coefficient values for the modeled variables in the keratoconus group.

Keratoconus Group with Mild Visual Limitation ($n = 80$)		
Measurement Correlation	Correlation Coefficient	p Value
A_{postapex}/CV	0.969	0.000
$A_{\text{ant}}/A_{\text{post}}$	0.853	0.000
CV/A_{tot}	0.699	0.000
A_{ant}/CM_z	0.627	0.000
A_{post}/CM_z	0.766	0.000
A_{tot}/CM_z	0.816	0.000
$A_{\text{postapex}}/A_{\text{postmct}}$	0.989	0.000
CV/A_{postmct}	0.978	0.000
$D_{\text{antmct}}/D_{\text{postmct}}$	0.996	0.000

Table 4. The significant correlation coefficient values for the modeled variables in the Normal group.

Normal Group ($n = 122$)		
Measurement Correlation	Correlation Coefficient	p Value
A_{postapex}/CV (mm^3)	0.987	0.000
$A_{\text{postapex}}/A_{\text{tot}}$	0.814	0.000
A_{tot}/CM_z	0.723	0.000
$A_{\text{ant}}/A_{\text{post}}$	0.774	0.000
$A_{\text{post}}/A_{\text{tot}}$	0.649	0.000
A_{post}/CM_z	0.719	0.000
CV/A_{tot}	0.858	0.000
CV/CM_z	0.768	0.000
A_{tot}/CM_z	0.943	0.000
A_{postapex}/CM_z	0.723	0.000
$A_{\text{postmct}}/A_{\text{postapex}}$	0.996	0.000
CV/A_{postmct}	0.987	0.000
$A_{\text{tot}}/A_{\text{postmct}}$	0.813	0.000
CM_z/A_{postmct}	0.730	0.000
$D_{\text{antmct}}/D_{\text{postmct}}$	0.988	0.000

The regression analysis among the mild KC group (Figure 5) revealed significant and strong correlations between the morpho-geometric variables ($p = 0.000$), which is shown below.

Figure 5. Scattergram plot showing the most significant relationships between the morpho-geometric variables for the keratoconus group ($n = 80$).

$$\text{Posterior minimum thickness point deviation} = 0.944 \times \text{Anterior minimum thickness point deviation} + 0.236 \quad (R^2 = 0.997) \quad (1)$$

$$\text{Sagittal plane area at minimum thickness point} = 1.05 \times \text{Posterior sagittal plane apex area} + 0.018 \quad (R^2 = 0.958) \quad (2)$$

$$\text{Total corneal volume} = 5.757 \times \text{Posterior sagittal plane apex area} + 1.197 \quad (R^2 = 0.953) \quad (3)$$

$$\text{Sagittal plane area at minimum thickness point} = 0.16 \times \text{Total corneal volume} + 0.136 \quad (R^2 = 0.955) \quad (4)$$

According to the regression analysis for the normal group (Figure 6), the most significant correlations between the corneal metrics extracted from the reconstructed model are shown below ($p = 0.000$).

$$\text{Center of mass Z} = 0.0195 \times \text{Total cornea surface area} - 1.255 \quad (R^2 = 0.907) \quad (5)$$

$$\text{Posterior sagittal plane apex area} = 1.005 \times \text{Sagittal plane area at minimum thickness point} - 0.031 \quad (R^2 = 0.994) \quad (6)$$

$$\text{Total corneal volume} = 5.829 \times \text{Posterior sagittal plane apex area} + 0.633 \quad (R^2 = 0.978) \quad (7)$$

$$\text{Sagittal plane area at a minimum thickness point} = 0.166 \times \text{Total corneal volume} + 0.034 \quad (R^2 = 0.978). \quad (8)$$

Figure 6. Scattergram plot showing the most significant relationships between the morpho-geometric variables for the normal group ($n = 122$).

4. Discussion

The validation of new methods for the diagnosis of incipient cases of KC or with mild visual loss is of great interest in the field of ophthalmology since there are several clinical treatments that would permit the end of further development of the disease [23]. For this reason, this work tries to perform a morphological analysis of the corneal structure's response to both the linear decompensation and the annular profile defined in the singular points of corneal surfaces. This procedure will contribute to a better differentiation between the corneas in a healthy scenario and in an incipient stage of the development of the disease based on a new approach and interpretation of the corneal architecture in KC corneas with visual limitations.

The first study [24] in KC corneas with mild visual limitation analyzed the corneal thinning and found that such thinning was moved with respect to the corneal vertex as an asymmetric response to the development of the pathology. Subsequently, another study analyzed the geometric response in normal eyes and the initial phases of KC. However, their conclusions were insufficient because they did not obtain consistent values of thinning measures in corneas with similar geometries [25]. A recent study showed that, when morphological analysis and corneal thickness of eyes are combined with KC, both are involved in the pathogenesis of the disease [26]. However, the geometric profile and the relationships that allow modeling of the progression of KC with mild visual loss have not yet been analyzed from these geometric models.

Other authors [25,27,28] consider a finite element model for KC aimed to simulate the behavior of the deformation on model corneas. However, they did not take into account the patient-specific corneal tomography. Alternatively, another study [29] that included progressive KC eyes was performed by gathering the elevation data from Zernike coefficients. Unlike our method, the x, y, and z coordinates from the elevation maps of Pentacam were linearly interpolated into the Zernike polynomials by a natural cubic spline. For this approach, the discretization of the model was derived from estimated data by using the blending function method. Therefore, the corneal surface reconstruction algorithm could not be properly inferred by this fitting procedure, which has been discussed in the literature [30–32]. In addition, the small sample size could be considered a drawback of these previously mentioned reports.

This analysis outlines the presence of mild visual impairment in the current series using a grading system primarily based on the criteria of visual evolution. In this regard, the present study set out the 3D characterization with patient-specific geometry of these KC cases in stages where a loss of visual function begins to occur. While the corneal refractive power is mostly determined by the anterior curvature [33], changes from the posterior surface are usually related to mild visual degradation [34]. The present report portrays the first study to assess the correlations of this geometrical method between the anterior and posterior corneal surfaces of keratoconic eyes with mild visual dysfunction.

In the present study, almost all mean differences were statistically significant ($p = 0.00$) between KC corneas with mild visual limitation and normal eyes. The proposed variables were obtained from the raw data of Sirius using a 3D point cloud, which generated a reliable solid model striving for consistent noise-suppressing properties. This Scheimpflug–Placido system used in a recent study [35] demonstrated more robust measurements in terms of repeatability (coefficients of variation = 0) and also outstanding levels of reproducibility and inter-device agreement in comparison to other devices studied.

Regarding the ROC analysis, the apex deviation of the posterior surface showed the highest discriminant coefficient (AUC, 0.904), which occurs because the apex is the maximum curvature point of the corneal surface. According to a previous publication [36], the posterior curvature might have an impact on visual performance. We postulate that measuring the posterior apex deviation value is the most proficient way of characterizing the geometric profile of the KC stage in which a decrease of the visual acuity begins to occur. Moreover, the anterior apex deviation also shows an acceptable discrimination capability (AUC, 0.866). However, its sensitivity was lower (76.3%) in this investigation.

Other authors [37] recently reported that topographic indices and posterior elevation values from the Galilei device were significantly correlated with visual function.

This study also assessed the relationship of the geometrical pattern of the anterior and posterior corneal curvatures. Other authors, for a different purpose, found strong statistical correlations between the anterior and posterior shape factors for keratoconic corneas [38]. Regarding the minimum thickness point deviations from both corneal surfaces, we found significant differences between groups. Furthermore, for keratoconic eyes, the strongest correlation value yielded in this investigation was between the anterior and posterior deviations of the thinnest point ($R^2 = 0.997$, $p = 0.000$). Lopes et al. [39] demonstrated a robust correlation between apex deviation and the pachymetric progression index of the front and back elevations with CDVA of the analyzed patients.

Although there are other methods [40–42] describing corneal volume reduction among the disease evolution, in our study, this metric was investigated in KC eyes based on the beginning of visual impairment. With respect to the total volume, we found a significant difference in comparison to the control group. We also found a significant positive correlation between the corneal volume with the sagittal plane apex area of the posterior surface ($R^2 = 0.953$, $p = 0.000$) and with the sagittal plane area at a minimum thickness point ($R^2 = 0.955$, $p = 0.000$). Likewise, the correlations described were strongly achieved for normal eyes that were analyzed.

In conclusion, the morphological analysis of the corneal response with geometric models to both the linear decompensation and the annular profile in the mentioned singular points support the hypothesis of a focal weakening in incipient phases of the KC development. The most predictive accuracy using this geometrical reconstruction of KC eyes associated with mild visual loss resulted clearly from the posterior apex displacement. The anterior and posterior deviations of the thinnest point were considerably correlated among mild keratoconic corneas in the specific geometry of the 3D model, which was obtained with the new method described. The proposed morpho-geometric metrics showed significant differences between groups, which may lead to a further advancement of a more tailored disease management based on the evolution of corneal visual impairment. This may also presumably be extended to other Scheimpflug systems. This computational custom approach determines the characterization profile of keratoconic modeling in eyes with mild visual limitation. This procedure provides the clinician with a three-dimensional view of corneal architecture when mild visual loss happens and allows a reliable diagnosis of mild forms of the disease.

Author Contributions: F.C.-M., D.G.F.-P., and J.L.A. designed the experiments, which were later executed by J.S.V.-B. and J.L.A. The analysis of the obtained data was performed by F.C.-M., D.G.F.-P., F.J.F.C., and J.M.B. Lastly, all authors contributed to the writing of the manuscript.

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Detection of Subclinical Keratoconus Using Biometric Parameters

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Abstract. The validation of innovative methodologies for diagnosing keratoconus in its earliest stages is of major interest in ophthalmology. So far, subclinical keratoconus diagnosis has been made by combining several clinical criteria that allowed the definition of indices and decision trees, which proved to be valuable diagnostic tools. However, further improvements need to be made in order to reduce the risk of ectasia in patients who undergo corneal refractive surgery. The purpose of this work is to report a new subclinical keratoconus detection method based in the analysis of certain biometric parameters extracted from a custom 3D corneal model.

This retrospective study includes two groups: the first composed of 67 patients with healthy eyes and normal vision, and the second composed of 24 patients with subclinical keratoconus and normal vision as well. The proposed detection method generates a 3D custom corneal model using computer-aided graphic design (CAGD) tools and corneal surfaces' data provided by a corneal tomographer. Defined bio-geometric parameters are then derived from the model, and statistically analysed to detect any minimal corneal deformation.

The metric which showed the highest area under the receiver-operator curve (ROC) was the posterior apex deviation.

This new method detected differences between healthy and sub-clinical keratoconus corneas by using abnormal corneal topography and normal spectacle corrected vision, enabling an integrated tool that facilitates an easier diagnosis and follow-up of keratoconus.

Keywords: Ophthalmology, Early Keratoconus, Computational Modelling, Scheimpflug Technology.

1 Introduction

Debilitating primary corneal ectasia shows changes in the corneal structure, including stromal thinning and progressive change of shape related to breakage of Bowman's membrane [1]. These morphological changes seriously affect the rigidity and elasticity-

ty of the tissues that form part of the corneal surface and behave very sensitively to variations in intraocular pressure [2]. Corneal shape shows changes such as conical focal corneal deformation located in the central or paracentral region [3]. This is followed by a progressive myopization, astigmatic shift with irregular astigmatism and progressive visual loss [4]. This disease usually begins in puberty and progresses to the third or fourth decade of life [5].

Several systems have been described in the literature for diagnosing and classifying keratoconus (KC) severity. Most of these grading systems have been developed by considering the patient's optical and geometric parameters [2]. These systems have proven essential as a therapeutic approach to manage keratoconus [6].

A sample of this disease with a located steepening pattern exists, but neither clinical signs of the disease, nor other causes that could explain an altered topographical pattern, are manifested, and patients present the sharpness of normal visual correction. Subclinical keratoconus was a term introduced by Amsler [7] and is a condition in which the clinician suspects the potential clinical development of keratoconus. Identifying keratoconus in early stages is crucial to monitor disease progression [6, 8, 9], to perform genetic studies with the patient [10], to indicate therapeutic approaches to avoid its evolution [11], even most importantly, when making the preoperative screening of candidates for refractive surgery. The last reason has been identified as one of the main risk factors for ectasia after LASIK, after PRK [6-10], and even after low myopic ablations [12], because refractive surgery can weaken corneal tissues, and failure can be detected in cornea's biomechanics in totally asymptomatic individuals [13]. For these reasons, it is a fundamental challenge for the ophthalmic community to improve the strategies, tools and techniques employed to detect those individuals at potential risk of developing this pathology.

So far, subclinical keratoconus diagnosis has been made by combining several clinical criteria: age, family history, genetic predisposition [7] and corneal topography [14]. The topographic data and optical parameters obtained in this way have defined univariate and multivariate indices for detection, and for the decision trees or neural networks based on these indices, now valuable tools for detecting subclinical keratoconus [9, 15].

However, further improvements should be made to detect subclinical keratoconus in order to enhance the strategies that diagnose this disease and to avoid the risk of ectasia in patients who undergo corneal refractive surgery. Progression from subclinical to clinical keratoconus is more likely to occur in patients aged 10-20 years, and is less likely to occur in patients over the age of 30 [7]. These cases are difficult to diagnose because symptoms are lacking in early disease stages. When patients come to consultations, the disease may have already advanced to the clinical keratoconus stage. Many studies are attempting to find an objective way to detect these cases and to treat them before their visual function is affected [11].

Accordingly, a subclinical keratoconus detection technique could be based on analysing the biometric morphometry of discrete landmarks [16] in the region where the focused curvature was initially manifested on corneal surfaces, because no other clinical signs are observed in this stage and patients present normal corrected visual acuity. In the biology and modern medicine fields, a geometric morphometric analysis

works on a multidimensional image of a discrete data set obtained from a three-dimensional reconstruction of biological structures [17]. These studies are characterized by both high sensitivity and specificity for structure characterization or pattern recognition, regardless of the technology used to generate the virtual model. This procedure could prove to be a methodological analysis process because the virtual environment provides a large number of hypotheses, which can avoid using complex analytical methods and can considerably reduce in vivo experimentation costs [17].

We have previously demonstrated that morphogeometric analysis of a custom virtual model of the cornea could be useful for the study of keratoconus characterization, and has been previously validated for the evaluation of disease progression across its different clinical stages [18-19]. It has also been recently used in ophthalmology, specifically in the cornea biomechanics field, where some authors propose a customized model of the cornea obtained from interpolating the topographic data, which is further used as a basis for biomechanical analyses [20-22].

The aim of this study is to provide new rational and objective indices that accurately quantify the morphogeometric changes associated to the clinical evidence of corneal ectatic disease, enabling the description of early local ectasia in a preclinical stage, and to allow healthy corneas to be differentiated from corneas with the so-called sub-clinical keratoconus in order to avoid idiopathic progression of the disease.

2 Materials and Methods

2.1 Participants

This observational case series study evaluated 91 subjects (only one cornea per patient, randomly selected to avoid interference) divided into two groups: the first group (healthy corneas) presented no ocular pathology and included 67 patients (36.51 ± 14.99 years). In the second group were included 24 patients diagnosed with subclinical keratoconus (33.99 ± 10.97 years). Participants with any kind of ocular pathology were excluded from both groups.

The classification protocol for normal or subclinical keratoconus cases was run according to reported state of the art of clinical and topography evaluations [23].

These evaluations were made in Visum Hospital (Alicante, Spain). The study follows ethical standards of the Declaration of Helsinki and was approved by the local Clinical Research Ethics Committee with informed consent.

2.2 Examination Protocol

Examination of all the selected patients was performed following a previous validated protocol created by our research group and using Sirius System® (CSO, Florence, Italy) [18-19]. In this protocol, only the data from the first stage of the tomographic data acquisition procedure, so called raw data, is registered. Using the tomographer's vision algorithm in this first stage, we obtained a finite set of discrete, real and representative spatial data from the corneal surfaces [18-19]. For obtaining the average

values that were used for later analyses, a set of three successive measures were taken, always by the same expert optometrists.

2.3 Detection Procedure

The procedure proposed in this article consisted in two stages: first, using raw data from the corneal tomographer, a virtual 3D model was reconstructed throughout computational geometry techniques; second, geometric parameters were determined from this model and analysed in order to characterize the cornea morphology.

First Stage: Virtual 3D Modelling.

The reconstruction of the cornea was performed by following the steps below (Fig. 1):

i) Acquisition of data from the corneal tomographer.

The Sirius device provides two 3D point clouds that make up both the anterior and the posterior corneal surface, respectively (see Fig. 1). With this procedure we obtained useful data avoiding the interpolation that manufacturers use to fill or substitute wrongly scanned data [24].

We have taken into account that major irregularity levels in the corneal morphology of keratoconic eyes for both the corneal surfaces were presented between radii of 0-4 mm, which encompasses 97% of all keratoconus cases [25]. Any case in which the data provided by the Sirius tomographer had some erroneous point in the study area ($r=0-4\text{mm}$) was discarded.

Spatial points for both surfaces are obtained in polar format. These points are distributed in regular circles (256 points for each circle) in the XY plane whose radii are incremented in intervals of 0.2 mm. [18-19]. To proceed with the reconstruction process, points' elevation data were then converted to Cartesian coordinates (X, Y, Z) using the following equations:

$$X=0.2i \cdot \cos\left(j \frac{360^\circ}{256}\right) ; Y=0.2i \cdot \sin\left(j \frac{360^\circ}{256}\right) ; Z=\text{value in the exported table} \quad (1)$$

For this study, an algorithm programmed in Matlab V R2015 (Mathworks, Natick, USA) was implemented to perform this task.

ii) Geometric Surface Reconstruction and Solid Modelling.

In a second stage, after the conversion of the spatial points into a Cartesian format, data were imported to the surface reconstruction CAD software Rhinoceros® V 5.0 (MCNeel & Associates, Seattle, USA). Non-uniform rational B-splines were used to generate surfaces applying point grid function, which allows a fitting of the reconstructed surface with regard to the point cloud of about $4.91 \times 10^{-16} \pm 5.19 \times 10^{-16}$ mm.

The generated surface was then imported into the software SolidWorks V 2017 (Dassault Systèmes, Vélizy-Villacoublay, France), which allowed the generation of an in vivo solid model representing the custom biometrics of each cornea.

Fig. 1. Corneal surface areas, apex deviation and minimum thickness point deviation

Second Stage: Biometric Parameters Analysis.

The final 3D virtual model of the cornea was then used to run an analysis of the determined biometric parameters. These geometric parameters studied herein, along with their characteristics have been previously described [19], and are shown in Table 1, being used in this case for the first time to detect subclinical keratoconus.

2.4 Statistical Analysis

A Kolmogorov-Smirnov test was run to assess the data engagement scores. According to this test and thereafter, a Student's t-test or U-Mann Whitney Wilcoxon test was employed, as and when appropriate. ROC curves were established to determine what parameters could be used to classify the diseased corneas by calculating optimal cut-offs, sensitivity and specificity [26-27]. All the analyses were performed by the Graphpad Prism V 6 (GraphPad Software, La Jolla, USA) and SPSS V 17.0 software (SPSS, Chicago, USA).

3 Results

Most of the modelled parameters showed statistically significant differences when comparing healthy and subclinical corneas, as shown in Table 1 below.

Table 1. Descriptive values and differences in the modelled biometric parameters among the normal and subclinic KC groups (SD: standard deviation, P: statistical test, Z: z-score).

<i>Biometric Parameters</i>	<i>Normal Group (n = 67)</i>				<i>Subclinical KC Group (n = 24)</i>				<i>z</i>	<i>P</i>
	<i>Mean</i>	<i>SD</i>	<i>Min</i>	<i>Max</i>	<i>Mean</i>	<i>SD</i>	<i>Min</i>	<i>Max</i>		
Total corneal volume (mm ³)	25.80	1.57	21.29	29.39	24.09	1.69	19.79	28.21	-8.39	0.00
Anterior corneal surface area (mm ²)	43.10	0.16	42.69	43.40	43.18	0.16	43.01	43.48	-6.88	0.00
Posterior corneal surface area (mm ²)	44.19	0.31	43.38	44.91	44.31	0.34	43.57	44.79	-5.80	0.00
Total corneal surface area (mm ²)	103.94	1.25	100.80	106.09	103.50	1.20	101.31	105.49	-3.17	0.00
Sagittal plane apex area (mm ²)	4.29	0.25	3.60	4.99	4.02	0.31	3.24	4.86	-9.02	0.00
Sagittal plane area in minimum thickness point (mm ²)	4.30	0.49	0.00	5.01	3.99	0.30	3.22	4.81	-9.01	0.00
Anterior apex deviation (mm)	0.00	0.00	0.00	0.01	0.00	0.01	0.00	0.21	-6.01	0.00
Posterior apex deviation (mm)	0.07	0.02	0.02	0.15	0.14	0.07	0.05	0.40	-10.42	0.00

Anterior minimum thickness point deviation (mm)	0.84	0.3	0.42	2.21	1.2	0.29	0.61	1.79	-4.72	0.00
Posterior minimum thickness point deviation (mm)	0.79	0.26	0.46	2.01	1.1	0.29	0.49	1.69	-4.89	0.00
Net deviation from centre of mass XY (mm)	0.05	0.03	0.01	0.09	0.08	0.04	0.00	0.12	-4.20	0.00
Centre of mass X (mm)	0.05	0.03	0.01	0.10	0.04	0.03	0.00	0.08	-3.46	0.28
Centre of mass Y (mm)	0.04	0.03	0.00	0.11	0.01	0.02	0.00	0.10	-7.70	0.14
Centre of mass Z (mm)	0.81	0.02	0.72	0.83	0.78	0.03	0.70	0.81	-0.82	0.08
Volume of corneal cylinder (mm ³) with Radius 0.5 mm	0.47	0.29	0.34	3.21	0.4	0.03	0.29	0.48	-1.02	0.00
Volume of corneal cylinder (mm ³) with Radius 1 mm	1.69	0.13	1.39	1.99	1.49	0.15	1.19	1.9	-1.58	0.00
Volume of corneal cylinder (mm ³) with Radius 1.5 mm	3.89	0.44	3.31	7.29	3.6	0.3	2.9	4.3	-1.9	0.00
Volume of corneal cylinder (mm ³) with Radius 2 mm	7.11	0.45	5.94	8.3	6.55	0.5	5.25	7.8	-2.3	0.00

3.1 Roc Analysis

The predictive value of the modelled parameters was established by a ROC analysis. Six biometric parameters were identified with an area under the ROC (AUROC) above 0.7 (see Fig. 2 and Table 2):

Table 2. Parameters with an AUROC above 0.7

<i>Biometric Parameters</i>	<i>AUROC</i>	<i>Sensitivity</i>	<i>Specificity</i>	<i>95% Confidence Interval</i>	
				<i>Lower limit</i>	<i>Upper limit</i>
Anterior corneal surface area (mm ²)	0.719	91.5	19.0	0.560	0.779
Posterior corneal surface area (mm ²)	0.701	90.0	20.4	0.521	0.749

Anterior apex deviation (mm)	0.767	67.0	99.9	0.639	0.869
Posterior apex deviation (mm)	0.891	91.6	36.0	0.799	0.959
Anterior minimum thickness point deviation (mm)	0.751	91.4	23.0	0.641	0.849
Posterior minimum thickness point deviation (mm)	0.761	88.1	19.1	0.649	0.858

Fig. 2. Curves for modelled parameters detecting subclinical KC with AUROC over 0.7.

4 Discussion

This study obtained good accuracy reconstruction of the intrinsic biometric morphology of the human cornea as a biological structure, making aberrometric analysis unnecessary, and creating a new concise global understanding of early corneal pathology in keratoconic eyes.

The deterioration process in keratoconus is characterized by a significantly reduced total corneal volume compared with healthy eyes, which is triggered by an alteration in corneal collagen fibres that causes stromal thinning and breaks in Bowman's membrane from disease subclinical stages [1]. The studied volumetric parameters and the volume of the analysed corneal cylinders (0.5-1-2 mm) showed a statistically significant reduced total corneal volume in the subclinical group compared with healthy eyes. A similar volumetric reduction of corneas has been described in several studies as a characteristic parameter for the differentiation of subclinical eyes [28-30]. Therefore, the 3D corneal model defined in this work for subclinical keratoconus, allows an accurate characterisation of small changes in its architecture, when the degree of alteration in corneal morphology is low.

Presence of corneal irregularities due to local steepening by a reduced curvature radius leads to increased corneal surface [1]. Eyes with subclinical keratoconus show significant differences for both the anterior and posterior surfaces compared with healthy corneas. In the disease group, these surfaces were larger given their local structural weakening, as fewer collagen fibres are present in each lamella [2]. However, the total cornea area, which included the area of the peripheral region, was larger in healthy corneas, because of their constant thickness compared with the thinning noted in the pathological group due to the influence of intraocular pressure on their weakened structure. This structural weakening is produced by the reduction in the number of stromal lamellae and a reduction in the interconnecting layer's area.

The average distances from the Optical axis to the apex of the anterior and posterior corneal surfaces differed between groups, with the largest deviations found in the group of eyes with subclinical keratoconus. This has been previously described when the disease has been clearly established [1].

The aforementioned presence of an irregular corneal surface, which created a protrusion in the keratoconic eye, also led to incremented corneal curvature [33] and, therefore, to an increase in the deviation distances of corneal apex (maximum curvature) and in the deviation distances of the minimum thickness points, each increase produced in both anterior and posterior surfaces (Table 1). The existence of structural instability in subclinical keratoconic corneas explained why the best disease discrimination results were obtained for the posterior apex deviation variable (ROC area: 0.891, $p < 0.000$, std. error: 0.039, 95 % CI: 0.799-0.959). The posterior corneal surface is more susceptible to variations given the forces exerted on tissue [34]. This is why the posterior apex deviation is one of the variables that most reliably represents early changes in patients in first disease stages. Several studies have concluded the importance of, and interest in, the posterior corneal surface [35]. Upon disease onset, structural changes occur on the posterior surface of the cornea, so analysing this surface can positively identify early subclinical keratoconus [29].

Due to all the mentioned above, this new technique could help improve the widely used and well-accepted assessment corneal irregularity methods, in line with the main conclusions drawn by the group of world experts in keratoconus who gathered for the Project "Global Consensus on Keratoconus and Ectatic Diseases" [36]. The existing limitations of current topographic methods (i.e., data interpolation, unknown internal algorithms, etc.) difficult study comparisons and data sharing, and could also lead to

relevant information losses. The method proposed in this study is based in a non-finite biometric parameters analysis of the human cornea, and it also does not depend on any restricted commercial algorithm, so could be implemented in all corneal topographers, allowing data comparison between different devices. This technique allows a good and accurate characterization of the corneal health status that will enable new detection paths and to follow-up corneal pathologies.

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Additional Information

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Research Article

Assessment of the Association between In Vivo Corneal Morphogeometrical Changes and Keratoconus Eyes with Severe Visual Limitation

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Assessing changes suffered by the cornea as keratoconus progresses has proven to be vital for this disease diagnosis and treatment. This study determines the corneal biometric profile in eyes considered as affected by keratoconus (KC) showing severe visual limitation, by means of in vivo 3D modelling techniques. This observational case series study evaluated new objective indices in 50 healthy and 30 KC corneas, following a validated protocol created by our research group, which has been previously used for diagnosis and characterization of KC in asymptomatic (preclinical) and mild visually impaired eyes. Results show a statistically significant reduction of corneal volume and an increase of total corneal area in the severe KC group, being anterior and posterior corneal surfaces minimum thickness points the best correlated parameters, although with no discrimination between groups. Receiving operator curves were used to determine sensitivity and specificity of selected indices, being anterior and posterior apex deviations the ones which reached the highest area under the curve, both with very high sensitivity (96.7% and 90%, respectively) and specificity (94.0% and 99.9%, respectively). The results suggest that once severe visual loss appears, anterior corneal topography should be considered for a more accurate diagnosis of clinical KC, being anterior apex deviation the key metric discriminant. This study can be a useful tool for KC classification, helping doctors in diagnosing severe cases of the disease, and can help to characterize corneal changes that appear when severe KC is developed and how they relate with vision deterioration.

1. Introduction

Keratoconus (KC) is a bilateral noninflammatory corneal ectasia with a prevalence of 54.5 per 100,000, which is characterized by a stromal thinning that makes the cornea acquire a conical shape, leading to mild to marked visual impairment [1].

The geometric decompensation that causes the conical shape is localized mainly in the temporal lower quadrant of the mean peripheral region [2] due to a loss of tenacity that the corneal structure suffer by a reorientation of its anatomophysiology [3]. In addition, this morphologic

decompensation induces an increase of the high-order optical aberrations [4], showing the patients high values of irregular astigmatism and presenting as their main refractive sign the impossibility of a complete optical compensation of their ametropia by spherocylindrical lenses. Consequently, their corrected visual acuity will be diminished with respect to patients without corneal pathology [5].

There are many classifications in the scientific literature about the degree of severity of keratoconus [6]; however, it is difficult in clinical practice to handle the multiple indices in which these classifications are based, for a proper evaluation

of the disease progression. Also, some of these classifications present some singularities, such as Keratoconus Severity Scores [2], which does not consider pachymetry, or the Amsler–Krumeich classification, which does not take into account that patients, depending on their manifest refraction, may show important refractive fluctuations caused by the corneal multifocality that generates the corneal shape [6]. Besides that, from an optical point of view, patients show a certainly deteriorated spectacle-corrected visual acuity during the disease development, in a way that their visual performance worsens with the progression of the severity degree of keratoconus. Following this criterion, a classification of the stages of the disease has been developed [5, 7], depending on the corrected distance visual acuity (CDVA).

Furthermore, our research group has developed a three-dimensional (3D) virtual model of the cornea by means of computational geometry [8]. These models have been validated for the diagnosis of keratoconus basing on geometric parameters of volume [9], to predict the response to refractive surgeries [10, 11] or the response to the intrastromal ring segment implantation in corneas with keratoconus [12], to analyse nonsurgical corneal modifications, such as applanation tonometry for intraocular pressure measurement [13], or to analyse the behaviour of corneal tissue properties in different scenarios [14]. However, to our knowledge the virtual model has not been used to define the biometric profile in keratoconus eyes with severe visual limitation.

Therefore, developing and validating new methods for the characterization of the changes suffered by the cornea in severe KC cases is important to help attaining a better clinical management of it and avoiding the possibility of irreversible vision losses. Thus, the purpose of this work is to evaluate the potential value of a virtual 3D model for the diagnostic of corneas affected by severe KC, conceiving cornea as a 3D refractive structure. To do so, we have based on the characterization of its biometric profile (Figure 1) by means of morpho-biometric indices that register the optic-geometric decompensation that takes place during this phase of the disease, as well as we have quantified the existence of correlations between these indices.

2. Materials and Methods

2.1. Participants. This observational case series study evaluated 80 corneas of 80 patients (selected at random to avoid interference) structured in two groups: a normal group (healthy corneas), which included 50 subjects presenting no ocular pathology (37.79 ± 14.76 years), and a second group, composed of 30 patients diagnosed with severe KC (31.63 ± 7.39 years). The classification protocol for normal or severe KC cases was run according to reported state of the art clinical and topographic evaluations [15]. Just one eye of each patient was selected at random, according to a software-generated dichotomic random number sequence (0,1), seeking to elude any possible correlation that might exist between both eyes of the same patient [9].

All patients were selected according to the RETICS grading [7]. To be included in the study, patients should have been

diagnosed as Grade IV keratoconus (severe visual limitation, $0.2 < \text{CDVA} \leq 0.4$ in decimal scale or $6/30 < \text{CDVA} \leq 6/15$ in Snellen chart), focal central/paracentral steepening and corneal thinning visible in corneal tomography, 3 mm (inferior-superior) I-S mean keratometric difference >1.5 D, and asymmetric bow tie with or without skewed radial axes over 21 degrees. Patients who had undergone any previous ocular surgical procedure, suffering from any irritation of the ocular surface, with signs of significant dry eye, or who wore contact lenses in the precedent four weeks to their first visit were excluded from the study [16].

Visum Instituto Oftalmológico, Alicante, Spain (Visum), was the place in which these evaluations took place where the patients were satisfactorily informed about the study and signed freely their will to participate. The study was endorsed by the hospital's Clinical Research Ethics Committee, according to the ethical guidelines dictated in the Declaration of Helsinki (Seventh revision, October 2013, Fortaleza, Brazil).

The data used for this investigation were included in the official database "Iberia" of keratoconus cases created for the purpose of multicentre study of keratoconus in the National Network for Clinical Research in Ophthalmology RETICS-OFTARED.

2.2. Examination Protocol. All subjects selected for this study were examined using Sirius System® (CSO, Florence, Italy), and following a validated protocol previously created by our research group, which has been thoroughly described in preceding studies [8, 9]. This protocol comprises two stages: first, a 3D virtual modelling and then geometric characterization (Figure 2), and it has proved itself successful when used for diagnosis and characterization of KC in asymptomatic (preclinical) and mild visually impaired eyes [17, 18].

The final output of this protocol after its application, is a patient-specific 3D virtual model of the cornea, which is then analysed to find several morpho-biometric indices (Figure 2). These indices studied herein, along with their characteristics, have been previously described in [19] and are summarized in Table 1, but are used for the first time to study KC eyes with severe visual impairment. In this work, the surface finally generated with Rhinoceros software was distorted looking for the minimisation of the nominal distance between the points in the space and the surface itself. This distance was ultimately estimated by the software, showing a mean value for its error of $4.370 \times 10^{-16} \pm 3.67 \times 10^{-16}$ mm (mean $\pm$ standard deviation).

2.3. Statistical Analysis. Both Kolmogorov–Smirnov test and Shapiro–Wilk test were run to check data normality. According to these tests and thereafter, a Student's *t*-test was used for normally distributed samples, while Mann–Whitney–Wilcoxon U test was chosen for not-normally distributed ones. Correlation between parameters was assessed by means of Pearson coefficient (for normally distributed data) or Spearman's coefficient (not normally distributed). A significance level of 0.05 was fixed for *p*-values in all statistical tests. Receiver operating characteristic (ROC) curves were used to determine which

FIGURE 1: Use of patient-specific morpho-biometric indices for diagnosis of keratoconus with severe visual limitation.

parameters could be useful in terms of characterization of diseased corneas, and optimal cutoffs were established using Youden's J index, basing on sensitivity and specificity values [20, 21]. Graphpad Prism V 6 (GraphPad Software, La Jolla, USA) and IBM SPSS V 23.0 software (SPSS, Chicago, USA) were used to make all the analyses.

3. Results

Most of the modelled morpho-biometric indices showed statistically significant differences when comparing healthy and severe KC corneas, as shown in Table 2 below.

3.1. ROC Analysis. The predictive value of the modelled indices was established by an ROC analysis (Figure 3). Five morpho-biometric indices were identified with an area under the ROC (AUROC) above 0.85 (Table 3).

Table 4 summarizes all significant correlations between the modelled biometric parameters for the severe KC group. Correlation coefficients between parameters for the normal group have not been included, as their mutual relations have already been addressed in a previous study [18].

4. Discussion

From a visual point of view, patients of keratoconus disease show a deteriorated spectacle-corrected visual acuity, in such a way that when the disease progresses towards a higher degree of severity, the visual performance of patients gets worse. Thus, it is of great interest evaluating in a jointly

manner both the geometric decompensation that takes place in corneal structure due to its structural weakening and the level of visual limitation that patients show during the disease progression. In this work, we analysed the biometric profile of the cornea conceived as a 3D refractive structure for advanced degrees of keratoconus, whose patients present a severe degree of visual limitation, according to the RETICS classification [7].

The volumetric morpho-biometric indices showed a statistically significant reduced total corneal volume in the severe KC group when compared with the healthy eyes group, which is in line with the corneal thinning described by some authors as the disease progresses [16, 22, 23] due to a loss of tenacity in the corneal structure [13, 24]. These results are consistent with the ones reported by previous studies, which have evaluated the same anatomic index with devices based on Scheimpflug technology [23, 25] and similar to the ones reported in previous studies for advanced degrees of keratoconus [9]. Also, some significant positive correlations between corneal volume and sagittal plane apex area of the posterior surface ($R^2 = 0.919$, $p \leq 0.001$), and with sagittal plane area at minimum thickness point ($R^2 = 0.931$, $p \leq 0.001$) were found, so that when the volume diminishes by the loss of structural resistance that takes place for the progression of the disease, the sagittal areas ($Splarea_{\text{apex}}/Splarea_{\text{minthk}}$) also diminish as the corneal curvature increases. This agrees with the findings of significant lower volumes associated with pachymetric reductions in grade II and higher keratoconus eyes [23].

FIGURE 2: Protocol followed for the creation of the 3D virtual model and its later analysis.

TABLE 1: Patient-specific morpho-biometric indices analysed in the study [19].

Morpho-biometric parameters	Description
Total corneal volume (Vol_{tot}) (mm^3)	Volume limited by front, back, and peripheral surfaces of the solid model generated
Anterior/posterior corneal surface area ($Corarea_{ant}/Corarea_{pos}$) (mm^2)	Area of the front/exterior and rear/interior surfaces
Total corneal surface area ($Corarea_{tot}$) (mm^2)	Sum of anterior, posterior, and perimeter corneal surface areas of the solid model generated
Sagittal plane apex area ($Splarea_{papex}$) (mm^2)	Area of the cornea within the sagittal plane passing through the optical axis and the highest point (apex) of the posterior corneal surface
Anterior and posterior apex deviation (Dev_{aapex}/Dev_{papex}) (mm)	Average distance from the optical axis to the highest point (apex) of the anterior/posterior corneal surfaces
Sagittal plane area in minimum thickness point ($Splarea_{minthk}$) (mm^2)	Area of the cornea within the sagittal plane passing through the optical axis and the minimum thickness point (maximum curvature) of the posterior corneal surface
Anterior and posterior minimum thickness point deviation ($Dev_{aminthk}/Dev_{pminthk}$) (mm)	Average distance in the XY plane from the optical axis to the minimum thickness points (maximum curvature) of the anterior/posterior corneal surfaces
Centre of mass X, Y, Z (COM_X, COM_Y, COM_Z) (mm)	Centre of mass coordinates X, Y, Z of the solid

In addition, regarding the morpho-biometric indices of the anterior and posterior surface areas, these present a statistically significant augmentation, being the greater the area of the posterior surface than the one of the anterior

surface, which can be explained by the tendency of the cornea to retain a conical-shaped architecture in the advanced stages of the disease, in which the relation between both surfaces is modified by a higher increase of the

TABLE 2: Descriptive values and differences in the modelled morpho-biometric indices among the normal and severe KC groups.

Morpho-biometric indices	Normal group ($n = 50$)				Severe KC group ($n = 30$)				z	p
	Mean	SD	Min	Max	Mean	SD	Min	Max		
Vol_{tot} (mm^3)	25.72	1.53	23.23	29.07	23.74	1.85	20.17	28.40	5.18	≤ 0.01
$Corarea_{ant}$ (mm^2)	43.08	0.14	42.77	43.33	43.80	0.59	42.66	45.11	-6.56	≤ 0.01
$Corarea_{pos}$ (mm^2)	44.24	0.26	43.53	44.71	45.44	0.95	43.78	47.97	-6.78	≤ 0.01
$Corarea_{tot}$ (mm^2)	103.89	1.12	100.73	105.66	105.20	2.13	102.35	112.68	-3.14	≤ 0.01
$Splarea_{papex}$ (mm^2)	4.32	0.26	3.93	4.87	3.86	0.40	2.96	5.02	6.33	≤ 0.01
$Splarea_{minthk}$ (mm^2)	4.31	0.26	3.92	4.86	3.84	0.40	2.97	5.03	6.41	≤ 0.01
Dev_{apex} (mm)	0.00	0.00	0.00	0.00	0.03	0.02	0.00	0.06	-8.26	≤ 0.01
Dev_{papex} (mm)	0.07	0.02	0.04	0.09	0.26	0.12	0.05	0.59	-6.68	≤ 0.01
COM_X (mm)	0.04	0.02	0.01	0.09	-0.01	0.06	-0.20	0.12	4.23	≤ 0.01
COM_Y (mm)	0.03	0.02	0.00	0.08	-0.01	0.09	-0.13	0.33	2.57	0.02
COM_Z (mm)	0.77	0.02	0.71	0.81	0.85	0.08	0.70	1.06	-5.56	≤ 0.01
$Dev_{aminthk}$ (mm)	0.83	0.21	0.44	1.27	0.91	0.36	0.16	1.68	-1.12	0.27
$Dev_{pminthk}$ (mm)	0.76	0.20	0.38	1.24	0.85	0.34	0.10	1.60	-1.23	0.23

SD: standard deviation; P : statistical test; z : z-score.

FIGURE 3: Curves for modelled indices detecting severe KC.

posterior surface curvature than the one in the anterior surface, motivated by the biomechanical weakening that cornea manifests for a reorientation of its anatomophysiology [26]. A tendency in this line of structural weakening has been reported in previous studies [13, 26, 27]. Vega-Estrada et al. [7] observed a significant increase in dioptric

power of the posterior corneal surface with respect to the anterior in advanced phases of the disease. According to these findings, corneal multifocality that produces the conical shape that locally acquires corneal surface, drives to a worsening in patient's visual performance. Besides, anterior, posterior, and total corneal surface areas show a strong positive correlation between them, and their values increase in the severe KC group, which can be explained by the fact that structural weakening caused by the presence of fewer collagen fibres in each lamella leads to a severe local protrusion that increases the corneal surface [2] by the effect of the intraocular pressure over a structurally weakened biomechanical architecture. These results are coincident with the ones presented in other studies [16, 22, 28].

The anterior and posterior corneal surface minimum thickness point deviations show the strongest correlation between them ($R^2 = 0.995$, $p \leq 0.001$). However, these are the only parameters that show no statistical difference for group discrimination ($p = 0.271$ and $p = 0.229$, respectively). This addresses the relationship between both corneal surface curvatures for keratoconus eyes, as it has already been made in previous studies for both diseased and normal eyes [16, 28], but also that in the case of severe visual limitation, this deviation varies so greatly among individuals that discrimination is impossible.

Anterior apex deviation and posterior apex deviation increase for the severe KC group. This displacement of the optical axis has been described as one of the signs of the later stages of the disease [1]. This is in concordance with some authors' findings [23] that suggest a strong correlation between apex deviation and pachymetric progression index of the front and back elevations with CDVA of the analysed patients. Also, posterior apex deviation presents an important variability with respect to the anterior apex deviation, this is motivated by the tendency of the aspheric profile to reproduce the cornea's physiologic prolatism in advanced phases of the disease [16, 28]. It can even be observed a paraboloid type geometry in virtual 3D models, a fact that can be relevant to explain the asymmetry that shows the posterior corneal surface in advanced keratoconus. This variability has been reported in previous studies [15, 29, 30],

TABLE 3: The area under the ROC results.

Morpho-biometric indices	AUROC	Sensitivity	Specificity	Cutoff value
Corarea _{ant}	0.874	83.3	96.0	$\geq 43.275 \text{ mm}^2$
Corarea _{pos}	0.890	86.7	96.0	$\geq 43.160 \text{ mm}^2$
Dev _{aapex}	0.977	96.7	94.0	$\geq 0.001 \text{ mm}$
Dev _{papex}	0.948	90.0	99.9	$\geq 0.098 \text{ mm}$
COM _Z	0.852	73.3	98.0	$\geq 0.809 \text{ mm}$

TABLE 4: The significant correlation coefficient values for the modelled variables in the severe KC group.

Measurement correlation	Severe KC group ($n = 30$)	
	Correlation coefficient	p value
Splarea _{papex} /Vol _{tot}	0.919	≤ 0.001
Corarea _{ant} /Corarea _{pos}	0.917	≤ 0.001
Corarea _{ant} /Corarea _{tot}	0.835	≤ 0.001
Corarea _{pos} /Corarea _{tot}	0.899	≤ 0.001
Vol _{tot} /Corarea _{tot}	0.439	0.015
COM _Y /Splarea _{papex}	0.448	0.013
COM _Z /Dev _{aapex}	0.366	0.046
COM _Z /Corarea _{ant}	0.925	≤ 0.001
COM _Z /Corarea _{pos}	0.874	≤ 0.001
COM _Z /Corarea _{tot}	0.873	≤ 0.001
Dev _{aminthk} /Dev _{papex}	0.597	≤ 0.001
Dev _{pminthk} /Dev _{papex}	0.611	≤ 0.001
Splarea _{minthk} /Splarea _{papex}	0.989	≤ 0.001
Vol _{tot} /Splarea _{minthk}	0.931	≤ 0.001
COM _X /COM _Y	-0.375	0.041
COM _X /Dev _{aminthk}	-0.429	0.018
COM _X /Dev _{pminthk}	-0.476	0.008
COM _Y /Splarea _{minthk}	-0.403	0.027
Dev _{aapex} /Dev _{papex}	0.995	≤ 0.001

being this one the first in which posterior surface asymmetry is quantified for keratoconus eyes with severe visual limitation. Besides, this geometric tendency is correlated with the increase of optical aberrations in advanced degrees of keratoconus [5, 22, 31].

Results also suggest a strong correlation between centre of mass Z and anterior, posterior, and total corneal surfaces ($R^2 = 0.925$, $p \leq 0.001$; $R^2 = 0.874$, $p \leq 0.001$; $R^2 = 0.873$, $p \leq 0.001$, respectively) as well as a displacement of the centre of mass along the Z-positive axis, which is logical, as the loss of corneal volume that steeps the surfaces, should also force the centre of mass to move towards the protrusion, as a consequence of the corresponding displacement of both apex points in the Z-coordinate. This is in line with the findings of some authors [32, 33], which found that the mean maximum anterior and posterior corneal elevations were higher in eyes with subclinical or clinical keratoconus.

Regarding the ROC analysis, the anterior apex deviation reached the highest area under the curve (AUC, 0.977) with very high sensitivity (96.7%) and specificity (94.0%) due to the fact that the apex is the maximum curvature point of the corneal surface. Moreover, the posterior apex deviation also shows high discrimination capability (AUC, 0.948) with very good sensitivity (90%) and excellent specificity (99.9%). Anterior and posterior corneal surfaces and centre of mass show high AUC, but although their specificity is high, their

sensitivity is not as good as the one for the deviation of the apices.

In conclusion, the analysis of corneal biometric parameters using patient-specific 3D modelling has ascertained statistically significant differences between normal and KC eyes with severe visual limitation. This computer-assisted custom approach has determined several indices that successfully characterize the profile of keratoconic eyes affected by severe visual limitation. Therefore, this analysis has proven to be a useful tool for KC classification, helping doctors to achieve reliable diagnoses in severe cases of the disease, as well as it has helped to better characterize corneal changes that take place when severe KC is developed and how they relate with vision deterioration.

Data Availability

The data used to support the findings of this study were supplied by "Iberia" under license and so cannot be made freely available. Requests for access to these data should be made to Dr. Jorge Alió, jlalio@vissum.com, National Network for Clinical Research in Ophthalmology RETICS-OFTARED.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Efficacy of Morpho-Geometrical Analysis of the Corneal Surfaces in Keratoconus Disease According to Moderate Visual Limitation

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Abstract. The cornea is a complex hemispheric structure, made of collagen fibres that provide it a homogenous and stable geometry. During keratoconus disease, a loss of tenacity takes place in the collagen fibres that form the corneal structure, producing an alteration of its geometry, this is, a change of its curvature, and therefore, a loss of visual quality of patients. The geometric characterization of the hemispheric structure by means of biometric parameters is a very solid technique of diagnosis, based in a virtual 3D model, which has already been validated for several degrees of severity of keratoconus pathology. In this prospective comparative study, 93 corneas (50 healthy subjects and 43 patients with keratoconus with moderate visual limitation) were geometrically modelled. The results obtained in this work suggest that the best predictive biometric parameters are anterior corneal surface area and posterior apex deviation, and that the strongest correlation is produced between sagittal plane apex area in minimum thickness point and sagittal plane apex area. The studied biometric parameters have shown significant differences between groups. Therefore, the analysis of the biometric parameters that register the geometric decompensation that locally appear in a corneal region, as a response to the asymmetry produced during the development of keratoconus disease with a moderate visual impairment, is a new approach that may lead to a better understanding of the disease with this degree of optical limitation.

Keywords: Computer-Aided Geometric Design (CAGD), Optical Aberrometry, Scheimpflug, 3D Modelling.

1 Introduction

The cornea is an avascular structure with a hemispheric shape that is part of the anterior segment of the human eye [1]. It is a highly differentiated tissue with five layers which

have different functions, being the most important the one of the first ocular refractive element, due to its properties of transparency and curvature along all the structure [2].

One of the main pathologies of the cornea is keratoconus, which is a clinical term that describes a corneal condition characterized by its progressive thinning, which causes a cone-shaped corneal protrusion [3]. This degenerative geometrical deformation leads to a decrease of cornea's optical quality.

The knowledge, from a clinical point of view, of the geometrical characteristics of the cornea is important in clinical practice [1]. There are several studies in scientific literature which have validated indexes or topographic descriptors of the cornea [3,4] in order to define the cut off values that allow the discrimination between normal and keratoconus corneas. From this indexes, several keratoconus classifications have been proposed, such as a morphological classification [1], keratometric [5], of keratoconus severity [6], or Amsler-Krumeich [1]. However, none of these classifications measures the degree of severity of keratoconus depending on the visual limitation level.

In addition, computer-aided design is a widespread tool for biological structure modelling [7-9], and its later use for disease diagnosis [10,11]. Our research group have developed some new virtual geometric models of the human cornea that have been used to characterize corneal ectasia disease basing on Amsler-Krumeich classification [12-14], and for other classification, named RETICS [15], which allows characterizing keratoconus' pathology considering visual performance of patients in its initial phases [16,17].

This investigation work proposes a way to characterize cornea's morphogeometry in keratoconus pathology with a moderate degree of visual performance, and also to quantify the existence of correlations between the geometries of corneal surfaces for this degree of severity of the disease.

2 Materials and Methods

2.1 Participants

This observational case series study evaluated 93 corneas of 93 patients (selected at random to avoid interference) structured in two groups: a normal group (healthy corneas), which included 50 subjects presenting no ocular pathology (36.80 ± 15.67 years); and a second group, composed of 43 patients diagnosed with moderate KC (46.67 ± 24.99 years). The classification protocol for normal or moderate KC cases was run according to reported state of the art of clinical and topographic evaluations [18].

All patients were selected according to the RETICS grading. Inclusion criteria were patients diagnosed as Grade III KC eyes (moderate visual impairment, $0.4 < CDVA \leq 0.6$ in decimal scale, or $6/15 < CDVA \leq 6/9.5$ Snellen), corneal topography revealing a localized steepening, and/or an asymmetric bowtie pattern with or without skewed radial axis. The exclusion criteria were the following: any previous ocular surgery, ocular surface inflammation, moderate to severe dry eye or other active ocular comorbidity, or use of contact lenses within the four weeks prior to the first visit.

These evaluations were made at Vissum Instituto Oftalmológico Alicante, Spain (Vissum) who were adequately informed about the clinical study and voluntarily signed

their consent to participate. The study was ratified by the clinic's Institutional Review Board in compliance with the ethical restrictions established in the Declaration of Helsinki (Seventh revision, October 2013, Fortaleza, Brasil).

2.2 Examination Protocol

All subjects selected for this study were examined using Sirius System® (CSO, Florence, Italy), and following a validated protocol previously created by our research group, which has been thoroughly described in preceding studies [14,12,13], and that has proved itself successful when used for diagnosis and characterization of KC in asymptomatic (pre-clinical) and mild visually-impaired eyes [17,16].

The final output of this protocol after its application, is a patient-specific 3D virtual model of the cornea, which is then analysed to find several biometric parameters (Figure 1). These biometric parameters studied herein, along with their characteristics, have been previously described in [19], and are summarized in Table 1, but are used for the first time to study KC eyes with moderate visual impairment. In this study, the Rhinoceros' surface was deformed to minimise the nominal distance between the spatial points and the surface. This deviation could be later calculated by the software, providing a mean value of the distance error for the solution surface of $5.560 \times 10^{-17} \pm 5.81 \times 10^{-17}$ mm (mean $\pm$ standard deviation).

Table 1. Biometric parameters analysed in the study.

<i>Biometric parameter</i>	<i>Description</i>
Total corneal volume (Vol _{tot}) [mm ³]	Volume limited by front, back and peripheral surfaces of the solid model generated
Anterior / posterior corneal surface area (Corarea _{ant} / Corarea _{pos}) [mm ²]	Area of the front/exterior and rear/interior surfaces
Total corneal surface area (Corarea _{tot}) [mm ²]	Sum of anterior, posterior and perimeter corneal surface areas of the solid model generated
Sagittal plane apex area (Splarea _{apex}) [mm ²]	Area of the cornea within the sagittal plane passing through the optical axis and the highest point (apex) of the posterior corneal surface
Anterior and posterior apex deviation (Dev _{aapex} / Dev _{papex}) [mm]	Average distance from the optical axis to the highest point (apex) of the anterior / posterior corneal surfaces
Sagittal Plane Area in minimum thickness point (Splarea _{minthk}) [mm ²]	Area of the cornea within the sagittal plane passing through the optical axis and the minimum thickness point (maximum curvature) of the posterior corneal surface
Anterior and posterior minimum thickness point deviation (Dev _{aminthk} / Dev _{pminthk}) [mm]	Average distance in the XY plane from the optical axis to the minimum thickness points (maximum curvature) of the anterior / posterior corneal surfaces
Centre of mass X, Y, Z (COM _X , COM _Y , COM _Z) [mm]	Centre of mass coordinates X, Y, Z of the solid

Fig. 1. Scheme of the procedure for the generation of a virtual model and later analysis of the corneal structure.

2.3 Statistical Analysis

Both Kolmogorov-Smirnov test and Shapiro-Wilks test were run to check data normality. According to these tests and thereafter, a Student's T-test or U-Mann Whitney Wilcoxon test were employed, when appropriate. Correlation between parameters was assessed by means of Pearson coefficients (for normally distributed data) or Spearman coefficients (not normally distributed). A significance level of 0.05 was fixed for p-values in all statistical tests. Receiver operating characteristics (ROC) curves were used to determine which parameters could be useful in terms of characterization of diseased corneas, and optimal cut-offs were established using Youden's J index, basing on sensitivity and specificity values [20,21]. Graphpad Prism V 6 (GraphPad Software, La Jolla, USA) and IBM SPSS V 23.0 software (SPSS, Chicago, USA) were used to make all the analyses.

3 Results

Most of the modelled parameters showed statistically significant differences when comparing healthy and moderate KC corneas, as shown in Table 2 below.

Table 2. Descriptive values and differences in the modelled biometric parameters among the normal and moderate KC groups. SD: standard deviation. P: statistical test, Z: z-score.

<i>Biometric Parameters</i>	<i>Normal Group (n = 50)</i>				<i>Moderate KC Group (n = 43)</i>				<i>z</i>	<i>P</i>
	<i>Mean</i>	<i>SD</i>	<i>Min</i>	<i>Max</i>	<i>Mean</i>	<i>SD</i>	<i>Min</i>	<i>Max</i>		
Vol _{tot} (mm ³)	25.71	1.53	23.23	29.07	23.97	1.52	21.06	28.74	-5.16	0.000
Corarea _{ant} (mm ²)	43.08	0.14	42.77	43.33	43.67	0.47	42.79	45.09	-7.37	0.000
Corarea _{pos} (mm ²)	44.24	0.26	43.53	44.71	45.22	0.80	44.17	47.53	-7.24	0.000
Corarea _{tot} (mm ²)	103.87	1.12	100.73	105.66	104.91	1.70	101.91	109.95	-3.47	0.001
Splarea _{papex} (mm ²)	4.32	0.26	3.93	4.87	3.93	0.29	3.19	4.83	6.72	0.000
Splarea _{minthk} (mm ²)	4.31	0.26	3.92	4.86	3.92	0.29	3.19	4.82	6.61	0.000
Dev _{aapex} (mm)	0.00	0.00	0.00	0.01	0.02	0.00	0.00	0.07	-7.57	0.000
Dev _{papex} (mm)	0.07	0.02	0.04	0.09	0.21	0.08	0.03	0.34	-7.37	0.000
COM _X (mm)	0.04	0.02	0.01	0.09	0.02	0.05	-0.15	0.20	3.39	0.001
COM _Y (mm)	0.03	0.02	0.00	0.08	0.00	0.05	-0.14	0.16	-5.14	0.000
COM _Z (mm)	0.77	0.02	0.71	0.81	0.83	0.06	0.72	1.00	-6.26	0.000
Dev _{aminthk} (mm)	0.83	0.21	0.44	1.27	0.81	0.09	0.35	1.81	0.37	0.713
Dev _{pminthk} (mm)	0.76	0.20	0.38	1.24	0.74	0.26	0.30	1.31	0.57	0.570

3.1 Roc Analysis

A ROC analysis was used to ascertain the predictive value of the modelled parameters (Figure 2). Five biometric parameters showed an area under the ROC (AUROC) above 0.7 (Table 3).

Table 3. The area under the ROC results.

<i>Biometric Parameters</i>	<i>AUROC</i>	<i>Sensitivity</i>	<i>Specificity</i>	<i>Cut off value</i>
Corarea _{ant}	0.945	86.0	96.0	$\geq 43.2595 \text{ mm}^2$
Corarea _{pos}	0.937	83.7	96.0	$\geq 44.6205 \text{ mm}^2$
Dev _{aapex}	0.910	83.7	94.0	$\geq 0.0010 \text{ mm}$
Dev _{papex}	0.945	93.0	99.9	$\geq 0.0965 \text{ mm}$
COM _Z	0.878	69.8	98.0	$\geq 0.0809 \text{ mm}$

Fig. 2. Curves for modelled parameters detecting moderate KC.

Table 4 summarizes all significant correlations between the modelled biometric parameters for the moderate KC group. Correlation coefficients between parameters for normal group have not been included, as their mutual relations have already been addressed in a previous study [16].

Table 4. The significant correlation coefficient values for the modelled variables in the moderate KC group.

Measurement correlation	Moderate KC group ($n = 43$)	
	Correlation coefficient	<i>P</i> value
$Splarea_{p apex} / Vol_{tot}$	0.965	0.000
$Corarea_{ant} / Dev_{p apex}$	0.313	0.041
$Corarea_{pos} / Dev_{p apex}$	0.361	0.017
$Corarea_{ant} / Corarea_{pos}$	0.941	0.000
$Corarea_{ant} / Corarea_{tot}$	0.778	0.000
$Corarea_{pos} / Corarea_{tot}$	0.864	0.000
$Vol_{tot} / Corarea_{tot}$	0.354	0.020
$COM_X / Corarea_{ant}$	-0.340	0.025
$COM_X / Corarea_{pos}$	-0.317	0.038
$COM_X / Corarea_{tot}$	-0.361	0.017

COM_X / COM_Z	-0.369	0.015
$COM_Z / Corarea_{ant}$	0.938	0.000
$COM_Z / Corarea_{pos}$	0.882	0.000
$COM_Z / Corarea_{tot}$	0.844	0.000
$Dev_{aminthk} / Dev_{papex}$	0.440	0.003
$Dev_{pminthk} / Dev_{papex}$	0.532	0.000
$Dev_{aminthk} / Dev_{pminthk}$	0.979	0.000
$Splarea_{minthk} / Splarea_{papex}$	0.997	0.000
$Vol_{tot} / Splarea_{minthk}$	0.963	0.000
Dev_{apex} / Dev_{papex}	0.403	0.007

4 Discussion

The cornea is a complex hemispheric structure, made of collagen fibres that provide it a homogenous and stable geometry. In a pathological scenario, a loss of tenacity takes place in the collagen fibres that form the corneal structure, producing an alteration of its geometry, this is, a change of its curvature, and therefore, a loss of visual quality of patients [22].

There are in scientific literature several works that have studied the geometry of corneas with a moderate degree of optical aberration [23,13,24]. Several studies [23] observed that corneal thickness is not constant in this pathology, as a thinning is produced in the region in which the loss of structural tenacity appears. These results are consistent with the ones obtained by other researchers [24] that analysed the thickness of corneas with an advanced degree of optical aberration. Other recent study has demonstrated that some morphological singularities as well as corneal thickness are related with disease progression [13]. Therefore, the cornea in this pathology shows a region of geometrical decompensation as a non-symmetric response to the disease progress. However, the parametrization and study of the correlation between the biometric parameters that register this decompensation, which allow to evaluate the progression of keratoconus with moderate visual loss, have not been analysed for each patient from a virtual model of their own eye.

In this study, all measures made have resulted consistent, and almost all mean differences have been statistically significant between healthy corneas and corneas with keratoconus showing a moderate degree of visual impair, except for the anterior/posterior minimum thickness point deviation. These results are in accordance with the ones reported by previous studies that evaluated some of these anatomic parameters with equipment based in Scheimpflug technology [25]. In our study, we have used a technology based in a double rotating camera based in the Scheimpflug projection system. This system has shown, in a previous study [26], being a robust and repeatable system for spatial data acquisition of the hemispheric structure, from which basing the generation of the virtual model with CAD software [17].

Regarding the AUROC, four parameters from all the ones analysed in our study showed very high discriminant values ($\text{AUROC} > 0.9$). Two parameters, which are the anterior and posterior corneal surface areas showed AUROC values of 0.937 y 0.945 respectively, due to the fact that in the pathological scenario a biomechanical weakening takes place, caused by the loss of tenacity of the hemispheric structure and consequently, an increase of the corneal surface curvature is produced. This tendency is in line with some previous works that made ratio studies between anterior and posterior areas for different degrees of severity of the disease [25]. The other two parameters with high discrimination values were anterior apex deviation ($\text{AUROC} = 0.910$) and posterior apex deviation ($\text{AUROC} = 0.945$), this is because the corneal apex is the point of maximum curvature in corneal surfaces, therefore, according with other authors [27], the apex deviation is a parameter that could affect the visual performance of the patients.

In this study, we have analysed the correlation between biometric parameters that register the structural alteration which manifests during the disease development. So, the parameters related with the areas show a strong positive correlation, specifically between anterior and posterior surface areas ($R^2 = 0.941$, $p = 0.000$), anterior surface area and total corneal surface area ($R^2 = 0.778$, $p = 0.000$) and posterior and total corneal surface areas ($R^2 = 0.864$, $p = 0.000$), due to the fact that corneal surfaces tend to behave proportionally during the evolution of the disease. These results are consistent with the ones obtained for corneal curvature in eyes with keratoconus, with the biomechanical weakening of the cornea, and with the possible effect of intraocular pressure in the weakened corneal structure [28].

Regarding anterior and posterior deviations, both between corneal apex points ($R^2 = 0.832$, $p = 0.000$) and minimum thickness points ($R^2 = 0.997$, $p = 0.000$), there is a strong positive correlation, this is in line with the results reported by other authors [25] that demonstrated a robust correlation between apex deviation and the minimum thickness points and their relation with the pachymetric progression of corneal thickness.

5 Conclusion

The analysis of the biometric parameters that register the geometric decompensation that locally appear in a corneal region, as a response to the asymmetry produced during the development of keratoconus disease with a moderate degree of optical aberration, is a procedure that provides the ophthalmologist a new tool for the diagnosis of this pathology with this degree of development. In this work it has been ascertained that the most predictive biometric parameters are the anterior corneal surface area and the deviation of the posterior apex, detecting that the strongest correlation is the one between the areas of the sagittal planes defined through the minimum thickness points and the posterior corneal apex. The studied biometric parameters showed significant differences between groups. Therefore, this new approach based in the personalised diagnosis from a computational model may lead to a better understanding of the disease with this degree of optical limitation.

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7 Additional Information

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Article

3D Printed Personalized Corneal Models as a Tool for Improving Patient's Knowledge of an Asymmetric Disease

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Abstract: Additive manufacturing is a vanguard technology that is currently being used in several fields in medicine. This study aims to evaluate the viability in clinical practice of a patient-specific 3D model that helps to improve the strategies of the doctor-patient assistance. Data obtained from a corneal topographer were used to make a virtual 3D model by using CAD software, to later print this model by FDM and get an exact replica of each patient's cornea in consultation. Used CAD and printing software were open-source, and the printing material was biodegradable and its cost was low. Clinic users gave their feedback by means of a survey about their feelings when perceiving with their senses their own printed cornea. There was 82 surveyed, 73.8% (9.74; SD: 0.45) of them considered that the model had helped them a lot to understand their disease, expressing 100% of them their intention of taking home the printed model. The majority highlighted that this new concept improves both quality and clinical service in consultation. Custom-made individualized printed models allow a new patient-oriented perspective that may improve the communication strategy from the ophthalmologist to the patient, easing patient's understanding of their asymmetric disease and its later treatment.

Keywords: computer-aided geometric design (CAGD); additive manufacturing (AM); scheimpflug; low cost

1. Introduction

Keratoconus (KC) is an asymmetric condition in which the cornea, at a local level, becomes thinner and develops a cone-like bulge. Prevalence of this corneal degeneration is variable: many studies suggest a value ranging from 50 to 230 cases per 10,000, due to variability of diagnostic criteria. Keratometry, slit-lamp biomicroscopy, corneal topography and retinoscopy are the most common exams used for KC diagnosis [1,2].

Currently, there is an increasing need from patients to be better informed about clinical practice [3], however, improving patient information in ophthalmology consultations remains a clinical challenge [4], as ophthalmologists develop their doctor-patient assistance strategies using conventional techniques based in bi-dimensional (2D) images [5]. Many of the patients that attend consultations suffer from severely diminished visual acuity, something that is particularly frequent in advanced cases of KC, impeding the explanation of their pathology to them by means of drawn pictures or 3D renders on

a screen. Consequently, as patients cannot take advantage from the benefits of three-dimensional (3D) images to spatially conceptualize the real extent of their pathology, new approaches need to be explored in the patient–doctor’s communication process.

The fundamental pillar for a successful clinical consultation is the ability that the ophthalmologist shows to manage patient expectations, as frequently patients do not understand the true nature of their medical condition in KC disease, which leads to a scenario of frustration and poor outcomes [6]. In clinical practice, several authors have demonstrated that the use of physical 3D models of biological structures improves the understanding of the disease by the patients [7–9], which suggests that the use of senses over a three-dimensional physical model makes patient’s learning easier, providing a better understanding of the pathology and its later treatment. Thus, it would be of great interest, in the field of ophthalmology, to develop a new concept of information and education of patients that promoted success in ophthalmological consultations (Figure 1).

Figure 1. New concept of information and education in clinical practice.

Additive manufacturing (AM) is a disruptive and sustainable innovation [10] that allows the fabrication of three-dimensional (3D) objects. This term comprises many subcategories, such as rapid prototyping, direct digital manufacturing (DDM) and 3D printing (3DP), among others [11], all of them increasingly useful in automotive [12,13] and aerospace/defense [14,15] industries. When combined with reverse engineering and CAD modeling techniques, AM technologies can end up the design process in engineering, allowing more freedom when designing, higher customization, less waste production and manufacturing complex structures in a faster way [16,17].

In the field of medicine, AM technology is used for the manufacture of highly customized vanguard devices, as well as printing tissues and soft organs [6]. In addition, the advent of new technologies has propelled AM to become an accessible and cost-effective technology for medical community [18], being it also used in different fields for the fabrication of personalized models used in surgical planning, residents teaching or patients education [19–29]. Furthermore, these designs are frequently available in the Internet in open access for the medical community, promoting the development of collaborative networks between doctors and researchers, which turns them into a fundamental tool in translational research [30,31].

Our research group has validated a virtual 3D model of the cornea for each specific patient by using proprietary software [32]. These models have been used for the diagnosis of KC in virtual environments [33,34], but can also be used for 3D printing, so the printed physical model will reflect the abnormal irregularities and asymmetry that characterizes the cornea as KC disease progresses, in a way that patients would be capable of conceiving the geometrical variability of their cornea comparing it with a healthy one. This way, patients will be able to conceptualize the physical cause that induces their loss of visual acuity, and consequently, their quality of life. Furthermore, and in the framework of promotion of the collaborative research networks, in this research work we propose the use of open-source software for the generation of the files of the virtual 3D models of the patients, so they can be used for any member of the international scientific community.

Thus, in this research work, it is proposed a new concept of patient information that uses 3D printed models of the cornea in the clinical practice of a hospital, using for its creation open-source software, both for the generation of the CAD models and the 3D printing files. The main objective pursued is improving the communication strategy of the ophthalmologist with the patient, easing the patient's process of understanding their disease and its later treatment, and avoiding a situation in which patients do not realize the real dimension of their disease, that could lead them to a scenario of frustration and poor outcomes.

2. Material and Methods

2.1. Patients

This article presents an observational comparative study that included 30 corneas of healthy patients (13 men and 17 women, average age 28.01 ± 14.19) and 52 of patients with keratoconus (22 men and 30 women, average age 26.71 ± 13.41). Keratoconus patients were also divided in several sub-groups, depending on the disease severity in the Amsler-Krumeich grading system [2,35]: 20 grade I, 14 grade II, 12 grade III and 6 grade IV.

The tenets of the Declaration of Helsinki (7th rev., Oct-2013, Fortaleza, Brazil) were followed for the development of the research, and it was backed up by the Committee of Ethics of the hospital participating in this study, signing all patients their consent to participate. The subjects whose data were used in this study were diagnosed in Visum Corporation Alicante (a centre in affiliation with Miguel Hernández University of Elche, Spain), and their data is stored in the "Iberia" database of KC eyes that has been developed for the National Network for Clinical Research In Ophthalmology RETICS-OFATARED.

The procedure to discriminate between normal and KC patients was made according to validated up-to-date topographical and clinical verifications [2,5]. The exclusion criteria were the subsequent: contact lenses use in the thirty days that preceded their initial visit, ocular surface irritation, any previous ocular surgical procedure, mild or acute dry eye or presence of any other ocular comorbidity. Healthy eyes selected were all those that did not coincide with any of the exclusion criteria, while the diagnosis of keratoconus according to standard guidelines was the criterion to be included in the KC group.

2.2. Methods

Corneal tomographers based on Scheimpflug technology allow us to obtain a file in comma-separated values (CSV format), which can be used for different studies [36–39]. This file is composed of a spatial cloud of points in matrix form that represent corneal surfaces [32].

In this research work, Sirius tomographer (CSO, Italy) has been used. It is equipment that has proved its validity in clinical practice [5]. For the selection of data, just the topographies showing the highest acquisition quality were included in the study.

The custom-made individualized printed model reconstruction procedure consists of the following successive stages (Figure 2): I) surface and 3D model generation, II) 3D printable model preparation and III) 3D model printing in clinical practice.

Figure 2. Proposed methodology for custom-made individualized model printing.

I. Surface and 3D model generation. At this point, a volumetric dataset was calculated from the available CSV file. This task can be performed by several software applications. In this study, CloudCompare 2.9.1 open-source software was the one used to generate the 3D model, using its “Delaunay 2.5D (best fitting plane)” option to generate a mesh from the point cloud of each surface. Then, the perimeter surface was created and, using Boolean operations, it was merged with the anterior and posterior corneal surfaces to create the final volume, which was then cut by a sagittal plane that passed through the optical axis and the minimum thickness points (anterior/posterior) of the corneal surfaces. CloudCompare entities are saved as BIN files, a format that is highly compatible with most open source 3D graphics software, so they can be easily used by any collaborative research network.

II. 3D Printable Model Preparation. 3D Printing process needs to define the surfaces of the solid model as a polygonal triangle mesh. However, even doing so, the virtual 3D model is still unfinished and its rough borders have to be refined. Other surface improvements can also be done, such as

inspecting and modifying any overlying surfaces, and simplifying the image file to increase printing efficiency. For this purpose, Cura 2.5 free software (Ultimaker, Netherlands) was used. To do so, files generated in CloudCompare were exported into STL (Stereolithography, Standard Triangle Language or Standard Tessellation Language) format [40], which is a very versatile and greatly compatible format with all 3D printers. Then, printing parameters were set in Cura, and a file containing all printing information (points, trajectories, speed, filling, etc.) was then generated as a GCODE file, which was lately uploaded to the 3D printer controller using a USB pendrive. 3D model files (.stl) and printing information files (.gcode) for both a healthy and an advanced KC cornea, complete and by a sagittal cut, have been attached as Supplementary Materials.

III. 3D Printing. The printer selected for this project was a FDM (fused deposition modeling) model designed by the UPCT-Makers organization, named “3D Printer ETSII –UPCT” [41]. This 3D printer is part of the RepRap project [42], so its drawings and technical data are open-source and available in the Internet, allowing its construction by any user. It was endowed with an Arduino MEGA controller, RAMPS 1.4 and drivers V. 88.25, and was programmed with Marlin software. It can be considered a low cost printer, as it had an approximate cost of less than 120 €, with an average life expectancy of 2000 duty hours.

The material used for 3D printing was polylactic acid (PLA), it is a rigid biodegradable polymer [43], that is stable to ultra-violet light, has low flammability and its characteristics are similar to PET polymer. Its properties, along with main printing parameters, can be checked in Table 1.

Table 1. 3D printer parameters.

Parameter	Values/Settings
Material	PLA
Quality: layer height	0.2–0.3 mm
Fusing material density	1.25 g/cm ³
Fusing material fusion point	160 °C
Printing temperature	225 °C
Nozzle diameter	1 mm
Flow rate	100%
Print speed	500 mm/s
Travel speed	130 mm/s
Printing area	22 cm × 23 cm × 20 cm

In our study, two physical models of cornea were printed per patient: a complete cornea, which corresponds to its full structure geometry, in which patient can see and perceive with his own senses the possible existence of morphological alterations at surface (anterior/posterior) level and the corneal volume; and another cornea, which corresponds to one half of a full cornea, defined by a sagittal plane that passes through the geometrical axis and the minimum thickness points (anterior/posterior) of the corneal surfaces (Figure 3), in which the patient can perceive with his senses the possible existence of morphological alterations in corneal thickness and the variation of curvature at surface (anterior/posterior) level.

As corneal real diameter is about 12 mm, and at that size corneal alterations were difficult to perceive, the use of a 1:1 scale for the model was discarded. Conversely, using big size models makes perception easier, but also significantly increases printing costs, so finally a 5:1 scale was used, as it was the smallest one that allowed an easy detection of slight changes in thickness and/or curvature.

The average time for all the process (3D modeling and 3D printing) was of 24.8 ± 3.4 min.

Figure 3. Healthy cornea (male patient of 24 years, Oculus Sinister (OS), Corrected Distance Visual Acuity (CDVA) = 1, astigmatism = 0.45, coma of like = 0.27, spherical-like = 0.23, Q8mm = −0.16 central thickness = 534). Advanced keratoconus (female patient of 20 years, Oculus Dexter (OD), CDVA = 0.44, astigmatism = 1.17, coma of like = 2.27, spherical-like = 2.50, Q8mm = −2.42 central thickness = 402).

2.3. Questionnaire

Finally, in order to assess the usefulness of the 3D model, a questionnaire was passed to each patient (82 in total). If the patient suffered from keratoconus, his custom 3D printed model was compared with a typical healthy cornea model, and their condition was explained to them, filling the questionnaire just after finishing the explanation. Questions made can be seen in Table 2. When selecting the scale for each question, for Q1, Q2 and Q5 we used 10 levels Likert items instead of the most common five level ones, looking for minimizing central tendency bias, while for questions Q3 and Q4, we opted for an absolute scale (yes/no/neutral).

Table 2. Questions made to the patients.

Number	Question Test	Possible Answer
Q1	What usefulness do you attribute to this custom 3D model?	From 1 = not useful at all to 10 = very useful
Q2	How much did the custom 3D model help you to better understand your condition?	From 1 = nothing at all to 10 = a huge lot
Q3	Would you like to take the custom 3D model with you after the consultation?	Yes/No/Neutral
Q4	Would you consider that using this custom 3D model improves the quality of our clinical service?	Yes/No/Neutral
Q5	How much do you consider that patients would benefit from the use of these custom 3D models in consultations?	From 1 = nothing at all to 10 = a huge lot

3. Results

The study lasted from January 2018 to March 2019, in Visum Hospital in Alicante (Spain). Table 3 reports the collected answers to the five questions proposed to the patients.

Table 3. Questionnaire results.

Number	Possible Answer	Percentage	Average	Standard Deviation (SD)
Q1	From 1 = not useful at all to 10 = very useful	-	9.67	0.53
Q2	From 1 = nothing at all to 10 = a huge lot	-	9.74	0.45
Q3	Yes	100.0	95.2	0.0
	No	0.0		
	Neutral	0.0		
Q4	Yes	95.2	4.8	0.0
	No	0.0		
	Neutral	4.8		
Q5	From 1 = nothing at all to 10 = a huge lot	-	8.62	0.58

Results of Q1 show that the majority of patients found the 3D custom model “very useful”, with more than half of the answers (69%) placed in top of the graduated scale (9.67; SD:0.53).

Similarly, 73.8% of patients considered that the use of the 3D personalized model had helped them “a huge lot” to understand their disease (9.74; SD: 0.45) when they answered question Q2.

In relation with question Q3, 100% of patients expressed their will to take the model home with them.

Results of question Q4 show that the vast majority of (95.2%) consider that the use of the personalized 3D model improves the clinical service rendered, being remarkable that only 4.8% believe that it does not make it better nor worse, and none of them consider that it makes it worse.

Finally, the results of question Q5 suggest that patients have considered that the use of personalized 3D models has improved the clinical service rendered in a high degree (8.62; SD:0.58).

To estimate the cost of realization of the 3D model, we considered the following: cost of data acquisition (0 €, included in consultation costs), proportional part of the cost of buying of the printer (120 € divided by 2000 h of life, 0.06 € per hour), labor of the laboratory technician (6 min at 5.66 €/hour, 0.57 €), software (0 €, as it was all open source) and material (30 g. of PLA at 18 €/kg, 0.47 €). The final estimated cost for each piece was around 1.10 €.

4. Discussion

In medical consultation, it has been demonstrated that a combination of both physical models and conventional 2D techniques of bone structures, gives patients a better comprehension of their disease [44]. Furthermore, in terms of teaching human anatomy, it has been proved that physical 3D models are more efficient to determine the existence of the disease than corpse models [45,46].

Physical 3D modeling has the capability of creating exact models of the human anatomy, thus being a fundamental tool not only for research [47], but also to educate patients [3].

However, using AM for biomedical applications has also its limitations: small anatomical features and structural details are difficult to replicate, and the number of biocompatible materials and resins available is limited, making AM expensive sometimes [48].

In the field of ophthalmology, AM applications are, conceptually speaking, not very different from the ones used in other fields of medicine. In scientific literature, there have been described works related with the printing of the first artificial cornea [49], fetal face modeling [50], intraocular lenses [51–54] or rigid permeable gas contact lenses [55], ocular prosthesis [56–59], intraocular tumor visualization [60], medical staff education [61,62], tissue bio-printing [63–65], printing of surgical instruments [66] or medical devices [67] or goggles for patients with deformations of unusual facial features [68]. However, we have not found proof of the use of the AM as a tool for improving doctor–patient communication strategies in KC disease.

In this research work, we describe our experience using AM techniques in ophthalmological clinical practice to obtain a custom-made individualized printed model, by means of a low-cost material, such as PLA. The objective is that patients acquire, basing on the physical model built, knowledge of the real dimension of the asymmetrical morphological changes that their cornea suffers when the disease progresses, and that affect their optical capacity, and therefore their quality of life.

For the building of the physical model, it is necessary to start from a virtual 3D model. However, in all different collaborative platforms of medical research related with virtual models [30,31,69], we have not found any virtual models of healthy or keratoconus-diagnosed corneas. Thus, virtual models have been generated from the data provided by the Sirius (CSO, Italy) tomographer, by using the open-source software CloudCompare, although these data can be obtained from any tomographer based in Scheimpflug technology [5]. In our study, two virtual models have been generated for each patient, one of a complete cornea, and another of a cornea with a sagittal cut defined from the minimum thickness points. These virtual models can be a fundamental tool in translational research, if shared through the collaborative open-access platforms [69].

From these patient-specific virtual models, and using open-source software, as well as low-cost and freely available manufacture hardware, the physical models used in this study were produced.

For this work, different printing speeds, layer thicknesses and nozzle sizes were tested, and it could be observed that a higher speed generally implied higher layer thicknesses, and therefore, a worse surface finishing in the model, which is in accordance with other authors works [70]. Finally, we opted for the speed, thickness and nozzle size indicated in Table 1 to get an acceptable surface finishing, with printing times below 30 min, that is the mean time that patients wait after the clinical tests to enter the doctor's consultation to be informed of the diagnosis. With these parameters, the printing is a bit cheaper than usual in other cases [71], and gives printed cornea a "stepped" aspect, although with enough precision to show, in an evident way, the differences between a normal cornea and one with its thickness locally diminished.

The fabrication cost of the 3D printed model, due to its simplicity and low cost of PLA, was of only 1.10 € each, which remains wide below the 490 € that can cost a model of more complex organs, such as kidneys, made in photopolymer materials [72].

Regarding the questionnaire answers, results of Q1 confirm the results obtained in other similar studies [73]. Similarly, answers to question Q2 are in line with what have been observed in other previous investigations, which used 3D models to explain patients their condition or the surgery that they will undergo [72]. Furthermore, the results obtained are in line with the ones obtained by Prece et al. [7], who demonstrated that the use of the touch and sight senses, with regard to a physical 3D model, improve the learning curve of the patients in relation with their disease.

In relation with question Q3, results contrast with the results obtained in other studies, in which 39% of the patients expressed that they would not be interested in buying the model [71], and can be explained by the fact that the low fabrication cost of the model allows the clinic to offer this service without any additional charge to the patient, integrating its cost in the cost of the medical consultation itself, making the patient more willing to take it home.

Results of question Q4 are in line with the ones presented by other authors, in which they demonstrated the usefulness of the 3D printing to improve the education in clinical practice [18], more precisely, in this study 95.8% of the surveyed considered useful the 3D models.

Finally, the results of question Q5 are in line with the values obtained for other studies (9.4/10) when patients have been asked about the degree of satisfaction with the medical services after the use of 3D models for their education [72].

Our study has, however, some limitations. First, the cross-sectional nature of the study presents a limited extension of the patient's cohort due to the low prevalence of this corneal degeneration; and second, the use of patients of just one hospital for the study. A longitudinal study with a larger sample size and including patients from different hospitals would be needed to further investigate the clinical

utility and viability, in clinical practice, of a patient-specific 3D model that helped to improve the strategies in doctor–patient assistance.

5. Conclusions

In this paper, the authors evaluated the possible benefits of using custom made 3D printed models of the cornea as a tool for increasing patient’s knowledge and understanding of their asymmetric condition, with the aim of improving the level of quality perceived for the services rendered in medical consultations.

The results show that owning a custom 3D printed model of their cornea was considered interesting for the totality of the patients that participated in the study, and that the comparison of their pathologic cornea with the 3D model of a healthy one, helped them “a lot” (9.71/10, SD:0.45) to understand their disease, considering the vast majority (>95%) of the participants that using the 3D printed realistic models increased the quality of services rendered in the clinic.

In addition, the use of open-source and free software, as well as a RepRap 3D printer, whose drawings are available for everyone, make the approach described in this work accessible not only to high-end clinics, but to any clinic, whatever its budget is.

In conclusion, 3D printing has allowed the creation of precise physical models that reflects asymmetric modifications due to keratoconus pathology. The visual and tactile perception of these models allow patients to better understand and manage the perspective of treatment of their disease, making the clinicians job more efficient and therefore increasing the perception of quality of the service they render.

Although the use of 3D printing is increasing currently, the true potential of this technology will be achieved when function and form become fully integrated, as for example happens in the bio printing of tissues or organs, such as the cornea, that even if it has not been fully reached yet, the first steps have started to be successfully taken [49].

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Article

A Machine-Learning Model Based on Morphogeometric Parameters for RETICS Disease Classification and GUI Development

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Featured Application: This work presents a Graphics User Interface that applies two automated learning models based on machine-procured independent variables to assist ophthalmology professionals in keratoconus disease diagnosis and classification.

Abstract: This work pursues two objectives: defining a new concept of risk probability associated with suffering early-stage keratoconus, classifying disease severity according to the RETICS (Thematic Network for Co-Operative Research in Health) scale. It recruited 169 individuals, 62 healthy and 107 keratoconus diseased, grouped according to the RETICS classification: 44 grade I; 18 grade II; 15 grade III; 15 grade IV; 15 grade V. Different demographic, optical, pachymetric and eometrical parameters were measured. The collected data were used for training two machine-learning models: a multivariate logistic regression model for early keratoconus detection and an ordinal logistic regression model for RETICS grade assessments. The early keratoconus detection model showed very good sensitivity, specificity and area under ROC curve, with around 95% for training and 85% for validation. The variables that made the most significant contributions were gender, coma-like, central thickness, high-order aberrations and temporal thickness. The RETICS grade assessment also showed high-performance figures, albeit lower, with a global accuracy of 0.698 and a 95% confidence interval of 0.623–0.766. The most significant variables were CDVA, central thickness and temporal thickness. The developed web application allows the fast, objective and quantitative assessment of keratoconus in early diagnosis and RETICS grading terms.

Keywords: Scheimpflug; 3D cornea model; early keratoconus; Corrected Distance Visual Acuity (CDVA)

1. Introduction

Corneal tomography is a validated technology for evaluating the changes occurring in the corneal morphology of keratoconus (KC) disease [1], which allows for the control of the geometric decompensation driven by the asymmetry present while this disease progresses [2,3]. However, no agreement has been reached about the relative importance of the indices and technologies to be used to detect which patients may suffer post-surgical corneal iatrogenic ectasia when evaluating patients' suitability for refractive surgery [4–10].

Some studies have evaluated the objective efficiency of different indices for early stages of this disease in an individualized way. These studies are generally related to values of curvature, elevation and pachymetry [11], and to patterns based on the combination of indices that come from the same [12–16] or different technologies [7,9,17–20]. The evaluation of these patterns is based on subjective analysis [7,21], which is critical to gain a better discrimination capability according to clinical experience. Nevertheless, there are still significant discrepancies in terms of the relative value of the results obtained in their evaluation of the risk probability associated with disease development.

In KC, geometric decompensation occurs and causes disease progression [11], which means increased high-order optical aberrations and high irregular astigmatism values [22], whose main refractive sign is the impossible complete optical compensation of their ametropia by spherical-cylindrical lenses. Consequently, corrected visual acuity will diminish compared to individuals with no corneal pathology [23]. The scientific literature contains many classifications for the degree of KC severity [24–31]. However in clinical practice, it is difficult to handle the many indices on which these classifications are based for proper optical-geometrical evaluations of disease progression. From an optical point of view, patients show a deteriorated spectacle-corrected visual acuity during disease development, insofar as their visual performance worsens as the degree of KC severity progresses. Following this criterion, a classification of disease stages has been developed [23,32]: the so-called RETICS grading. This grading takes into account four geometrical parameters (Internal Astigmatism, RMS Coma-Like, Q_{8mm} and Pachymetry) and a functional one (Corrected Distance Visual Acuity (CDVA)) to establish five KC degrees: I to V.

This study develops and validates a Graphics User Interface (GUI) that combines two automatic learning models based on a set of independent variables with two aims: defining a new concept of risk probability associated with the development of early-stage KC and classifying disease severity according to the RETICS (Thematic Network for Co-Operative Research in Health) scale to assist ophthalmology professionals in disease management.

2. Materials and Methods

2.1. Patients

This research work was conceived as an observational comparative study. It comprised 169 eyes of 169 subjects divided into two groups. To avoid potential biases, those cases showing any other ocular comorbidity that could affect the present study parameters, who had undergone any ocular surgical procedure, or had worn contact lenses in the 4 weeks prior to the topographical evaluation, were excluded from both groups.

The first group, called the “control” group, comprised 62 healthy eyes of 62 patients (48.4% males, 51.6% females) whose ages ranged from seven to 60. The cases included in the control group were randomly selected from the refractive surgery candidates, and the data used for this study were acquired during their pre-surgical appointments, always with the same experienced technician.

The second group was formed by 107 KC candidates (63.2% males, 36.8% females) aged from 15 to 98. They were classified into five subgroups in accordance with the RETICS grading system [32].

The procedure followed for KC group diagnosis and classification was based on state-of-the-art clinical and topographical evaluations (Figure 1), including uncorrected distance visual acuity (UDVA), CDVA, manifest refraction (sphere and cylinder), slit-lamp biomicroscopy, Goldmann tonometry, fundus evaluation and ultrasonic pachymetry [33]. In all cases, pre-surgical evidence for KC was assessed: asymmetric bowtie pattern with or without skewed axes, localized stromal thickness reduction, conical protuberance at the apex, Fleischer ring, Vogt striae or anterior stromal scar.

Figure 1. Methodology proposed for Keratoconus Score Calculator generation.

All the evaluations were made at Vissum Corporation Alicante (a centre affiliated with the Miguel Hernández University of Elche, Elche, Spain), and now form part of the official “Iberia” database of KC cases created for the National Network for Clinical Research in Ophthalmology RETICS-OFTARED.

Patients were adequately informed about the study and agreed to freely participate in it. The study was also ratified by the hospital's Ethical Committee for Clinical Research according to the ethical guidelines in the Declaration of Helsinki (7th revision, October 2013, Fortaleza, Brazil).

2.2. Methods

Each case selected to form part of this research was examined using a Sirius System[®] tomographer (Costruzione Strumenti Oftalmici, Florence, Italy), following the specifications of a validated procedure previously created by our research group, which is clearly explained in former research works [2,34]. This procedure is effective when used for both the diagnosis and characterization of KC [35,36], and comprises two phases: 3D virtual modeling, followed by a morpho-geometric analysis.

The product of this procedure is a patient-specific 3D custom corneal model, which can be studied to determine several morpho-geometric parameters that have already been described and used in a previous study [37]. Of them all, anterior corneal surface area (anterior surface area), posterior corneal surface area (posterior surface area) and total corneal volume (total volume) were selected to be used, along with demographic, pachymetry and clinical parameters (Figure 1).

2.3. Statistical Analysis

The quantitative variables were summarized using mean $\pm$ standard deviation (SD), median and interquartile range (25th and 75th percentiles). The Shapiro–Wilk test was employed to assess if the quantitative variables followed normal distribution. The Student's *t*-test was run to compare the normally distributed variables between two groups, while an ANOVA was used when there were three groups or more. For the non-normally distributed variables, the Mann–Whitney test and the Kruskal–Wallis test were, respectively, carried out. Differences in the qualitative variables among independent groups were compared by the χ^2 test. The predictive score model for early KC detection was defined using multivariate logistic regression with the control and RETICS grade I groups. Seventeen variables were included in the model: two demographic (age and gender), seven optical (CDVA, coma-like, Q_{8mm} , spherical-like, RMS total, high-order, astigmatism), five pachymetry (central thickness, temporal, nasal, superior, inferior) and three morpho-geometric (total volume, anterior surface area, posterior surface area). Model discriminative efficiency was evaluated by receiver operating characteristic (ROC) curves, when area under curve (AUC), sensitivity and specificity were taken as performance indicators. An internal cross-validation procedure was followed using bootstrap aggregating (bagging) [38]. This procedure works as follows: it first generates a new dataset of equal size by sampling with replacement from the original dataset. The model is then trained with these data. Finally, this model is used to make predictions on those cases not used during training. This procedure is repeated 100 times to obtain a set of quality parameters that can be averaged, and confidence intervals that can be calculated. On average, 63.2% of the original data were used in all these 100 training steps. The remaining 36.8% were used for validation. Ordinal multivariate logistic regression was utilized to determine the RETICS grade with the same predictor variables. In this case, the confusion matrix was employed to estimate model performance by means of sensitivity, specificity and balanced accuracy per group. Data were evaluated by R Statistics v3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) [39].

Packages “tidyr”, “dplyr”, “dlookr” and “smbinning” were used for data loading, exploration and transformation. Packages “corrplot”, “yarr” and “FactoMiner” were employed for data visualization. Packages “pROC”, “ROCR” and “Epi” were utilized for the ROC curve analysis and representation. Logistic regression models were trained with the “glm” function from the base package. Ordered logistic regression models were trained with the “polr” function from the MASS package. Confusion matrices were analyzed by the “caret” package. Optimal sample size calculations were made by the “rcompanion” and “pmsampsize” packages.

The statistical power analysis was conducted with simulation using the Wald test to estimate the power for each covariate according to sample size, as described in the literature [40,41].

A web application was developed using Shiny v1.3.2 (RStudio Inc., Boston, MA, USA) [42] and the ShinyAuthr v0.0.99 authentication module (Paul Campbell, Paris, France) [43]. This application was deployed in a private secure institutional network (because patients' clinical data were used, and the application was, therefore, accessible only from controlled computers to minimize the security risks linked to using patients' data).

Application landing page, shown in Figure 2, is a login form that adds a secured authentication layer. No registering possibility was included, and new users can only be directly added by the administrator. After logging in, users view a form with text boxes corresponding to all the model predictors that are filled by default with sample values from a healthy individual. Users can type in new values and, after pressing the "get score" button values, they are passed to trained models and predictions are made (Figures 3–8), including the early detection KC score (known as "keratoscore"), the RETICS grade prediction and a brief graphical description of the hypothetical cornea, with a schema indicating the representation of the different parameters.

Figure 2. Application landing page showing the login form with a secured authentication layer.

Figure 3. Screenshot of healthy individuals (Ctrl) with the typical 3D virtual corneal model schematic representation.

Figure 4. Screenshot of keratoconus grade I individuals (RETICS) with the typical 3D virtual corneal model schematic representation.

Figure 5. Screenshot of keratoconus grade II individuals (RETICS) with the typical 3D virtual corneal model schematic representation.

Figure 6. Screenshot of keratoconus grade III individuals (RETICS) with the typical 3D virtual corneal model schematic representation.

Figure 7. Screenshot of keratoconus grade IV individuals (RETICS) with the typical 3D virtual corneal model schematic representation.

Figure 8. Screenshot of keratoconus grade V-Plus individuals (RETICS) with the typical 3D virtual corneal model schematic representation.

In summary, the GUI application was developed using a responsive design, which makes it accessible from any network-connected device because it does not require any software or driver being installed, apart from an up-to-date web browser.

3. Results

Sixty-two healthy eyes (36.7%) (control group, Ctrl) and 107 KC eyes (63.3%) (KC group, KC) were herein considered. Several subgroups were established in the KC group depending on the disease stage according to the RETICS grading system: grade I (44 eyes, 41.1%), grade II (18 eyes, 16.9%), grade III (15 eyes, 14.0%), grade IV (15 eyes, 14.0%) and grade Plus-V (15 eyes, 14.0%). The main demographic information in the control and KC subgroups are displayed and summarized in Table 1. No significant differences were found in age and gender terms among all the groups.

Table 1. Demographic information for healthy individuals (Ctrl) and the RETICS-classified keratoconus patients, graded between I and V.

	Ctrl	I	II	III	IV	V	p
Number of cases	62	44	18	15	15	15	
Age in years (mean $\pm$ SD)	37.5 $\pm$ 14.4	41.2 $\pm$ 16.6	47.4 $\pm$ 22.5	40.3 $\pm$ 12.6	34.0 $\pm$ 14.3	36.3 $\pm$ 18.0	0.161
Female/Male	32/30	12/32	6/12	7/8	6/9	4/11	0.146

Table 2 summarizes the descriptive analysis outcomes obtained for all the quantitative variable analyses in the control vs. RETICS I and the control vs. KC groups. The descriptive analysis indicated that most variables did not follow normal distribution. Statistically significant *p*-values were found for all the variables between the control group (Ctrl) and the RETICS grade I group, except for age (*p* = 0.665). When testing for differences within all the groups (Ctrl and RETICS grade I to V), every *p*-value was significant, except for age (*p* = 0.344).

Table 2. Descriptive analysis for the quantitative variables and *p*-values for normality and differences between RETICS groups. CDVA: Corrected Distance Visual Acuity; Q: asphericity; RMS, root mean square

Variables	Mean	SD	Median	Range	Normality	Ctrl vs. RETICS I	Ctrl-RETICS I-II-III-IV-V
Demographic							
Age	39	16	38	7–98	<0.001	0.665	0.344
Optical							
CDVA	0.77	0.32	0.96	0.05–1.20	<0.001	<0.001	<0.001
Coma-like	1.85	2.15	1.01	0.08–13.0	<0.001	<0.001	<0.001
Q8mm	−0.63	0.70	−0.45	−2.80–2.82	<0.001	0.025	<0.001
Spherical-like	0.70	0.93	0.44	0.15–7.20	<0.001	<0.001	<0.001
RMS total	3.22	3.09	2.38	0.33–15.6	<0.001	<0.001	<0.001
High-order	2.02	2.33	1.12	0.24–13.8	<0.001	<0.001	<0.001
Astigmatism	2.31	2.25	1.57	0.04–11.22	<0.001	<0.001	<0.001
Pachymetry							
Central thickness	499	62	508	285–633	<0.001	<0.001	<0.001
Temporal	545	50	546	385–645	0.073	<0.001	<0.001
Nasal	579	48	579	451–692	0.835	<0.001	<0.001
Superior	591	50	590	408–695	0.062	<0.001	<0.001
Inferior	559	57	563	332–762	<0.001	<0.001	<0.001

Table 2. Cont.

Variables	Mean	SD	Median	Range	Normality	Ctrl vs. RETICS I	Ctrl-RETICS I-II-III-IV-V
Morpho-Geometric							
Total volume	24.7	1.9	24.4	19.8–29.1	0.335	<0.001	<0.001
Anterior surface area	43.35	0.59	43.24	42.49–47.44	<0.001	<0.001	<0.001
Posterior surface area	44.70	0.93	44.53	43.53–51.14	<0.001	<0.001	<0.001

The multivariate logistic regression model results are summarized in Table 3 with the coefficients for each variable. The variables that made a statistically significant contribution in the model are shown below: gender, coma-like, central thickness, high-order and temporal.

Table 3. Summary of the multivariate logistic regression model for the Ctrl vs. RETICS I patients. CDVA: Corrected Distance Visual Acuity; Q: asphericity; RMS, root mean square

		Std.	Z	p		95% CI	
Variables	Coefficient	Error	Value	Value	OR	Lower	Upper
Demographic							
Age	0.135	0.078	1.727	0.084	1.145	1.021	1.416
Gender	5.267	2.520	2.090	0.037	193.907	4.154	2.14 × 10 ⁵
Clinical							
CDVA	−6.345	4.613	−1.376	0.169	0.002	0.001	1.821
Coma-like	4.072	1.917	2.124	0.034	58.687	3.615	1.16 × 10 ⁴
Q8mm	6.027	4.618	1.305	0.192	414.459	0.070	3.02 × 10 ⁷
Spherical-like	1.673	1.259	1.329	0.119	5.329	0.671	1.08 × 10 ²
RMS total	2.482	1.591	1.560	0.119	11.969	1.071	8.65 × 10 ²
High-order	5.534	2.484	2.227	0.026	253.143	5.830	3.12 × 10 ⁵
Astigmatism	−1.054	1.218	−0.866	0.387	0.348	0.014	2.963
Pachymetry							
Central thickness	−0.242	0.116	−2.083	0.037	0.785	0.577	0.941
Temporal	0.028	0.012	2.248	0.025	1.028	1.009	1.064
Nasal	0.007	0.011	0.641	0.522	1.007	0.987	1.034
Superior	0.092	0.058	1.587	0.113	1.096	0.995	1.263
Inferior	−0.051	0.034	−1.479	0.139	0.951	0.870	0.995
Morpho-Geometric							
Total volume	0.067	0.547	0.124	0.901	1.070	0.349	3.908
Anterior surface area	−0.326	0.532	−0.614	0.539	0.722	0.218	2.105
Posterior surface area	−1.189	0.779	−1.525	0.127	0.305	0.044	1.199
Constant	135.027	61.595	2.192	0.028	-	-	-

The ROC curve in Figure 9 shows an optimal cut-off point of 0.475 with a training AUC of 0.990, a sensitivity of 0.977 and a specificity of 0.919, corresponding to 59 true negative cases, 41 true positive cases, three false-positive cases and three false-negative cases. The bootstrapped validation values corresponding to the 95% CI are 0.843 ± 0.058 for AUC, 0.844 ± 0.095 for sensitivity and 0.838 ± 0.081 for specificity.

Figure 9. Logistic regression model ROC curve indicating the optimal cut-off point and the bootstrapped validation parameters.

Figure 10 shows the distribution of the calculated scores in both groups, where the vast majority of the control cases obtained a score between 0 and 0.1, and between 0.9 and 1 for RETICS I.

Figure 10. Distribution of the logistic regression scores between the Control and RETICS I patients, and the optimal cut-off.

The parameters for the multivariate ordinal logistic regression model are summarized in Table 4. In this case, the variables that made a statistically significant contribution to the model were: CDVA, central thickness and temporal.

The confusion matrix for the training dataset is shown in Table 5, with an overall accuracy of 0.698 at a 95% CI between 0.623 and 0.766. Sensitivity, specificity and balanced accuracy are also shown for each group.

Figure 11 depicts power according to the simulated sample size for both models, including only the variables with maximum power over 0.9 at some point within the range, plus Age and Gender. The remaining variables and their respective maxima for both the binary logistic regression and ordinal logistic regression models were Coma-Like Deviation (0.61 and 0.62), Q_{8mm} (0.55 and 0.57), Spherical-Like Deviation (0.49 and 0.55), Nasal Thickness (0.81 and 0.83), Superior Thickness (0.88 and 0.89), Inferior Thickness (0.72 and 0.77), Volume (0.69 and 0.71), Anterior Surface (0.83 and 0.89) and Posterior Surface (0.58 and 0.60). For both models, the variables of High-Order Aberration, CDVA, Central Thickness, Total RMS and Temporal Thickness have power values over 0.80 for the sample

sizes exceeding 150, and the powers for the ordinal logistic model at small sample sizes (below 100) are somewhat lower than for the binary logistic regression models.

Table 4. Summary of the ordinal logistic regression model for the Ctrl and RETICS grade I-V patients. CDVA: Corrected Distance Visual Acuity; Q: asphericity; RMS, root mean square

		Std.	<i>t</i>	<i>p</i>		95% CI	
Variables	Coefficient	Error	Value	Value	OR	Lower	Upper
Demographic							
Age	0.016	0.011	1.475	0.140	1.016	0.995	1.037
Gender	−0.073	0.361	−0.203	0.839	0.929	0.458	1.885
Clinical							
CDVA	−5.495	0.865	−6.355	0.001	0.004	0.001	0.022
Coma-like	0.106	0.348	0.304	0.761	1.111	0.562	2.197
Q8mm	0.184	0.359	0.512	0.609	1.201	0.595	2.423
Spherical-like	−0.063	0.250	−0.250	0.803	0.940	0.575	1.535
RMS total	−0.422	0.298	1.416	0.157	1.526	0.850	2.737
High-order	0.621	0.345	1.797	0.072	1.860	0.945	3.660
Astigmatism	−0.250	0.239	−1.046	0.296	0.779	0.488	1.244
Pachymetry							
Central thickness	−0.024	0.007	−3.298	0.001	0.977	0.963	0.991
Temporal	0.006	0.002	2.662	0.008	1.006	1.002	1.010
Nasal	−0.002	0.003	−0.771	0.441	0.998	0.992	1.004
Superior	0.006	0.007	0.933	0.351	1.006	0.993	1.019
Inferior	−0.002	0.005	−0.522	0.601	0.998	0.989	1.007
Morpho-Geometric							
Volume	0.071	0.141	0.500	0.617	1.073	0.814	1.414
Anterior area	−0.204	0.133	−1.533	0.125	0.816	0.623	1.058
Posterior area	0.046	0.129	0.361	0.718	1.048	0.814	1.348
Intercepts							
Ctrl vs. RETICS I	−16.769	0.017	−98.428	<0.001	-	-	-
RETICS I vs. II	−13.926	0.396	−35.205	<0.001	-	-	-
RETICS II vs. III	−12.270	0.522	−23.530	<0.001	-	-	-
RETICS III vs. IV	−9.998	0.765	−13.072	<0.001	-	-	-
RETICS IV vs. V	−6.691	1.057	−6.330	<0.001	-	-	-

Table 5. The ordinal logistic regression confusion matrix showing sensitivity, specificity and balanced accuracy for each group. The total sum of cells by rows shows the total number of true cases present, while each column represents how many cases the model classified in that category.

True Value	Predicted Value					
	Ctrl	I	II	III	IV	V
Ctrl	55	7	0	0	0	0
I	12	26	4	2	0	0
II	2	9	6	3	1	0
III	0	3	3	6	3	0
IV	0	1	0	1	12	1
V	0	0	0	1	1	13
Sensitivity	0.887	0.591	0.333	0.400	0.800	0.867
Specificity	0.869	0.840	0.954	0.955	0.968	0.994
Balanced accuracy	0.878	0.715	0.643	0.677	0.884	0.930

Figure 11. Power analysis results for (a) the binary logistic regression model; (b) the ordinal logistic regression model.

Graphics User Interface

Figure 3 is a screenshot corresponding to one healthy individual (Ctrl). It includes a 3D image of a characteristic cornea showing a schematic representation of how different predictors are calculated based on physical measurements.

Figures 4–8 are five screenshots corresponding to five representatives of the five RETICS grades I–V. The score rapidly rises when passing from Ctrl to grade I and remains at 100% for the other grades, which is consistent with the high sensitivity and specificity in the model. Each prediction includes a 3D image of a characteristic cornea from the corresponding RETICS group, along with a schematic representation of how different predictors are calculated based on physical measurements.

The four examples in Figure 12 indicate the difficulty of detecting early-stage KC. Indeed, some cases are wrongly classified. We must bear in mind that this early KC detection model was trained using diagnostics made by ophthalmological professionals as a “gold standard”, and some inevitable undetermined amount of subjective information was taken for granted. During the fitting process, the model attempted to find some generalization to bind predictors and prediction with the best possible performance, but some samples might not match any kind of generalization given by training data’s subjective nature. Therefore, it is reasonable to expect some lack of accuracy, which does not necessarily mean failure in the model’s fitting capability. Our model quantitatively confirmed the difficulty of discerning both control and grade I groups as 17 of 106 cases (16%) and obtained a score between 0.1 and 0.9 which is, therefore, in the aforementioned “halfway” situation, and thus confirmed this tool’s utility.

Figure 12. Screenshots showing: (a) a correctly classified healthy individual (true negative); (b) an incorrectly classified healthy individual (false-positive); (c) a correctly classified grade I KC individual (true positive); (d) an incorrectly classified grade I KC individual (false-negative).

4. Discussion

The range of techniques that allow the characterization and evaluation of the degree of KC severity vary, but the ultimate trends use machine-learning [44] and neural networks [45].

This study defines two automated learning models based on a set of independent variables (demographic, optical, pachymetric, morpho-geometric) to characterize the optical-geometrical cornea structure in different KC phases. More specifically, it considered a probability model of the risk associated with suffering early-stage KC, as well as another model to classify the degree of KC severity depending on patients' visual limitation levels.

This approach offers some very useful advantages. First, it summarizes information that derives from many parameters of different natures (qualitative or quantitative, measured in distinct units) in a single number that can be easily read and understood, which minimizes the risk of some key pieces of information going unnoticed. Otherwise, this risk is fairly high, as common analytical reports usually contain many printed pages of different parameters, which often include no associated normality range and must be read in a matter of seconds. Second, it evaluates the combined action of these different parameters, which could imply a high value in a particular key parameter, clearly indicative of disease being present, but might be less evident when the increase in many different key parameters is slight. In this situation, a score can assist health professionals in their decision-making process as it provides an objective and quantitative scale that takes into account the joint action of a set of diverse parameters [3].

A multivariate logistic regression model was fitted using healthy (Ctrl) and RETICS grade I individuals, which always made predictions ranging between 0 and 1 when applied to new data. This prediction came closer to 0 when input data were similar to those that characterized healthy controls, and close to 1 if they were similar to grade I KC patients. All those individuals with an intermediate

score were considered to be more or less halfway between both groups, i.e., they showed some kind of abnormality vs. healthy controls, which indicates KC-developing patients, but had not yet reached the cut-off point to be diagnosed as diseased. Therefore, this multivariate logistic regression output could be considered to be proportionally associated with the probability of suffering KC. A higher model output indicated a stronger probability. Even though this relationship is not linear, such scores are frequently used as predicting tools to assess patient status and prognosis in different fields [3,46–48].

For initial KC development, the analyzed model-based studies generally showed a good discrimination between normal and early KC eyes. However, one of the main challenges faced by ophthalmologists today is that no consensus has been reached by experts about the characterization patterns of early corneal ectasia [7,49]. This is mainly the result of the diversity of designations used to refer to subtler KC manifestations. It is also due to the fact that the wide variety of indices used for detection are technology-specific, which does not make them easily interchangeable [19,49]. As it is difficult to directly compare these studies, we resorted to using authors' own writings to compare them to our work.

Several studies have reported similar results to ours about models based on Scheimpflug metrics [5–7,20]. Hwang et al. [7] proposed a first model based on the combination of five metrics (AUC: 0.86, Sensitivity: 83%, Specificity: 83%). Similar results have been obtained by other authors [5,6,20] in the model development phase and based on the exclusive metrics of the same Scheimpflug technology. In contrast, our study obtained higher performance values for model development (AUC: 0.95) and similar ones in the validation phase (AUC: 0.85), and was composed of metrics that are not exclusive to the same Scheimpflug technology.

Smadja et al. [50] used a machine-learning algorithm based on decision trees to analyze 55 parameters deriving from anterior and posterior corneal measurements. They found that the most discriminant variables related to posterior surface asymmetry and thickness spatial distribution achieved 93.6% sensitivity and 97.2% specificity when discriminating between normal and forme fruste KC. However, some authors [51] considered that including eyes from patients who had already been diagnosed with KC in one eye was inappropriate because it biases the sample if we contemplate that the genetic determinants for KC appearing are already present in them.

In our study, the performance measurements of the early detection model in AUC, specificity and sensitivity terms indicated very high performance with the training dataset, with all three values reaching around 0.95, and very few false positives and false negatives. These figures are significantly lower for the validation procedure, which dropped to about 0.85, but were well over 80% in all cases. These findings indicate good model-validated performance, but also suggest the presence of some overfitting. This is otherwise reasonable if we take into account the relatively few training cases (62 healthy individuals and 44 RETICS grade I patients), which were significantly lower than the training values.

Other authors have proposed using a multivariate system based on combining two different technologies. Saad et al. [9] combined two technologies to propose a model based on 54 variables and six discriminant functions, and reported 93% sensitivity and 92% specificity in the model development phase. It was validated in a later study with 92% sensitivity and 96% specificity [52]. Other studies have suggested combining several different technologies [53–55], but the authors defined a more advanced form of KC when they included patients with manifest inferior steepening [49,56].

The only reference found in the scientific literature with a classification system that uses visual acuity as a parameter is that by Wisse et al. [3], who established a scoring system that relied on five parameters (age, quality of vision, uncorrected distance visual acuity, refraction difference, maximum keratometry difference). However, this score did not classify disease grades, but disease progression. Consequently, its aim was to determine if crosslinking treatment would be necessary or not.

Our work presents and validates a probability model of the risk associated with suffering KC. Our research group is unaware of any previous study that combined demographic, optical, pachymetric and morpho-geometric variables successfully and in real-time to detect early KC.

Finally regarding the clinical KC development phase, experts' criteria have converged to diagnose this disease as the degree of severity of progressing KC [24]. Although there are several classifications that characterize clinical KC, to the authors' knowledge, there is no disease severity classifier based on patients' visual limitation. Our classifier is based on an ordinary logistic regression model that combines 17 variables and presents an overall accuracy of 0.698; that is, our model correctly classifies almost 70% of patients. The performance indicators for ordinal logistic regression are fairly lower, particularly for the RETICS grade I, II and III patients, with balanced accuracies ranging between 0.623 and 0.766. Grade II patients present the worst accuracy, with nine in every 18 patients being wrongly classified as grade I. Once again, a small sample size is the most probable explanation for such behavior, along with its non-homogeneity (controls and grade I patients are much more abundant than grade II–V patients). It could also indicate that these three groups are not clearly differentiated. Therefore, all the conclusions drawn from the ordinal logistic regression model must be considered very carefully. Even when the results are reasonably good, the training process should be repeated with a bigger and more homogeneous sample. It would also be desirable to validate our results with other ethnicities and populations.

Another limitation of our study is the proven dependence that clinical metrics has on the technology employed to measure it [19], which means that our results are only valid for those eyes tested with a Sirius tomographer (CSO, Florence, Italy).

5. Conclusions

A web application was developed and deployed that combines two machine-learning models to support ophthalmologic professionals: a multivariate logistic regression model for early KC predictions and an ordinal logistic regression model to assign diagnosis grades on the RETICS scale. This application has a responsive design, and it allows any sort of device to be used (computer, tablet or smartphone). It also incorporates security measurements (authentication layer and accession from intranet only). The early KC prediction model shows high-performance indicators, even though some overfitting appears, while the RETICS grading prediction model's accuracy is remarkably lower, particularly for grade I, II and III patients. In both cases, repeating the training process with a bigger sample should be considered. This falls in line with recently published recommendations for sample size calculations by multivariate prediction models [57] which, for this case, proposes an optimal sample size of 374 individuals, with a minimum of 125. An optimal figure could not be reached, given our biobank's limited database size. Moreover, even though multivariate and ordinal logistic regressions are state-of-the-art and widely used techniques for modeling biomedical research data, many other powerful artificial intelligence techniques are available (particularly deep learning techniques), and their use is strongly advised for improving the quality of results.

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Comparison of Corneal Morphologic Parameters and High Order Aberrations in Keratoconus and Normal eyes

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Abstract. The aim of this study is evaluating the influence of corneal geometry in the optical system's aberrations, and its usefulness as diagnostic criterion for keratoconus. 159 normal eyes (normal group, mean age 37.8 ± 11.6 years) and 292 eyes with the diagnosis of keratoconus (keratoconus group, mean age 42.2 ± 17.6 years) were included in this study. All eyes received a comprehensive ophthalmologic examination. A virtual 3D model of each eye was made using CAD software and different anatomical parameters related with surface and volume were measured. Statistically significant differences were found for all anatomical parameters (all $p < 0.001$). AUROC analysis showed that all parameters reached values above 0.7, with the exception of the total corneal surface area (TCSAA-S). In conclusion, the methodology explained in this research, that bases in anatomical parameters obtained from a virtual corneal model, allow to analyze the diagnostic value of corneal geometry correlation with optical aberrations in keratoconus pathology.

Keywords: Ophthalmology, Corneal Apex, Computer-Aided Design (CAD), Computational Modelling, Scheimpflug Technology.

1 Introduction

The human eye is an optical instrument that projects images from outside into the retina [1]. However, the eye is characterized by a lack of symmetry in its surfaces, as these do not present revolution symmetry because of their de-alignment and de-centration. This causes a degradation in the quality of image by means of aberrations of the optical system [2,3]. This refractive anomaly can elicit the well-known astigmatism, myopia or hyperopia in patients.

In keratoconus (KCN) disease, that is an affection in which the cornea acquires a conical structure as a result of a progressive corneal thinning [4], corneal thickness reduction causes optical aberrations.

There are different indices for the detection of KCN basing on astigmatism [5], like the AST or the SRAX index. Both quantify irregular astigmatism, but these indices are characterized for using only data of the anterior surface of the cornea. Other authors [6,7] use wave-front based technologies to detect astigmatism, yet it has been demonstrated that aberrations are difficult to measure with these methods, as they do not cover the whole corneal surface. Consequently, it would be interesting to measure astigmatism from geometrical data obtained from the corneal topographies, as this data in fact register almost completely anterior and posterior corneal surfaces.

Our research group has validated a geometrical patient-specific virtual model for the diagnosis of KCN from a morpho-geometric point of view [8,9,2,10]. This patient-specific model has been used in other fields, such as the Finite Elements one [11-14], in which it has been used to analyze the biomechanical behavior of the cornea to refractive surgeries or the response to the intra-stromal ring segment implantation in corneas with keratoconus [11,13], and also to analyze the behavior of corneal tissue properties in different scenarios [14].

Also, there are many different approaches in which KCN classification can be based, usually relying in lens refraction, corneal thickness, keratometry data, corrected distance visual acuity (CDVA), internal astigmatism, root mean square, central keratometry, corneal asphericity at 8 mm, pachymetry and myopia, among others [5]. This study proposes using a classification based in high order aberrations (HOA), the one known as Alió-Shabayek [15].

Therefore, in this research work it is evaluated the influence of the corneal geometry in optical aberrations, and its usefulness as a criterion for the diagnosis of keratoconus.

2 Patients and Methods

2.1 Patients

A total number of 451 eyes of 451 individuals with ages ranging from 16 to 75 years were evaluated at Visum Hospital (Alicante). All the procedures adhered to the tenets of the Declaration of Helsinki (Fortaleza, 2013) and were approved by the Ethical Board of the hospital. All patients were informed and authorized their inclusion in the study by signing an informed consent. These data are included in the “Iberia” database of KCN eyes created for the National Network for Clinical Research in Ophthalmology RETICS-OFTARED.

A thorough and detailed ophthalmic exam was made to all the subjects [10] and they were divided into two different groups (normal and keratoconus) according to the Alió-Shabayek grading system [15].

The first group did not present any ocular pathology and consisted in 159 healthy eyes of 159 patients (89 men / 70 women, mean age 37.8 ± 11.6). Inclusion criterion was: any patient who did not present any ocular or corneal pathology. Exclusion criterion was: patient whose eyes had undergone any previous surgical procedure.

The second group corresponded to diseased eyes, and consisted in 292 eyes of 292 patients. (162 men / 130 women, mean age 42.2 ± 17.6). Inclusion criterion was:

presence of a localized corneal topography steepening and / or the presence of an asymmetric bow tie with or without topographical angulated principal meridians, and any microscopic keratoconic sign: Fleischer ring, Vogt striae, stromal thinning, protrusion apex or anterior corneal scars in the corneal stroma. Exclusion criterion was: any previous eye surgical procedure and any other eye pathology different from the keratoconus.

2.2 Methods

The procedure followed in our research work can be described by two main phases (see Fig. 1): a first phase of 3D corneal model generation and a second one of geometrical analysis of the 3D model.

First Phase. Systems based on the projection of a slit of light onto the cornea and on the principle of Scheimpflug photography [5] allow the exportation of data containing the geometrical readings of each specific patient. These data are known as “raw data” [8,9], and are used to create patient-specific models [8,9,2,13,14,10] in the fields of Finite Elements and Computer-Aided Design.

In our study, we have used Sirius tomographer (Costruzione Strumenti Oftalmici, Italy), a device based in principle of Scheimpflug photography, that allows the characterization of the optical aberrations present in the patient’s eye, as well as the exportation of geometrical data into a .CSV format file. [14]. These data are transformed into Cartesian coordinates, as we are working with a set of spatial points (see Fig. 1), so our team has programmed an algorithm using Matlab® V R2014 software (Mathworks, Natick, USA), in order to:

- Transform the set of spatial data given in polar coordinates in the .CSV file to a set of spatial data in Cartesian format in a .TXT file (see Figure 1, First Phase). We made this transformation because Rhinoceros® V 5.0 software (MCNeel & Associates, Seattle, USA) uses this set of spatial data in Cartesian format to generate the corneal surfaces.
- b) Validate those sets of spatial data that present invalid reading values of the corneal surface’s geometry (see Figure 2). Due to the existence of factors extrinsic to the patient while measures are being taken [5], like tear film stability, tabs that block the visual field or improper opening of the eyelids, data acquired by the Sirius device for determined points located in the peripheral zones can be not valid, getting in those cases a value of -1000 in the corresponding matrix cells. To avoid including these invalid cyphers, all the CSV files created for each cornea went through a filtering process, being selected for this research just those cases that held correct values in their first 21 rows (256 values per row; radii values ranging from 0 mm to 4 mm in reference to the normal corneal vertex), discarding from the research any cornea that included invalid -1000 values located within this range. This filtering procedure guaranteed that all data utilized for generating clouds of points was real, and interpolation was not used [8,9,16].

Fig. 1. Procedure followed for the 3D corneal model generation and later analysis. Data obtained from Sirius tomographer allow the generation of a personalized 3D model, in which several morphogeometric variables are studied.

Fig. 2. Description of the algorithm followed for the coordinate transformation

Once anterior and posterior surfaces of the cornea have been generated in Rhinoceros®, they are both exported into SolidWorks V2017 software (Dassault Systèmes, Vélizy-Villacoublay, France) to create a complete 3D model of the cornea.

Second Phase. Over the 3D model and within the graphical environment of the modelling software, a structural characterization of the corneal morphology was done through a geometrical analysis of the model, that was made with the measurement tools integrated in the program. These tools allow the definition of a set of variables

of superficial and volumetric nature that have already been used in previous works (see Table 1), although it is the first time that they are used to evaluate the influence of corneal geometry in optical aberrations.

Table 1. Set of geometrical parameters analyzed for the Alió-Shabayek classification. [10]

<i>Geometric variable</i>	<i>Description</i>
Total corneal volume (TCV _{A-S}) [mm ³]	Volume limited by front, back and peripheral surfaces of the solid model generated
Anterior corneal surface area (ACSA _{A-S}) [mm ²]	Area of the front/exterior surface
Posterior corneal surface area (PCSA _{A-S}) [mm ²]	Area of the rear/interior surface
Total corneal surface area (TCSA _{A-S}) [mm ²]	Sum of anterior, posterior and perimetral corneal surface areas of the solid model generated
Sagittal plane apex area (SPAP _{A-S}) [mm ²]	Area of the cornea within the sagittal plane passing through the optical axis and the highest point (apex) of the anterior corneal surface
Sagittal Plane Area in minimum thickness point (SPAMTP _{A-S}) [mm ²]	Area of the cornea within the sagittal plane passing through the optical axis and the minimum thickness point (maximum curvature) of the anterior corneal surface
Corneal volume R-x (CV _{A-S} R-x) [mm ³]	Corneal volume R-x defined by the anterior corneal apex at radii 0.5, 1.0 and 1.5 mm

2.3 Statistical Analysis

Just a single eye per patient was selected in a dichotomous sequence (0 and 1), made by a computer software, to elude any potential correlations between eyes of the same patient. Graphpad Prism v7.0 for MAC OS X (Graphpad Inc., La Jolla, USA) and SPSS 24.0 software (SPSS Inc., Chicago, USA) were the two software chosen for the analysis of the data. Data normality was tested by means of Kolmogorov-Smirnov test. Comparison between groups was performed by one-way analysis of variance (ANOVA) if variables were normally distributed, whereas Kruskal-Wallis non-parametric test was used for non-normally distributed ones. Bonferroni test was selected for post-hoc comparative analysis for the ANOVA when the variances were homogeneous and T2 Tamhane test was the option when variances did not show homogeneity. P-values < 0.05 were considered statistically significant for the differences. Lastly, receiver operating characteristic (ROC) curves were used to determine which parameters better characterized diseased corneas.

3 Results

This study comprised a total number of 451 eyes: 159 healthy eyes (35.25%) and 292 (64.75%) diagnosed as suffering from KCN according to the Alió-Shabayek grading scale, presenting High Order Aberrations (HOA) of third order.

With respect to the healthy eyes, 74 individuals were men (46.5%) and 85 were women (53.5%), being 82 right eyes (51.4%) and 76 left eyes (49.6%).

Clinical data that these individuals presented for optical aberrations were: Root Mean Square High Order Aberrations (RMS HOA) was 0.41 μm (range 0.23 to 0.73 μm); Spherical Aberration (SA) was 0.23 μm (range 0.07 to 0.43 μm); Root Mean Square Coma (RMS Coma) was 0.30 μm (range 0.03 to 0.69 μm); Root Mean Square Coma-like was 0.35 μm (range 0.09 to 0.72 μm) and Root Mean Square Spherical-like was 0.25 μm (range 0.10 to 0.50 μm).

Finally, regarding astigmatism, corneal asphericity was calculated at 4.5 mm and at 8 mm. In this respect, the one at 4.5 mm was -0.1 (range -0.62 to 0.87) and the one at 8 mm was -0.28 (range -0.70 to 0.17).

With respect to the eyes diagnosed as KCN, 125 subjects were men (42.8%) and 167 were women (57.2%), being 134 right eyes (45.8%) and 158 left eyes (55.2%).

Clinical data that these individuals presented for optical aberrations were: Root Mean Square High Order Aberrations (RMS HOA) was 2.6 μm (range 0.33 to 13.9 μm); Spherical Aberration (SA) was -0.19 μm (range -7.9 to 1.40 μm); Root Mean Square Coma (RMS Coma) was 2.1 μm (range 0.05 to 12.9 μm); Root Mean Square Coma-like was 2.34 μm (range 0.21 to 13.01 μm) and Root Mean Square Spherical-like was 0.89 μm (range 0.14 to 8.3 μm).

As with the healthy group, corneal asphericity was calculated at 4.5 mm and at 8 mm, being at 4.5 mm -0.6 (range -7.39 to 4.09) and at 8 mm -0.81 (range -3.0 to 2.85).

Analyzing descriptive values and their differences when comparing healthy and KCN eyes (see Table 2), all the geometrical variables ($p < 0.05$) showed good capability of discrimination between groups, without exceptions.

Table 2. Descriptive values and differences in the modelled geometric variables among the normal and keratoconus groups. SD: standard deviation. P: statistical test.

Measurement	Normal Group (n = 159)				Keratoconus Group (n = 292)				z	P
	Mean	SD	Min	Max	Mean	SD	Min	Max		
TCV _{A-S} (mm ³)	25.55	1.58	25.51	25.61	23.91	1.89	23.85	23.96	25.08	<0.001
ACSA _{A-S} (mm ²)	43.10	0.15	43.07	43.14	43.45	0.54	43.32	43.64	175.59	<0.001
PCSA _{A-S} (mm ²)	44.27	0.30	44.22	44.32	44.82	0.87	44.69	44.99	151.62	<0.001
TCSA _{A-S} (mm ²)	103.87	1.18	103.81	103.91	104.07	1.99	104.01	104.16	36.16	<0.001
SPAP _{A-S} (mm ²)	4.28	0.26	4.22	4.34	3.96	0.33	3.91	4.00	34.46	<0.001
SPAMTP _{A-S} (mm ²)	4.27	0.27	4.22	4.33	3.94	0.33	3.89	3.97	36.38	<0.001
CV _{A-S} R-0.5 (mm ³)	0.41	0.03	0.35	0.45	0.36	0.05	0.23	0.40	221.38	<0.001
CV _{A-S} R-1 (mm ³)	1.69	0.11	1.63	2.01	1.47	0.08	1.38	1.50	221.20	<0.001
CV _{A-S} R-1.5 (mm ³)	3.86	0.25	3.80	3.91	3.43	0.37	3.36	3.46	73.39	<0.001

In addition, an area under the receiver-operator curve (AUROC) analysis was made for the nine geometrical studied variables (Fig. 3), with good values of area under the curve (above 0.7), for all variables except total corneal surface, as shown in Table 3.

Table 3. The area under the ROC results.

<i>Measurement</i>	<i>Area</i>	<i>Sensitivity</i>	<i>Specificity</i>	<i>Standard error</i>	<i>95% Confidence Interval</i>	
					<i>Lower limit</i>	<i>Upper limit</i>
TCV _{A-S}	0.751	60.6	78.0	0.023	0.706	0.796
ACSA _{A-S}	0.782	62.3	83.6	0.021	0.741	0.824
PCSA _{A-S}	0.754	47.6	90.6	0.023	0.710	0.799
TCSA _{A-S}	0.501	17.5	93.7	0.021	0.447	0.545
SPAP _{A-S}	0.781	50.3	94.3	0.021	0.739	0.823
SPAMTP _{A-S} (mm ²)	0.781	48.3	95.0	0.021	0.739	0.823
CV _{A-S} R-0.5 (mm ³)	0.860	70.2	89.9	0.017	0.826	0.894
CV _{A-S} R-1 (mm ³)	0.853	72.3	85.5	0.017	0.819	0.887
CV _{A-S} R-1.5 (mm ³)	0.836	61.6	91.8	0.018	0.800	0.873

Fig. 3. Curves for modelled parameters detecting KC.

4 Discussion

Patients suffering from KCN present values in optical aberrations significantly higher than the ones of those with normal eyes [17]. This is caused by the deformation that the wave front suffers when it reaches the corneal surface, due to the de-centration of the point of maximum curvature in KCN. However, one of the aspects to which less attention has been paid is the potential diagnostic value of the optical aberrations correlated with corneal geometry in KCN pathology. This work develops a methodology that analyses the relationship between different anatomical parameters and optical aberrations.

For this study, a Sirius corneal tomographer (Construzione Strumenti Oftalmici, Italy) has been used. It is a device that provides consistent and repeatable measures for each patient [18]. In reference with the anatomical parameters studied in the virtual model, volume parameters and surface parameters should be considered separately.

Regarding the first ones, total corneal volume (TCV_{A-S}) presented significant differences between the studied groups, but they were not remarkable, not coinciding this result with the ones reported in other previous studies. [16,19,20]. This can be explained by the fact that the KCN group includes an important amount of eyes with advanced KCN. In addition, this result is in line with the existence of significant differences in measured corneal volumes at $R = 0.5$, $R=1$ and at $R = 1.5$, as the tendency of corneal structure is being more irregular or oblate (more curved) in central zone than in peripheral zone, in which it is more regular or prolate.

Regarding anatomical surface parameters, all variables presented statistically significant differences between groups, being these remarkable for anterior corneal surface area and posterior corneal surface area. This finding is in line with other studies that have used the same Sirius technology [21,20]. Piñero et al [20] proved that corneal curvature increases with disease progression, this is, the areas of both corneal surfaces grow as they become steeper. Also, Ishi et al [21] demonstrated that a correlation between surfaces existed for the more advanced degrees of the disease. An explanation of the finding in our study can be that posterior surface curves, in proportion, more than the anterior one, because of the relation of mechanical feebleness that corneal tissues present [12]. Other less significant superficial parameters were also studied, such as the sagittal areas obtained from the apex and from anterior the minimum thickness point of the cornea, although these variables were not significant for the study. This can be caused by the fact that the local change inducted by the intraocular pressure in corneal surface is not representative in these areas for the study of a wave front (aberrometry). This has been reported by our research team in previous studies [8-10].

Sensibility analysis of the measured variables revealed that some variables presented values of $AUROC > 0.7$, more precisely TCV_{A-S} AUC, $ACSA_{A-S}$, $PCSA_{A-S}$, $SPAP_{A-S}$, $SPAMTP_{A-S}$, $CV_{A-S} R-0.5$, $CV_{A-S} R-1$ and $CV_{A-S} R-1.5$. Consequently, these variables can be used for diagnosing KCN.

5 Conclusion

Anatomical variables of surface and volume obtained from a virtual model of the cornea for each patient allow to characterize and discriminate, in a reliable way, healthy corneas from corneas with optical aberrations, diagnosed with KCN according to the Alió-Shabayek optical classification. These anatomical variables can be a helpful tool that may allow measuring the optical quality of vision of the patients. However, the discrimination power of several variables used conjointly has not been studied in this research work, and opens a new way to explore for future ones, using techniques such as logistic regression.

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Subclinical keratoconus detection with three-dimensional (3-D) morphogeometric and volumetric analysis

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Subclinical keratoconus detection with three-dimensional (3-D) morphogeometric and volumetric analysis

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Subclinical keratoconus detection with three-dimensional (3-D) morphogeometric and volumetric analysis

Short title: Subclinical keratoconus detection with 3-D corneal modelling

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Abstract

Purpose: To assess the efficacy of morphogeometric and volumetric characterization of the cornea based on three-dimensional (3-D) modelling in diagnosis of subclinical keratoconus (KC).

Methods: Cross-sectional study. Ninety-three eyes with subclinical KC with a best spectacle-corrected distance visual acuity $\geq 20/20$ (grade zero KC according to the RETICS classification) and 109 control eyes were included. Computer-based 3-D corneal morphogeometric model was generated using raw topographic data. Distance, area and volume based parameters were used for statistical analysis. Distance parameters included deviation of anterior (D_{apexant})/posterior (D_{apexpost}) apices and minimum thickness points (D_{mctant} , D_{mctpost}) from corneal vertex, and $D_{\text{apexant}} - D_{\text{apexpost}}$ difference. Areal variables were derived from anterior (A_{ant}) and posterior (A_{post}) corneal surfaces, sagittal plane passing through corneal apices (A_{apexant} , A_{apexpost}) and thinnest point (A_{mctant} , A_{mctpost}). Total corneal volume (V_{total}) and volumetric distribution (with 0.1mm steps) centered to thinnest corneal point (VOL_{mct}) and anterior (VOL_{aap})/posterior (VOL_{pap}) apices comprised the volume-based parameters.

Results: In the subclinical KC group, all D values, $D_{\text{apexant}} - D_{\text{apexpost}}$ difference, A_{ant} , A_{post} and A_{apexant} values were higher ($p < 0.001$), while A_{apexpost} , A_{mctpost} , V_{total} , VOL_{mct} , VOL_{aap} and VOL_{pap} values were lower when compared to the control group ($p < 0.001$).

Regression analysis-based formula correctly classified 96.8% of the eyes with subclinical KC and 94.5% of the normal ones ($p<0.0001$).

Conclusions: Eyes with subclinical KC seem to represent asymmetrically displaced anterior and posterior corneal apex, corneal thinning and volume loss. 3-D morphogeometric and volumetric parameters and differentiation formula can be incorporated into topography software to detect subclinical KC with high sensitivity and specificity in clinical practice.

Keywords

Corneal dystrophy, corneal model, corneal volume, keratoconus, keratoconus diagnosis, subclinical keratoconus, topography

1. Introduction

Diagnosis of moderate to severe keratoconus (KC) is made with high precision based on clinical findings and corneal topography analysis.(Rabinowitz and Rasheed, 1999, Mas Tur et al., 2017, Alio et al., 2011, Toprak et al., 2015) However, detecting eyes with subclinical KC, which refers to the mildest form of topographical KC with a 20/20 vision and no clinical signs of KC, remains to be a major challenge in the area of laser refractive surgery.(Ambrosio, 2019, Li et al., 2016, Ambrosio et al., 2017)

Increasing number of ocular diagnostic devices allow researchers to combine different technologies to develop a powerful algorithm for detecting subclinical KC. In recent years, corneal epithelial thickness mapping, corneal biomechanical measurements and neural networks gained popularity in diagnosis of early KC, in parallel to advances in corneal topography/tomography devices.(Li et al., 2016, Ambrosio et al., 2017, Arbelaez et al., 2012, Saad and Gatinel, 2016, Ruiz Hidalgo et al., 2017) However, none of the presented formulas or algorithms is able to distinguish all cases with subclinical KC from normality. Consequently, the need for a powerful and practical formula in discrimination of subclinical KC is still remaining.

Recently, *Cavas et al*(*Cavas-Martinez et al., 2017b, Cavas-Martinez et al., 2017a*) introduced an innovative three-dimensional (3-D) solid model of the cornea with novel morphogeometric indices in diagnosis of clinical KC. This model allows point-to-point and spatial analysis of the cornea for both anterior and posterior surfaces, and assumes that deviations in morphogeometric parameters could be strongly associated with disorganization in the corneal collagen matrix and related to biomechanical instability as

seen in eyes with keratoconus.(Cavas-Martinez et al., 2017b, Cavas-Martinez et al., 2017a, Meek et al., 2005)

The aim of the current study was to determine, for the first time, the diagnostic ability of morphogeometric and volumetric parameters in the diagnosis of subclinical KC based on previously described 3-D corneal modelling.(Cavas-Martinez et al., 2017b, Cavas-Martinez et al., 2017a)

2. Methods

This cross-sectional study was conducted according to the tenets of Declaration of Helsinki on the use of human subjects in research and institutional ethics committee approved the study protocol.

2.1. Study population

The study included 93 eyes with a confirmed diagnosis of subclinical KC and 109 healthy control eyes with normal corneal topography (Sirius System®, CSO, Florence, Italy). All data was provided from VISSUM Innovation (Cornea, Cataract and Refractive Surgery Unit, Alicante, Spain), which is also affiliated by Miguel Hernandez University and Keratoconus IBERIA database.

2.1.1. Subclinical KC group

A single experienced cornea specialist (JLA) verified the diagnosis of subclinical KC based on the following criteria (Alio et al., 2011, Arbelaez et al., 2012, Ucakhan et al., 2011, Pinero et al., 2010);

- **No retinoscopic and biomicroscopic signs of KC (such as scissoring, Vogt's striae, Fleischer's ring, Munson's sign and Rizzuti's phenomenon),**
- **Presence of *any* typical pattern for KC on axial curvature map (such as round, oval, superior steep, inferior steep, irregular, inferior-steep asymmetric bowtie, superior-steep asymmetric bowtie and symmetric or asymmetric bowtie with skewed radial axes [SRAX] >21 degrees) accompanied with central/paracentral or inferior focal steepening (anterior and/or posterior) and/or corneal thinning,**
- **Best spectacle-corrected visual acuity (BSCVA) $\geq 20/20$ Snellen equivalent (≤ 0 logMAR),**
- **Coma-like aberration root mean square (RMS) < 2.5 microns**
- **8-mm Q-value < -0.35 microns**
- **3-mm inferior-superior mean keratometry difference (I-S) >1.5 D.**

This study group also corresponds to *grade zero* KC based on the RETICS (Thematic Network for Co-Operative Research in Health) KC classification system, which was previously introduced and validated by Alió *et al.* (Alio et al., 2011).

2.1.2. Control group

Clinically and topographically normal (none of the above-mentioned findings present) eyes with a BSCVA $\geq 20/20$ Snellen equivalent (≤ 0 logMAR equivalent) were assigned as the control group.

2.1.3. *Exclusion criteria*

History of corneal surgery, scarring, infection, corneal thinning disorders, poor compliance to topography measurements and low test quality were defined as the exclusion criteria.

2.2. ***Examination and measurements***

All subjects were asked to remove their contact lenses prior to the measurements for at least two weeks (*for soft contact lenses*) or three weeks (*for hard contact lenses*).

Participants underwent ophthalmological examinations including corrected distance visual acuity (CDVA, *Snellen*) measurement, slit-lamp biomicroscopic examination, applanation tonometry, dilated fundus examination, retinoscopy and anterior segment tomography.

A single experienced optometrist performed the topography measurements after adjusting focus and proper alignment of the patient. **At least three measurements were performed for each case and one test with the best image acquisition quality (both coverage and centration scores were >90% and also confirmed with a green coloured checkmark by the software) were used for analysis. Images with acquisition quality below 90% were excluded.**

Sphere, cylinder and spherical equivalent values, intraocular pressure (IOP, Goldmann applanation tonometer), 8-mm minimum corneal thickness (MCT), central corneal thickness (CCT) measurements and standard KC screening result (as “KC compatible”, “KC suspect”, “Abnormal or treated” and “Normal”) obtained from the Sirius (CSO, Florence, Italy) topographer were noted.

2.3. 3-D Corneal modelling, morphogeometric and volumetric parameters

A thorough examination of the whole set of patients selected for the study was performed by using a Sirius System® (CSO, Florence, Italy) tomographer, following the steps indicated in a procedure previously set up by our research group.(Cavas-Martinez et al., 2017b, Cavas-Martinez et al., 2017a)

This procedure has two clearly separated stages; a 3-D virtual modelisation one (Fig. 1, 1st stage), followed by a second of morphogeometric description (Fig.1, 2nd stage).

The result obtained after applying the procedure, is a customized virtual 3-D model of the patient's cornea (Fig. 1.A), that is finally analysed to determine a set of morphogeometric indices (Fig. 1.B, Table 1). Furthermore, several volumetric parameters directly related with volumes around anterior and posterior apices and minimum thickness points were calculated for this research (Fig. 1.C, Fig. 2 and Table 1). These parameters were set up in previous works by Cavas *et al* (Cavas-Martinez et al., 2017b, Cavas-Martinez et al., 2017a, Cavas-Martínez et al., 2018) and they were used with success in diagnosis and categorization of clinical KC (Cavas-Martinez et al., 2017b, Cavas-Martinez et al., 2017a, Cavas-Martínez et al., 2018).

Finally, the variation of the centre of mass coordinates in all X, Y and Z axes were also studied in order to characterize changes in eyes with subclinical KC. The details of the proposed morphogeometric and volumetric parameters were presented in Table 1.

The corneal tomographer used in this research allows obtaining a cloud of points that represent the corneal surfaces by using its artificial vision algorithm. **This device is based in the projection of a slit light onto the cornea, integrating a dual technology. The first one implies the projection of a Placido disc, whose mirror image is obtained by reflection. A ray-tracing procedure is followed for each point in each meridian, considering the positions of the disc (by its construction) and the distances from the points in the plane of the image to the keratometric axis. Thus, information of the normal surface is obtained by an arc-step algorithm. The second one, consists in the projection of a slit of light onto the cornea; due to the transparent structure that cornea presents, and according to Rayleigh dispersion, it is possible to photograph it (Scheimpflug photography principle), providing these images precise data of corneal elevation, in form of a cloud of points corresponding to the corneal surfaces.**

These point clouds are a discrete set of data in a M x N matrix format. **In this matrix, rows represent circles in the corneal map, while columns represent semi-meridians (256 points per radius). Each row is a sample taken following the plot of a circle of radius $i \cdot 0.2$ mm, with “i” being the number of the row, and each column is a sample taken following the plot of a semi-meridian in the direction of $j \cdot 360/256^\circ$, with “j” being the number of the column. Finally, an [i, j] matrix is generated, in which each Z value represents the point P ($i \cdot 0.2, j \cdot 360/256^\circ$) in polar**

coordinates. These are later transformed into Cartesian coordinates by an algorithm programmed in the software Matlab® V R2015 (Mathworks, Natick, USA). Rhinoceros® V 5.0 (MCNeel & Associates, Seattle, USA) software allows importing these point clouds and generate surfaces. The output surface generated by Rhinoceros was then exported to SolidWorks® V 2017 (Dassault Systèmes, Vélizy-Villacoublay, France) software for its final morphogeometric analysis. The surfaces generated in Rhinoceros® were deformed prior to their exportation, in search of minimizing the nominal separation between the spatial points and the surface itself. This distance was eventually measured by the software for the anterior corneal surface of a sample eye with subclinical KC (23-year-old male, OD, CCT= 477 microns) with a mean error of $7.73 \times 10^{-16} \pm 5.54 \times 10^{-16}$ mm (mean $\pm$ SD) as shown in Fig. 3.

2.4. Sample size calculation

The sample size was calculated assuming an effect size (d) of 0.7 and found to be at least 55 eyes per each group at 95% power and 95% confidence level (G*Power version 3.1.9.2 computer software, Universität Düsseldorf, Germany).

2.5. Statistical analysis

Statistical Package for Social Sciences (SPSS) version 24 (IBM SPSS Statistics Inc., Chicago, IL, USA) software was used for statistical analysis. Categorical data (*gender*) was analysed using the *chi square* test. *Kolmogorov–Smirnov test* was used to evaluate normality of the variables. Quantitative variables (age, refractive, topographic, morphogeometric and volumetric measurements) were expressed as *mean $\pm$ standard*

deviation (SD). A **Student's t-test** was performed to compare quantitative variables between the *control and subclinical KC* groups when parametric test assumptions were met (MCT, morphogeometric and volumetric parameters). Otherwise, *Mann Whitney U test* (age, sphere, cylinder and spherical equivalent values, IOP and CCT) was used. A binary logistic regression analysis was performed to predict influence of each variable on having subclinical KC. A multivariate model was created using powerful variables based on the *Wald* values. Diagnostic ability of the individual parameters and the created regression model were tested using receiver operating characteristic (ROC) analysis. Area under the ROC curve (AUC) was calculated to test the ability of these variables on discrimination of eyes with subclinical KC from healthy controls. AUC values were graded as follows; excellent (0.90–1.00), good (0.80–0.89), fair (0.70–0.79), poor (0.60–0.69) and worthless (0.50–0.59). ROC curve plots true positive rate (sensitivity) against the false positive rate (1-specificity) for different threshold values, and values with the best sensitivity–specificity pair on the ROC curve were accepted as the threshold. Sensitivity was defined as (true positives) / (true positives + false negatives) ratio, while the specificity indicated the ratio of (true negatives) / (true negatives + false positives).

A *p* value <0.05 was accepted as **statistically significant** at 95 % confidence interval (CI).

3. Results

The subclinical KC (n= 93) and control (n= 109) groups were statistically similar in terms of age, gender and sphere value ($p > 0.05$, Table 2). Cylinder and spherical equivalent values were significantly higher, whereas IOP, CCT and 8-mm MCT measurements were significantly lower in the subclinical KC group when compared to the control group ($p < 0.05$). Table 2 presents details of the clinical data.

3.1 Morphogeometric parameters

The subclinical KC group had significantly higher D_{apexant} , D_{apexpost} , D_{mctant} , D_{mctpost} , A_{ant} , A_{post} and A_{apexant} values than in the control group ($p < 0.05$). On the other hand, A_{total} , A_{apexpost} , A_{mctpost} , C_x , C_y and C_z values were lower in the subclinical KC group compared to the control group ($p < 0.05$). Table 3 shows comparison of morphogeometric data between the subclinical KC and control groups.

$D_{\text{apexant}} - D_{\text{apexpost}}$ difference (absolute value) was significantly higher in the subclinical KC group than in the control group (-0.15 ± 0.07 vs. -0.07 ± 0.02 mm, respectively, $p < 0.0001$), whereas $D_{\text{mctant}} - D_{\text{mctpost}}$ difference was similar between the subclinical KC and control groups (0.07 ± 0.03 vs. 0.06 ± 0.03 mm, respectively, $p = 0.535$, **Student's t-test**).

3.2. Volumetric parameters

The V_{total} (23.97 ± 1.60 vs. 25.66 ± 1.54 mm³, $p < 0.0001$, **Student's t-test**), VOL_{mct} , VOL_{aap} and VOL_{pap} (for each 0.05 mm step of the radius value, within 0.1 to 1.5 mm diameter, **Student's t-test**) were significantly lower in the subclinical KC group compared to the control group ($p < 0.001$, **Student's t-test**, Fig. 4).

3.3. Diagnostic value of the variables

The ROC analysis showed that $D_{apexpost}$ (AUC= 0.890, $p<0.0001$), MCT (AUC= 0.888, $p<0.0001$), $D_{apexant}-D_{apexpost}$ difference (AUC= 0.887, $p<0.0001$), CCT (AUC= 0.844, $p<0.001$), VOL_{mct} , VOL_{aap} and VOL_{pap} (AUC= ranged between 0.828 to 0.866, $p<0.001$ for all) and $A_{mctpost}$ (AUC= 0.800, $p<0.0001$) showed the highest individual performance for distinguishing eyes with subclinical KC from normal ones.

A binary logistic regression analysis was performed, and developed multifactorial model explained 88.4% (*Nagelkerke R²*) of the variance in subclinical KC ($p<0.0005$) and this model correctly classified 95% of the eyes (as subclinical KC and normal) at 95% CI.

The variables in the equation were (from the highest *Wald* value to lowest);

- **$D_{apexant}-D_{apexpost}$ difference:** $p<0.0001$, $B= -55.928$, Wald value= 15.665, $Exp(B)= 0$ (0-0) at %95 CI
- **$VOL_{aap}-1.0$ mm:** $p= 0.001$, $B= -12.712$, Wald value= 12.794, $Exp(B)= 0$ (0-0) at %95 CI
- **C_x :** $p<0.0001$, $B= -52.021$, Wald value= 10.304, $Exp(B)= 0$ (0-0) at %95 CI
- **Cylinder:** $p= 0.004$, $B= -0.951$, Wald value= 8.176, $Exp(B)= 0.386$ (0.201-0.741) at %95 CI
- **CCT:** $p= 0.016$, $B= -0.028$, Wald value= 5.801, $Exp(B)= 0.973$ (0.951-0.995) at %95 CI
- **IOP:** $p= 0.047$, $B= -0.349$, Wald value= 3.954, $Exp(B)= 0.705$ (0.500-0.995) at %95 CI

The regression analysis-based following formula provided 96.8% sensitivity and 94.5% specificity in discrimination of subclinical KC from normal when the cut-off value set ≥ -1.07 (AUC= 0.984, $p < 0.0001$, CI= 0.970-0.999 at 95%, Fig. 5).

$$\text{Diagnostic formula} = 35.470 \text{ (constant)} - (55.928 * [D_{\text{apexant}} - D_{\text{apexpost}} \text{ difference}]) - (12.712 * \text{VOL}_{\text{aap}} 1.0 \text{ mm}) - (52.021 * C_x) - (0.028 * \text{CCT}) - (0.951 * \text{cylinder}) - (0.349 * \text{IOP})$$

Based on this formula, the subclinical KC group had significantly higher mean values when compared to the control group (6.89 ± 5.65 vs. -4.52 ± 2.47 , respectively, $p < 0.0001$).

3.4. Diagnostic value of the Sirius KC screening algorithm

In the subclinical KC group ($n = 93$), Sirius KC screening standard algorithm classified 41 eyes (44.1 %) as KC, 38 eyes (40.9%) as KC suspect and 14 eyes (15%) as normal. However, in the control group ($n = 109$), 105 (96.3%) eyes were correctly classified as normal, whereas 4 eyes were classified as KC suspect (3.7%). It means that Sirius KC screening algorithm had 44.1% sensitivity and 96.3% specificity in discrimination of subclinical KC from normal in the current study.

4. Discussion

Diagnosis of KC in its earliest forms remains to be challenging. Growing number of attempts to develop more powerful diagnostic algorithm using advanced technologies

such as epithelial thickness mapping, dual imaging devices and biomechanical analysers indicate the necessity for different perspectives in diagnosis of subclinical KC.(Ucakhan et al., 2011, Pinero et al., 2010, Silverman et al., 2017, Golan et al., 2019, Kataria et al., 2019)

The present study introduced a powerful formula with 96.8% sensitivity and 94.5% specificity in diagnosis subclinical KC based on morphogeometric, volumetric and clinical parameters ($D_{apexant}-D_{apexpost}$ difference, $VOL_{aap}-1.0mm$, C_x , cylinder, CCT and IOP). These sensitivity/specificity values seem to be higher than that of the **Sirius KC screening standard algorithm (44.1% sensitivity and 96.3%specificity) and** previously reported parameters in detection of subclinical KC.(Ucakhan et al., 2011, Pinero et al., 2010, Huseynli and Abdulaliyeva, 2018, Cui et al., 2016, Hashemi et al., 2016, Chan et al., 2018). Furthermore, higher sample size can be considered as another strength of the current study.

Table 4 allows comparison of sample size, the best diagnostic parameter(s) and sensitivity/specificity values between the present study and previously published studies, which used similar subclinical KC definition with ours.(Ucakhan et al., 2011, Pinero et al., 2010, Huseynli and Abdulaliyeva, 2018, Cui et al., 2016, Hashemi et al., 2016, Chan et al., 2018) Studies that included clinically and topographically normal (also no atypical or suspicious findings) fellow eye of a patient with manifest KC in the other eye (what corresponds to forme fruste KC definition) were not compared with our study to prevent bias, even if these eyes were defined as subclinical KC in those studies.

The current study was performed based on 3-D morphogeometric and volumetric analysis of the cornea in patients with subclinical KC. The used 3-D corneal model was introduced by *Cavas et al*(*Cavas-Martínez et al., 2017b, Cavas-Martínez et al., 2017a, Cavas-Martínez et al., 2018, Cavas-Martínez et al., 2018*) and validated in diagnosis of clinical KC.(*Cavas-Martínez et al., 2017b, Cavas-Martínez et al., 2017a, Cavas-Martínez et al., 2018*) However, this is the first study applying this corneal model to eyes with subclinical KC for diagnostic purposes. In our study, eyes with subclinical KC had higher $D_{apexant}$, $D_{apexpost}$, D_{mctant} and $D_{mctpost}$ values when compared to the normal controls. These results verify significant displacement (from vertex) of anterior and posterior corneal apex and thinnest corneal point in eyes with subclinical KC compared to the controls. Moreover, posterior apical deviation ($D_{apexpost}$) was greater than anterior apex deviation ($D_{apexant}$) in both groups. However, in the subclinical KC group, difference (absolute value) between anterior-posterior apex displacement ($D_{apexant}-D_{apexpost}$) was significantly higher (about two-fold) than in the control group. On the other hand, difference in anterior-posterior thinnest corneal point deviation ($D_{mctant}-D_{mctpost}$) did not differ between the subclinical KC and control groups. Higher A_{ant} and A_{post} values found in our study might indicate presence of focal elevations in anterior and posterior cornea, which increase the surface area in eyes with subclinical KC when compared to the control eyes. However, A_{total} value was lower in the subclinical KC group than in the control group. The A_{total} equals to sum of A_{ant} , A_{post} and lateral surface area (correlated with corneal thickness) and lower corneal thickness in the subclinical KC group appear to reduce the A_{total} value significantly by affecting lateral surface area.(*Cavas-Martínez et al., 2017b, Cavas-Martínez et al., 2018, Cavas-*

Martinez et al., 2018) Similarly, $A_{apexpost}$ and $A_{mctpost}$ were significantly lower in the subclinical KC group than in the control group. These findings indicate that posterior apex was located where the overlying cornea is thinner (might be due to stromal thinning seen in KC or isolated posterior focal elevation) in eyes with subclinical KC, because thinner cornea diminishes sagittal surface area value. This explanation can be reasonable for the lower $A_{mctpost}$ value.(Cavas-Martinez et al., 2017b, Cavas-Martinez et al., 2018, Cavas-Martinez et al., 2018)

In the present study, total corneal volume (V_{total}) and corneal volume distribution profiles were also evaluated (VOL_{mct} , VOL_{aap} and VOL_{pap}) based on 3-D corneal model.(Cavas-Martinez et al., 2017a) Three different profiles were generated by calculating corneal volume for each 0.05 mm of radius value (diameter steps of 0.1 mm) of the revolution cylinder (up to 1.5 mm) centred to MCT, anterior apex and posterior apex.(Cavas-Martinez et al., 2017a) It was found that all volumetric parameters for all radius (of revolution cylinder) values were significantly lower in the subclinical KC group than in the control group. Reduction in corneal volume in eyes with subclinical KC was probably due to corneal thinning, which was also confirmed by topographical corneal thickness measurements in our study. On the other hand, slacking of corneal collagen matrix might also contribute to volume loss in eyes with subclinical KC.(Meek et al., 2005) Although several studies(Ucakhan et al., 2011, Cui et al., 2016, Ahmadi Hosseini et al., 2013) reported that eyes with subclinical KC had lower corneal thickness and volume; corneal volume distribution profile was presented by *Ambrosio et al*(*Ambrosio et al.*, 2006) in 2006 (in which corneal volume was calculated within diameters from 1.0 to 7.0 mm with 0.5 mm steps centred on MCT). They demonstrated that corneal-thickness

spatial profile, corneal volume distribution, percentage increase in thickness, and percentage increase in volume were significantly altered in eyes with mild to moderate KC.(Ambrosio et al., 2006) The current study differs from the study by *Ambrosio et al*(Ambrosio et al., 2006) in several aspects. First, we calculated volumes using radius increases in steps of 0.05 mm, unlike *Ambrosio et al*(Ambrosio et al., 2006) did (they utilized steps of 0.25 mm of radius). Thus, our measure scale size could be 5 times more sensitive to detect any change in corneal volume. Secondly, we analysed discrete values in the measures made to avoid an incremental biasing, whereas *Ambrosio et al*(Ambrosio et al., 2006) used average values of measure and percentages. Third, in our study, corneal volume distribution was calculated using three different critical reference points (MCT, anterior and posterior apex) as the centre, while they performed their analysis only based on MCT as the centre of volumetric distribution. Consequently, anterior apex-centred corneal volume value at 1.0 mm ($VOL_{aap-1.0\text{ mm}}$) provided significant contribution to discrimination of subclinical KC in our study.

In conclusion, **the presented discriminating formula and morphogeometric/volumetric calculations can be added to the software of any brand of topographer in the future to accurately detect (with high sensitivity and specificity) eyes with subclinical KC prior to corneal refractive surgery.**

Furthermore, 3-D corneal analysis demonstrated that eyes with subclinical KC show highly asymmetric displacement between posterior and anterior corneal apex, and remarkable decrease in corneal volume compared to the control eyes.

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Figure Legends

Fig. 1. Procedure followed for the virtual modelisation and later morphogeometric description of the cornea.

Fig. 2. (A) Corneal volume (VOL_{aap}) defined by the anterior corneal apex and a cylinder with radius $R=0.3$ mm, (B) Corneal volume (VOL_{pap}) defined by the posterior corneal apex and a cylinder with radius $R=0.7$ mm, (C) Corneal volume (VOL_{mct}) defined by the points of minimal thickness and a cylinder with radius $R=0.4$ mm.

Fig. 3 Point-surface deviation analysis for reconstruction of the anterior surface of a cornea with subclinical KC.

Fig. 4. Subclinical keratoconus group had significantly decreased corneal volume for each 0.05 mm step of the radius value (diameter ranges from 0.1 to 1.5 mm), when the axis was defined by anterior and posterior points of minimum corneal thickness (VOL_{mct}), anterior (VOL_{aap}) apex and posterior apex (VOL_{pap}).

Fig. 5. Receiver operating characteristic (ROC) curve shows sensitivity and 1-specificity values for our formula in discrimination of eyes with subclinical keratoconus from normal (AUC= 0.984, CI= 0.970-0.999 at 95%, $p<0.0001$, 96.8% sensitivity and 94.5% specificity when the cut-off value set ≥ -1.07)

Procedure followed for the virtual modelisation and later morphogeometric description of the cornea

340x289mm (300 x 300 DPI)

Fig. 2. (A) Corneal volume (VOL_{aap}) defined by the anterior corneal apex and a cylinder with radius $R = 0.3$ mm, (B) Corneal volume (VOL_{pap}) defined by the posterior corneal apex and a cylinder with radius $R = 0.7$ mm, (C) Corneal volume (VOL_{mct}) defined by the points of minimal thickness and a cylinder with radius $R = 0.4$ mm.

131x143mm (300 x 300 DPI)

Fig. 3 Point-surface deviation analysis for reconstruction of the anterior surface of a cornea with subclinical KC.

179x122mm (300 x 300 DPI)

Fig. 4. Subclinical keratoconus group had significantly decreased corneal volume for each 0.05 mm step of the radius value (diameter ranges from 0.1 to 1.5 mm), when the axis was defined by anterior and posterior points of minimum corneal thickness (VOLmct), anterior (VOLAap) apex and posterior apex (VOLpap).

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135x133mm (96 x 96 DPI)

Table 1. Morphogeometric and volumetric indices proposed for subclinical keratoconus detection

Morphogeometric parameters	Acronym
Total corneal volume [mm ³]	V_{tot}
Anterior / posterior corneal surface area [mm ²]	A_{ant} / A_{post}
Total corneal surface area [mm ²]	A_{tot}
Anterior / Posterior sagittal plane apex area [mm ²]	$A_{apexant} / A_{apexpost}$
Sagittal Plane Area in posterior minimum thickness point [mm ²]	$A_{mctpost}$
Anterior and posterior apex deviation [mm]	$D_{apexant} / D_{apexpost}$
Anterior and posterior minimum thickness point deviation [mm]	$D_{mctant} / D_{mctpost}$
Anterior and posterior apex point deviation difference [mm]	$D_{apexant} - D_{apexpost}$
Anterior and posterior minimum thickness point deviation difference [mm]	$D_{mctant} - D_{mctpost}$
Corneal volume R-x defined by the points of minimal thickness [mm ³]*	VOL_{mct}
Corneal volume R-x defined by the anterior corneal apex [mm ³]**	VOL_{aap}
Corneal volume R-x defined by the posterior corneal apex [mm ³ ***]	VOL_{pap}
Centre of mass X, Y, Z [mm]	C_X, C_Y, C_Z

* VOL_{mct} : volume contained in the intersection between the solid model of the cornea and a cylinder of revolution with radius x and its axis defined by the points of minimum corneal thickness of the anterior and posterior corneal surface. This volume was calculated for different radius values (with 0.1 mm of diameter steps) of the revolution cylinder, ranging from 0.1 to 1.5 mm.

** VOL_{aap} : volume contained in the intersection between the solid model of the cornea and a cylinder of revolution with radius x and its axis defined by a straight line perpendicular to the tangent plane to the anterior corneal surface at the apex. As VOL_{mct} , this volume was also calculated for different radius values (with 0.1 mm of diameter steps) of the revolution cylinder, ranging from 0.1 to 1.5 mm.

*** VOL_{pap} : volume contained in the intersection between the solid model of the cornea and a cylinder of revolution with radius x and its axis defined by a straight line perpendicular to the tangent plane to the posterior corneal surface at the apex. As VOL_{mct} and VOL_{aap} , this volume was also calculated for different radius values (with 0.1 mm of diameter steps) of the revolution cylinder, ranging from 0.1 to 1.5 mm.

Table 2. Comparison of the control and subclinical keratoconus groups in terms of age, gender, refraction, intraocular pressure and pachymetric data.

	Control group (n= 109)	Subclinical KC group (n= 93)	p
	Mean±SD	Mean±SD	
Age (years)	38.0±14.5	38.5±14.3	0.605 ^a
Gender (F/M)	55/54	36/57	0.119 ^b
Sphere (diopters)	-0.77±3.57	-1.35±2.87	0.102 ^a
Cylinder (diopters)	-0.56±0.56	-1.67±1.34	<0.0001 ^a
Spherical equivalent (diopters)	-1.05±3.58	-2.19±3.01	0.002 ^a
Intraocular pressure (Goldmann) (mmHg)	15.2±2.7	12.7±2.2	<0.0001 ^a
8-mm Minimum corneal thickness (microns)	540.9±32.2	483.4±36.3	<0.0001 ^c
Central corneal thickness (microns)	544.2±32.5	500.8±29.5	<0.0001 ^a

KC= keratoconus, SD= standard deviation, F/M= female/male
p<0.05 and bold values indicate statistical significance, ^a Mann Whitney U test ^b Chi square test ^c Student's t test

Table 3. Comparison of morphogeometric parameters between the control and subclinical keratoconus groups.

	Control group	Subclinical KC group	p ^a
	Mean±SD	Mean±SD	
D_{apexant} (mm)	0	0.002±0.005	<0.0001
D_{apexpost} (mm)	0.072±0.023	0.160±0.079	<0.0001
D_{mctant} (mm)	0.871±0.264	1.074±0.359	<0.0001
D_{mctpost} (mm)	0.802±0.249	1.002±0.339	<0.0001
A_{ant} (mm²)	43.09±0.14	43.18±0.19	<0.0001
A_{post} (mm²)	44.25±0.29	44.38±0.31	0.001
A_{tot} (mm²)	103.90±1.24	103.21±1.19	<0.0001
A_{apexant} (mm²)	0	1.19±1.83	<0.0001
A_{apexpost} (mm²)	4.30±0.26	4.00±0.27	<0.0001
A_{mctpost} (mm²)	4.29±0.25	3.99±0.27	<0.0001
C_x (mm)	0.043±0.016	0.010±0.047	<0.0001
C_y (mm)	0.033±0.016	0.025±0.036	0.037
C_z (mm)	0.770±0.024	0.762±0.028	0.024

(D_{apexant}) and (D_{apexpost}): Average distance from the Z axis to the highest point (apex) of the anterior and posterior corneal surfaces.

(D_{mctant}) and (D_{mctpost}): Average distance in the XY plane from the Z axis to the minimum thickness points of the anterior and posterior corneal surfaces.

(A_{ant}) and (A_{post}): Area of the anterior and posterior corneal surfaces. (A_{tot}): sum of anterior, posterior and perimetric corneal surface areas.

(A_{apexant}) and (A_{apexpost}): Sagittal plane apex area of the cornea within the sagittal plane passing through the Z axis and the highest point (apex) of the anterior and posterior corneal surfaces.

(A_{mctant}) and (A_{mctpost}): Sagittal plane area of the cornea within the sagittal plane passing through the Z axis and the minimum thickness points in the anterior and posterior corneal surfaces.

(C_x, C_y, C_z): Center of mass coordinates (X, Y, Z) of the solid.

SD: Standard deviation, F/M: Female/Male, p<0.05 and bold values indicate statistical significance, ^a Student's t test

Table 4. Comparison of the current study with previous published studies (which used similar study group definition) regarding sample size, best diagnostic parameter(s) and sensitivity/specificity values in discrimination of subclinical keratoconus from normal controls.

Studies by and Year	Sample size (eyes)		Subclinical KC definition	Best diagnostic parameter	Sensitivity %	Specificity %
	Subclinical KC group	Control group				
Current study	93	109	No retinoscopic and biomicroscopic signs of KC (such as scissoring, Vogt's striae, Fleischer's ring, Munson's sign and Rizzuti's phenomenon), presence of any typical pattern for KC on axial curvature map (such as round, oval, superior steep, inferior steep, irregular, inferior-steep asymmetric bowtie, superior-steep asymmetric bowtie and symmetric or asymmetric bowtie with SRAX >21 degrees) accompanied with central/paracentral or inferior focal steepening (anterior and/or posterior) and/or corneal thinning, BSCVA ≥20/20 Snellen equivalent, coma-like RMS < 2.5 microns, 8-mm Q-value < -0.35 microns and 3-mm I-S >1.5 D. Also corresponds to grade zero KC based on the RETICS KC classification system	Combination of morphogeometric, volumetric and clinical parameters (D _{apexant} -D _{apexpost} difference, VOL _{aap} -1.0mm, C _x cylinder, CCT and IOP)	96.8	94.5
Huseynli <i>et al</i> 2018 [20]	24 (Bilateral subclinical KC)	30	Bilateral eyes with abnormal localized steepening or an asymmetric bow-tie pattern, a normal-appearing cornea on slit-lamp biomicroscopy and at least 1 of the following signs: steep K >47.0 D, oblique cylinder >1.5 D, central corneal thickness less than 500 mm	BAD-D score	97.7	79.2
Hashemi <i>et al</i> 2016 [22]	63	97	Categorized from subclinical to severe based on the criteria developed by McMahon <i>et al.</i> (Suspect topography: No corneal scarring consistent with keratoconus, no slit-lamp signs for keratoconus, axial pattern with isolated area of steepening, average corneal power ≤49.00 D or HOA RMS >1.00, ≤1 50 micrometers)	Combination of BAD-D score, index of vertical asymmetry, index of surface variance and vertical coma values	83.6	96.9
Chan <i>et al</i> 2018 [23]	23	37	Atypical or suspect topography not meeting criteria for KC diagnosis, average corneal power ≤ 49 diopters or high order aberrations ≤ 1.5 microns or normal topography in one eye but manifest KC in the other eye	Tomographic biomechanical index, which was derived from the Pentacam and Corvis ST	84.4	82.4
Piñero <i>et al</i> 2010 [15]	13	20	Abnormal localized steepening or an asymmetric bow-tie pattern, a normal-appearing cornea on slit-lamp biomicroscopy, and at least 1 of the following signs: steep K >47.0 D, oblique cylinder >1.5 D, central corneal thickness less than 500 mm or clinical keratoconus in the fellow eye.	Anterior astigmatism	85.7	65
Cui <i>et al</i> 2016 [21]	19	29	Fellow eye of a patient with clinical keratoconus, a normal slit-lamp biomicroscopy, keratometry, retinoscopy, and ophthalmoscopy; inferior-superior asymmetry and/or bow-tie pattern with skewed radial axes detected on tangential Placido disk-based videokeratography	Combination of CCT, MCT, maximum progression index, average progression index, minimum progression index and corneal volume values for the 3.0 mm and 7.0 mm from the Scheimpflug system	79.3	94.7
Ucakhan <i>et al</i> 2011 [14]	44	63	A normal appearing cornea on slit-lamp examination, keratometry, retinoscopy, and ophthalmoscopy and inferior-superior asymmetry and/or a bow-tie pattern with skewed radial axes detected on tangential Placido disk-based topography	Combination of corneal power, corneal thickness and posterior elevation parameters	77.3	92.1

BAD-D= Belin/Ambrosio Enhanced Ectasia Display-D score, **BSCVA**= Best spectacle-corrected distance visual acuity, **CCT**= central corneal thickness, **C_x**= center of mass coordinate-X, **CV**= Corneal volume, **D**= diopters, **D_{apexant}** and **D_{apexpost}**= average distance from the Z axis to the highest point (apex) of the anterior and posterior corneal surfaces, **HOA**= high order aberrations, **I-S**= inferior-superior keratometric difference, **IOP**= intraocular pressure, **KC**= Keratoconus, **MCT**= minimum corneal thickness, **RETICS**= Thematic Network for Co-Operative Research in Health, **RMS**= root mean square, **SRAX**= skewed radial axes

For Peer Review

Morphogeometric analysis for characterization of keratoconus considering the spatial localization and projection of apex and minimum corneal thickness point

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GRAPHICAL ABSTRACT

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ABSTRACT

This work evaluates changes in new morphogeometric indices developed considering the position of anterior and posterior corneal apex and minimum corneal thickness (MCT) point in keratoconus. This prospective comparative study included 440 eyes of 440 patients (age, 7–99 years): control (124 eyes) and keratoconus (KC) groups (316 eyes). Tomographic information (Sirius[®], Costruzione Strumenti Oftalmici, Italy) was treated with SolidWorks v2013, creating the following morphogeometric parameters: geometric axis apex line angle (GA-AP), geometric axis MCT line angle (GA-MCT), apex line MCT line angle (AP-MCT), and distances between apex and MCT points on the anterior (anterior AP-MCTd) and posterior corneal surface (posterior AP-MCTd). Statistically significant higher values of GA-AP, GA-MCT, AP-MCT and anterior AP-MCTd were found in the keratoconus group ($p \leq 0.001$). Moderate significant correlations of corneal aberrations ($r \geq 0.587$, $p < 0.001$) and corneal thickness parameters ($r \leq -0.414$, $p < 0.001$) with GA-AP and AP-MCT were found. Anterior asphericity was found to be significantly correlated with anterior and posterior AP-MCTd ($r \geq 0.430$, $p < 0.001$). Likewise, GA-AP and AP-MCT showed a good diagnostic ability for the detection of keratoconus, with optimal cutoff values

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of 9.61° (sensitivity 85.5%, specificity 80.3%) and 18.08° (sensitivity 80.5%, specificity 78.7%), respectively. These new morphogeometric indices allow a clinical characterization of the 3 D structural alteration occurring in keratoconus, with less coincidence in the spatial projection of the apex and MCT points of both corneal surfaces. Future studies should confirm the potential impact on the precision of these indices of the variability of posterior corneal surface measurements obtained with Scheimpflug imaging technology.

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Introduction

The morphogeometric analysis of the corneal structure has been shown to be a valuable tool to characterize the keratoconic cornea, allowing a better understanding of the macrostructural consequences of the degenerative process associated to this disease [1]. This is especially useful for the generation of new indices, which allows for sensitive and specific detection of keratoconus (KC), even in the most incipient stages [2,3]. It should be taken into account that the analysis of the geometry of the anterior corneal surface is insufficient for the detection of subclinical or incipient KC; therefore, it is necessary to consider other additional descriptors, such as corneal asphericity and aberrations, pachymetry, or corneal biomechanics [4–10].

The analysis of corneal symmetry has been also evaluated as a potential tool to ease the detection of incipient ectatic stages, especially in terms of decentration of the apex position [11–14]. Wahba et al. [11] found that one of the parameters showing the highest diagnostic ability for early keratoconus compared to normal corneas was the diagonal decentration of the thinnest point from the apex. Abu Ameerh et al. [12], in a study evaluating a sample of Jordanian patients, found that the vertical pachymetric apex position had a good correlation with KC severity grades, while the horizontal position seemed to remain unaffected. Likewise, Fredriksson and Behndig [13] confirmed that many astigmatic values in keratoconus differed between the 3 mm pupil centred and the 3 and 6 mm apex centred zones. In the current study, a new approach based on corneal morphogeometric analysis considering the symmetry of vertex position and the point of minimum corneal thickness (MCT) has been proposed and evaluated. Specifically, the focus of this research was to evaluate changes occurring in these new morphogeometric indices with consideration of the position of anterior and posterior corneal apices and the MCT point in keratoconus and the correlation of these changes according to the severity of the disease.

Material and methods

Patients

This prospective comparative study enrolled 440 eyes from 440 patients with ages varying from 7 to 99 years old. A random selection of just one eye from each subject was made to elude the potential bias associated to the correlation between both eyes of the same individual. The study was supervised at the Keratoconus Unit of Visum Corporation Alicante, Spain, (a center affiliated with Miguel Hernández University of Elche, Spain) and was ratified by the Ethics Commission of this institution following ethical standards of the Declaration of Helsinki (7th revision, October 2013, Fortaleza, Brazil). The sample, which is part of the official database “Iberia” of keratoconus cases created for the National Network for Clinical Research In Ophthalmology RETICS OFATARED, was divided into two groups: a control one, that included 124 healthy eyes, and a KC other, composed of 316 eyes diagnosed with KC.

Inclusion criteria were the presence of a healthy eye not meeting the exclusion criteria for the control group and a KC diagnosis according to the standard criteria for the KC group [15,16]. These criteria are based on the presence of the following signs: anterior corneal topographic asymmetric bowtie pattern, KISA ≥ 100 , and one or more biomicroscopic keratoconus signs, such as Fleischer ring, significant corneal thinning, Vogt striae or conical protrusion on the cornea at the apex. Previous ocular surgery, presence of opacities and/or any other active ocular disease were considered as exclusion criteria. Keratoconus eyes with previous corneal surgeries, such as corneal collagen crosslinking or intrastromal ring segment insertion, were excluded from the KC group.

Examination protocol

A thorough clinical eye examination was conducted in all subjects including measurement of uncorrected (UDVA) and corrected distance visual acuity (CDVA), anamnesis, objective and subjective refraction, slit lamp biomicroscopy, and corneal analysis with the Sirius topographic system (Costruzione Strumenti Oftalmici, Italy). All tests were performed by a single experienced examiner. A minimum of three corneal topographies were successively obtained for each cornea and the best one (the topography with the highest acquisition quality for the Scheimpflug image and keratoscopy) was selected to provide data for this study. According to this exam, each keratoconus case was graded in terms of severity using the Amsler Krumeich grading system [17]. Besides this, all corneal tomographic files were exported in .csv format to be analyzed in detail using a morphogeometric analysis procedure developed and endorsed by our research group [1–3].

Morphogeometric analysis

The method of morphogeometric examination used in this research work was based on the following steps (Fig. 1):

1. Generation of the point cloud. A coordinate system for a three dimensional space was used to generate the surface according to the point cloud data. Exported CSV tomographic files from Sirius tomographer provide spatial points that conform to corneal surfaces, coordinates of each scanned point are given in polar format (radii and semi meridians), and some scanned points can present a reading error caused by extrinsic factors [18], so an algorithm programmed using Matlab® V R2014 (Mathworks, Natick, USA) software was developed to: i) obtain the Cartesian format of the polar coordinates included in each topography file, and ii) eliminating the topography files that contain invalid reading data in polar coordinates (value = -1000). Regarding the CSV topography files from Sirius tomographer, every row was considered a representation of a circle in the corneal map, with every column representing a semi meridian (256 points per radius). Each row represents a sample taken following the plot of a circle of radius $i \cdot 0.2$ mm, with “i” being the number of the row, and each column represents a sample taken following the plot of a semimeridian in the direction of

Fig. 1. Scheme of the procedure for the generation of a virtual corneal model and morphogeometrical variables definition, based on angular-spatial relations. GA-AP: Geometrical axis-apex line angle; GA-MCT: Geometrical axis-minimum thickness line angle; AP-MCT: Apex line-minimum thickness line angle; Anterior/Posterior AP-MCTd: Distance between apex and minimal corneal thickness points on the anterior/posterior corneal surface.

$j \times 360/256u$, with “j” being the number of the column. Finally, an $[i, j]$ matrix was generated, in which each Z value represents the point P ($i \times 0.2, j \times 360/256u$) in polar coordinates. With this organization, a cloud of points was generated specifically for a zone extending from the normal corneal vertex (corneal geometric centre, $r = 0$ mm) to the mid peripheral zone ($r = 4$ mm), this criterion is mainly justified by the following two reasons: Geometric principle [1,2] and Clinical principle [19], as this zone of analysis tends to include most information on corneal morphology, not only for healthy but also for diseased eyes.

- Geometric rebuild of corneal surface. An importation of the cloud of points representative of the corneal architecture into the surface reconstruction software Rhinoceros® V 5.0 (McNeel & Associates, Seattle, USA) was performed. This software uses a mathematical model to generate surfaces based on non uniform rational B splines (NURBS) [20], and its validity in the Biomedical Engineering field [21–24] and the Ophthalmology field [2,3,25–28] has been widely demonstrated, as when these functions are based on a dense and uniform distribution of scanned sample points, they bestow the geometric fidelity of the original surface upon the new structure. In our study, the Rhinoceros’s patch surface function was selected to find the surface best fitting the cloud of points, with a minimization of the nominal separation between the three dimensional cloud of points and the generated surface. This deviation can be later calculated by the software, providing a mean value of the distance error for the solution surface [25]. The following configuration settings were used for the function: sample point spacing 256, surface span planes 255 for both u and v directions, and stiffness of the solution surface [1].
- Solid Modelling. The surface obtained in the previous step was then imported into the solid modelling software SolidWorks® V 2012 (Dassault Systèmes, Vélizy Villacoublay, France). Using this software, the custom model that represents the corneal geometry was created [1].

- Calculation of different morphogeometrical parameters from the solid model generated. Some of these variables have been defined in detail in previous studies of our research group [1–3]: anterior corneal surface (ACS) area (A_{ant}), posterior corneal surface (PCS) area (A_{post}), total corneal surface area (A_{tot}), and corneal volume (CV). Regarding the areas, the measured area comprises the corneal surface for a radius = 4 mm from its normal corneal vertex, which included the central and paracentral regions [18]. Regarding the geometrical axis [29], given that the cornea does not have a perfect symmetry axis, and that the optical axis is not real, the geometrical axis is defined as the centreline that can be used as a reference in modelling applications in computer aided design (CAD) or finite element (FE) modelling packages, and is calculated as an axis normal to the tangent plane in the geometric centre (vertex). Likewise, the following new morphogeometrical variables were defined for healthy (Fig. 2) and advanced keratoconus eyes (Fig. 3):

- Geometrical axis apex line angle (GA AP): angle between the optic axis and the line joining the apex points of ACS and PCS.
- Geometrical axis minimum thickness line angle (GA MCT): angle between the optic axis and the line joining the points of the ACS and PCS in the corneal section containing the minimum corneal thickness.
- Apex line minimum thickness line angle (AP MCT): angle between the line joining the apex points of the ACS and PCS and the line joining the points of the ACS and PCS in the corneal section containing the minimum corneal thickness.
- Distance between apex and minimal corneal thickness points on the ACS (Anterior AP MCTd): length of the segment joining the apex and point and minimum thickness point on the ACS.
- Distance between apex and minimal corneal thickness points on the PCS (Posterior AP MCTd): length of the segment joining the apex and point and minimum thickness point on the PCS.

Fig. 2. Graphical representation of angles and linear distances calculation for a healthy eye (male patient of 31 years, OD, CDVA = 1, astigmatism = 1.18, comma-like = 0.43, spherical-like = 0.16, $Q_{8mm} = -0.51$ central thickness = 483), GA-AP = 6.48°, GA-MCT = 6.57°, AP-MCT = 12.95°, Anterior AP-MCTd = 0.604 mm, Posterior AP-MCTd = 0.495 mm). GA-AP: Geometrical axis-apex line angle; GA-MCT: Geometrical axis-minimum thickness line angle; AP-MCT: Apex line-minimum thickness line angle; Anterior/Posterior AP-MCTd: Distance between apex and minimal corneal thickness points on the anterior/posterior corneal surface.

Fig. 3. Graphical representation of angles and linear distances calculation for an advanced keratoconus eye (male patient of 20 years, OD, CDVA = 0.44, astigmatism = 1.77, comma-like = 2.27, spherical-like = 2.50, $Q_{8mm} = -2.42$ central thickness = 447), GA-AP = 9.08°, GA-MCT = 11.04°, AP-MCT = 18.16°, Anterior AP-MCTd = 1.159 mm, Posterior AP-MCTd = 0.796 mm). GA-AP: Geometrical axis-apex line angle; GA-MCT: Geometrical axis-minimum thickness line angle; AP-MCT: Apex line-minimum thickness line angle; Anterior/Posterior AP-MCTd: Distance between apex and minimal corneal thickness points on the anterior/posterior corneal surface.

Statistical analysis

The SPSS statistics software package, version 15.0 (IBM, Armonk, EEUU), was the one chosen to perform the statistical analysis of data. The normality of all data was checked by means of a Kolmogorov Smirnov test. The unpaired Student's *t* test was used to assess the statistical significance of differences between control and keratoconus groups. Furthermore, the correlation between anterior and posterior geometric parameters was assessed with the calculation of the Pearson correlation coefficient. All differences for which the related *p* value was < 0.05 were considered statistically significant.

The intrasubject repeatability for the pachymetrical parameters CCT and MTC was assessed by using the following statistical variables: the within subject standard deviation (S_w) of the consecutive measurements (three in total), intrasubject repeatability (IR), the coefficient of variation (CoV), and the intraclass correlation coefficient (ICC). The S_w is an easy way of estimating the magnitude of the measurement error. The intraobserver precision was as $\pm 1.96 \times S_w$, giving this value an estimation on the size of the error of the consecutive measures for 95% of the observations. The ICC is a correlation based in the analysis of variance (ANOVA) that measures the relative homogeneity within groups (for the set of repeated measurements) with regards to the total variation. The ICC will tend to 1.0 when the variance within the repeated

measures tend to zero, indicating that the total variation in measurements can only be attributed to variability in the measured parameter.

The spherocylindrical refraction in each case was converted to vectorial notation using the power vector method of Thibos and Horner [30]. With this method, all spherocylindrical refractive errors in conventional script notation (S [sphere], C [cylinder] $\times \phi$ [axis]) could be converted to power vector coordinates and overall blurring strength (B) using the following formulae: $M = S + C/2$; $J_0 = (C/2) \cos(2\phi)$; $J_{45} = (C/2) \sin(2\phi)$; and $B = (M^2 + J_0^2 + J_{45}^2)^{1/2}$.

Finally, the diagnostic ability of the parameters defined from the morphogeometric analysis performed to detect keratoconus was evaluated using the receiver operating characteristic (ROC) curve analysis for half of the population evaluated. This subgroup of eyes was selected randomly. ROC curves show the relationship between sensitivity (pathological cases that are correctly detected) and 1 specificity (non pathological cases that have a negative test result). Furthermore, this analysis provides the area under the curve and its corresponding statistical significance, which allows the clinician to determine the diagnostic accuracy of any clinical parameter evaluated. Likewise, an optimal cutoff is defined, which corresponds to the point of the curve which has high sensitivity while maintaining a high specificity (compromise between sensitivity and specificity). In the current study, once obtained the

ROC curve, its diagnostic ability for the detection of keratoconus was validated with the other half of the sample not included in the previous analysis, detecting the percentage of true positives (TP) and negatives (TN). Specifically, false positive (FP) and false negative (FN) rates were calculated as well as positive (PPV = TP/(TP + FP)) and negative predictive values (NPV = TN/(TN + FN)).

Results

A total amount of 124 healthy eyes from 124 subjects (28.2%) (control group, C) and 316 keratoconus eyes from 316 subjects (71.8%) (keratoconus group, KC) were considered in the study. The mean age of the sample was 38.4 years (standard deviation, SD: 15.6; median: 36.0; range: 7 to 99 years). According to the Amsler Krumeich grading system, the severity of the disease was distributed as follows in the analyzed sample: 223 eyes with grade I (70.6%), 57 eyes with grade II (57 eyes), 9 eyes with grade III (2.8%), and 27 eyes with grade IV (8.5%). The main clinical characteristics in the control and KC group are summarized in Table 1. As shown, statistically significant differences were found between groups in refraction, CDVA, anterior and posterior corneal asphericity, corneal higher order aberrations and pachymetry ($p \leq 0.001$).

Table 2 shows the intrasubject repeatability results for the pachymetrical variables analyzed with the Sirius system. An S_w value below $4 \mu\text{m}$ was observed for the pachymetry measurements for both the control and keratoconus groups, with ICC values close to 1 and a CoV below 0.7% in all cases. No significant differences were found in the S_w values associated with the minimum and central pachymetry measurements ($p = 0.47$).

Table 3 summarizes the outcomes obtained in the morphogeometric analysis in control and KC groups. Statistically significant higher values of A_{ant} and A_{post} were obtained in the KC group compared to the control group ($p < 0.001$). Likewise, statistically significant higher values of corneal volume were found in the keratoconus group ($p < 0.001$). Concerning the new morphogeometric parameters, statistically significant higher values of GA AP, GA MCT, AP MCT and anterior AP MCTd were also found in the KC group compared to the control group ($p \leq 0.001$).

In the control group, very weak correlations were found between the new morphogeometric parameters and other clinical parameters measured ($-0.209 \leq r \leq 0.246$, $p \geq 0.006$). In contrast, in the KC group, several significant correlations were found, as summarized in Table 4. Moderate significant correlations of corneal aberrations ($r \geq 0.587$, $p < 0.001$), especially coma RMS (Figs. 4 and 5), and corneal thickness parameters ($r \leq 0.414$, $p < 0.001$) with GA AP and AP MCT were found. Anterior Q for 4.5 mm and 8 mm areas were found to be significantly correlated with anterior AP MCTd ($r \geq 0.430$, $p < 0.001$) (Fig. 6) and posterior AP MCTd ($r \geq 0.550$, $p < 0.001$) (Fig. 7). Finally, the correlations of keratoconus grade severity with the morphogeometric parameters evaluated were more limited ($0.225 \leq r \leq 0.418$, $p < 0.001$).

Concerning the ROC curve analysis, with half of the population evaluated, GA AP and AP MCT had the best diagnostic ability for the detection of keratoconus, with areas under the curve (AUC) of 0.908 and 0.891, respectively ($p < 0.001$). The optimal cutoff values for these parameters were 9.61° (sensitivity 85.5%, specificity 80.3%) and 18.08° (sensitivity 80.5%, specificity 78.7%), respectively. For the rest of the morphogeometric parameters, the AUC ranged from 0.682 ($p < 0.001$) for GA MCT to 0.543 ($p = 0.320$).

Table 1

Summary of the visual acuity, refractive, pachymetric, and corneal topographic and aberrometric data obtained in control and keratoconus groups. The statistical significance (p-value) of the difference between these two groups for each parameter evaluated is displayed. Abbreviations: SD, standard deviation; D, diopter; SE, spherical equivalent; J_0 and J_{45} , astigmatic power vector components; B, overall blur strength; CDVA, corrected distance visual acuity; Q, asphericity; HOA, higher-order aberrations; RMS, root mean square; SA, spherical aberration; CCT, central corneal thickness; MCT, minimum corneal thickness.

Mean (SD) Median (Range)	Control	Keratoconus	p-value
Sphere (D)	-0.64 (3.62) 0.00 (-12.50 to 8.00)	-2.43 (4.47) -1.00 (-20.00 to 5.00)	<0.001
Cylinder (D)	-0.62 (0.75) -0.50 (-5.75 to 0.00)	-2.80 (2.37) -2.25 (-17.00 to 0.00)	<0.001
SE (D)	-0.95 (3.61) 0.00 (-12.88 to 8.12)	-3.83 (4.62) -2.38 (-21.75 to 4.00)	<0.001
J_0 (D)	0.12 (0.41) 0.00 (-0.59 to 2.70)	-0.21 (1.24) -0.17 (-4.25 to 5.00)	<0.001
J_{45} (D)	-0.01 (0.23) 0.00 (-0.98 to 1.37)	0.15 (1.33) 0.00 (-4.00 to 7.36)	0.139
B (D)	2.65 (2.66) 1.93 (0.00 to 12.88)	4.53 (4.34) 3.02 (0.00 to 21.82)	<0.001
LogMAR CDVA	0.00 (0.04) 0.00 (-0.08 to 0.22)	0.20 (0.28) 0.10 (-0.18 to 1.30)	<0.001
Anterior Q 4.5 mm	-0.09 (0.27) -0.07 (-0.65 to 0.84)	-0.60 (1.54) -0.59 (-7.42 to 4.10)	0.001
Anterior Q 8.0 mm	-0.25 (0.19) -0.25 (-0.78 to 0.13)	-0.88 (0.84) -0.76 (-3.00 to 2.82)	<0.001
HOA RMS (μm)	0.42 (0.11) 0.40 (0.24 to 0.76)	2.91 (2.37) 2.31 (0.32 to 13.84)	<0.001
Coma RMS (μm)	0.28 (0.12) 0.26 (0.02 to 0.61)	2.36 (2.12) 1.88 (0.04 to 12.85)	<0.001
SA (μm)	0.22 (0.06) 0.22 (0.08 to 0.42)	-0.30 (1.19) 0.11 (-7.85 to 1.32)	<0.001
Spherical-like RMS (μm)	0.24 (0.06) 0.24 (0.11 to 0.48)	1.05 (1.15) 0.67 (0.15 to 8.29)	<0.001
Coma-like RMS (μm)	0.33 (0.13) 0.32 (0.08 to 0.70)	2.62 (2.16) 2.19 (0.20 to 12.95)	<0.001
CCT (μm)	544.33 (32.27) 544.50 (482 to 639)	468.38 (59.82) 475.00 (285 to 633)	<0.001
MCT (μm)	541.09 (32.03) 541.00 (480 to 634)	449.56 (66.09) 455.00 (231 to 602)	<0.001

Table 2

Intrasubject repeatability results for the pachymetrical variables analyzed with the Sirius system. Abbreviations: SD, standard deviation; CCT, central corneal thickness; MCT, minimum corneal thickness; S_w : within-subject standard deviation; CoV: coefficient of variation; IR: intrasubject repeatability; ICC: intraclass correlation coefficient; CI: confidence interval.

	Variables	Mean (SD) Median (Range)	S_w	CoV (%)	IR	ICC	Range 95% CI
Control	CCT (μm)	544.33 (32.27) 544.50 (482 to 639)	2.79	0.51	5.50	0.996	0.995, 0.997
	MCT (μm)	541.09 (32.03) 541.00 (480 to 634)	2.81	0.51	5.51	0.996	0.995, 0.997
Keratoconus	CCT (μm)	468.38 (59.82) 475.00 (285 to 633)	2.29	0.49	4.48	0.997	0.996, 0.998
	MCT (μm)	449.56 (66.09) 455.00 (231 to 602)	3.21	0.69	6.19	0.989	0.982, 0.994

Table 3

Summary of the different corneal parameters defined and obtained from the morphogeometric analysis performed in both control and keratoconus groups. The statistical significance (p-value) of the difference between these two groups for each parameter evaluated is displayed. Abbreviations: SD, standard deviation; A_{ant} , anterior corneal surface area; A_{post} , posterior corneal surface area; A_{tot} , total corneal surface area; CV, corneal volume; GA-AP, geometrical axis–apex line angle; GA-MCT, geometrical axis–minimum thickness line angle; AP-MCT, apex line–minimum thickness line angle; anterior AP-MCTd, distance between apex and minimum corneal thickness points on the anterior corneal surface; posterior AP-MCTd, distance between apex and minimum corneal thickness points on the posterior corneal surface.

Mean (SD) Median (Range)	Control	Keratoconus	p-value
A_{ant} (mm^2)	43.09 (0.15) 43.10 (42.73 to 43.39)	43.48 (0.55) 43.36 (42.49 to 47.44)	<0.001
A_{post} (mm^2)	44.26 (0.29) 44.26 (43.49 to 44.90)	44.87 (0.90) 44.69 (43.57 to 51.14)	<0.001
A_{tot} (mm^2)	104.01 (1.19) 103.93 (100.72 to 106.15)	104.15 (2.00) 103.81 (99.96 to 114.88)	0.622
CV (mm^3)	25.85 (1.49) 25.95 (22.99 to 29.50)	23.87 (1.82) 23.81 (16.95 to 28.96)	<0.001
GA-AP °	7.19 (2.20) 7.03 (2.49 to 13.33)	21.99 (11.15) 21.23 (1.32 to 67.26)	<0.001
GA-MCT °	8.26 (5.30) 7.59 (0.53 to 50.12)	9.76 (5.28) 9.05 (0.44 to 52.37)	<0.001
AP-MCT °	15.03 (6.02) 14.07 (4.15 to 56.68)	30.89 (13.12) 29.81 (0.15 to 75.19)	<0.001
Anterior AP-MCTd (mm)	0.87 (0.25) 0.84 (0.44 to 1.98)	1.02 (0.40) 0.96 (0.17 to 3.20)	0.001
Posterior AP-MCTd (mm)	0.74 (0.24) 0.71 (0.34 to 2.20)	0.76 (0.37) 0.71 (0.05 to 2.86)	0.722

Table 4

Summary of the different statistically significant correlations found between corneal parameters defined and obtained from the morphogeometric analysis and different clinical data in the keratoconus group. The statistical significance (p-value) of correlations is also displayed. Abbreviations: SD, standard deviation; A_{ant} , anterior corneal surface area; A_{post} , posterior corneal surface area; A_{tot} , total corneal surface area; CV, corneal volume; GA-AP, geometrical axis–apex line angle; GA-MCT, geometrical axis–minimum thickness line angle; AP-MCT, apex line–minimum thickness line angle; anterior AP-MCTd, distance between apex and minimum corneal thickness points on the anterior corneal surface; posterior AP-MCTd, distance between apex and minimum corneal thickness points on the posterior corneal surface; CDVA, corrected distance visual acuity; Q, asphericity; HOA, higher-order aberrations; RMS, root mean square; SA, spherical aberration; CCT, central corneal thickness; MCT, minimum corneal thickness.

Morphogeometric parameters	Correlated with	Correlation coefficient	p-value
GA-AP °	CDVA	0.428	<0.001
	HO RMS	0.753	<0.001
	Coma RMS	0.75	<0.001
	Coma-like RMS	0.749	<0.001
	Spherical-like RMS	0.655	<0.001
	Anterior Q in central 8 mm	−0.487	<0.001
	KC grade severity	0.418	<0.001
	MCT	−0.618	<0.001
	CCT	−0.486	<0.001
	KC grade severity	0.155	0.006
GA-MCT °	HO RMS	0.667	<0.001
	Coma RMS	0.664	<0.001
	Coma-like RMS	0.662	<0.001
	Spherical-like RMS	0.587	<0.001
	KC grade severity	0.367	<0.001
	MCT	−0.55	<0.001
	CCT	−0.414	<0.001
	Anterior Q in central 4.5 mm	0.6	<0.001
	Anterior Q in central 8 mm	0.43	<0.001
	KC grade severity	−0.18	0.001
Posterior AP-MCTd (mm)	Anterior Q in central 4.5 mm	0.65	<0.001
	Anterior Q in central 8 mm	0.55	<0.001
	KC grade severity	−0.225	<0.001

Fig. 4. Scatterplot showing the relationship between the geometrical axis–apex line angle (GA–AP) defined from the morphogeometric analysis performed and the level of corneal primary coma aberration in terms of the root mean square (RMS) obtained in the keratoconus group. The adjusting line to the data obtained by means of the least-squares fit is shown.

Fig. 5. Scatterplot showing the relationship between the apex line–minimum thickness line angle (AP–MCT) defined from the morphogeometric analysis performed and the level of primary coma aberration in terms of root mean square (RMS) obtained in the keratoconus group. The adjusting line to the data obtained by means of the least-squares fit is shown.

for posterior AP MCTd. When the cutoff point obtained for GA AP was validated with the other half of the sample, FP and FN rates of 9.7% and 15.2% were found, respectively. Likewise, PPV and NPV of 95.8% and 71.8% were obtained, respectively. Considering the cut off point obtained for AP MCT, FP, FN, PPV, and NPV values of 24.2%, 15.2%, 89.9%, and 66.2%, respectively.

Discussion

Several technological advances have been introduced in clinical practice to characterize and evaluate in detail the corneal changes occurring in keratoconus [15,31]. Besides a great variety of tools for early detection of keratoconus [15,31], even considering the cornea as a solid with a determined volume [2,3], different tomographic, pachymetric, optical and biomechanical indices have been devel-

oped to characterize the level of severity of the disease and to monitor the potential progression of the structural weakening of the cornea [11,12,17,31–39]. In the current study, we have used a Scheimpflug imaging based tomographer that have been previously validated, the Sirius system, which can provide repeatable geometric and pachymetric measurements in healthy [40–43] and keratoconus eyes [44,45]. Likewise, previous comparative clinical studies have demonstrated the good interchangeability level of pachymetric measurements obtained with the Sirius system and anterior segment optical coherence tomography systems [46–48]. The variability of repeated measurements of pachymetry parameters evaluated in the current study was below 4 μm , which is not clinically relevant, and coincides with the results of previous studies [43,44].

Regarding the geometric calculations performed with the data obtained with the tomographer used, we have considered the

Fig. 6. Scatterplot showing the relationship between the distance between apex and minimum corneal thickness points on the anterior corneal surface (Anterior AP-MCTd) defined from the morphogeometric analysis performed and the anterior corneal asphericity (Q) in the central 4.5 mm area obtained in the keratoconus group. The adjusting line to the data obtained by means of the least-squares fit is shown.

Fig. 7. Scatterplot showing the relationship between the distance between apex and minimum corneal thickness points on the posterior corneal surface (Anterior AP-MCTd) defined from the morphogeometric analysis performed and the anterior corneal asphericity (Q) in the central 4.5 mm area obtained in the keratoconus group. The adjusting line to the data obtained by means of the least-squares fit is shown.

cornea as a solid, with the definition of new morphogeometric parameters by means of a new mathematical approach [1] in order to characterize potential changes in the symmetric distribution of some reference points on the two surfaces of the cornea. Specifically, the geometrical axis (GA), the line joining the apex points of the ACS and PCS (AP), and the line joining the points of the ACS and PCS in the corneal section containing the minimum corneal thickness (MCT) have been considered as reference lines to define different angular metrics and distances: GA AP, GA MCT, AP MCT, anterior AP MCTd, and posterior AP MCTd. This kind of analysis may help obtain a better clinical characterization of the level of severity and progression of corneas with keratoconus.

In the current series, we found significantly higher values of the areas of the ACS and PCS of the generated custom 3 D model (A_{ant} , A_{post}) in the groups of eyes with KC, which is consistent with the

results of our previous studies [1–3]. This confirms that the local steepening occurring in the ACS and PCS in KC [5,9,11,12,15,17,31] leads to an increase in the area occupied by each surface. Indeed, the combination of A_{post} and A_{tot} with other morphogeometric parameters has been shown to provide good diagnostic ability for the detection of grade I KC, with sensitivity of 97.4% and specificity of 97.2% [2]. Likewise, significantly lower values of corneal volume were found in the KC group when compared with the control group, which is consistent with the significantly lower pachymetric values obtained. Ahmadi Hosseini et al. [49] demonstrated that the presence of a reduction in corneal volume in keratoconus eyes was related to the lower percentage thickness increase from center to periphery.

Concerning the new morphogeometric parameters, significantly higher values of GA AP, GA MCT, and AP MCT were found in the KC

group compared to the control group. This confirms the loss of the revolution symmetry of the cornea when a KC is present, with more discrepancy in the position of the optic axis (line joining the geometric center of both corneal surfaces) in KC with respect to the line joining the apex points of both corneal surfaces and the line joining the points of the ACS and PCS in the corneal section containing the minimum corneal thickness. This is in line with the results of previous studies that evaluate the changes occurring in the location of the apex of the ACS in KC eyes, with an inferior displacement in most cases [2,11,12]. Furthermore, in our series, statistically significant correlations of GA AP, GA MCT and AP MCT with the severity of the disease graded using the Amsler Krumeich classification were found, although the strength of these correlations was limited. This shows a trend of the severity of keratoconus to be associated with a progressively more remarked discrepancy between geometric center and anterior and posterior apex and MCT localizations, leading to a more distorted 3 D configuration of the corneal structure, more significant geometric asymmetries in both corneal surfaces and consequently, a poorer optical performance. In agreement with our results, Abu Ameerh and colleagues [12] demonstrated that the vertical apex location in keratoconus was effectively correlated with the level of severity of the disease, but this correlation was weaker for the horizontal location of the apex. Likewise, the asymmetry in pachymetric maps has also been found to be a valuable tool to characterize the structural asymmetry in keratoconus, as well as to provide a consistent detection of the disease [50–52].

In contrast to GA AP, GA MCT, and AP MCT, no clear trends were observed for anterior and posterior AP MCTd in keratoconus compared to controls. In spite of the significant differences found in the line joining the apex and MCT points of both corneal surfaces, no significant differences in the length of the segment joining the apex and point and minimum corneal thickness on the posterior corneal surface were found between control and keratoconus groups. A small (in magnitude) but statistically significant difference was only found in anterior AP MCTd between control and keratoconus groups. This confirms that the difference between the apex and MCT point in each surface is less critical than the difference in the projection of these positions on each corneal surface. Therefore, in keratoconus, the correlation between the geometry of both corneal surfaces is altered as has been demonstrated in previous studies [51]. When the correlation of AP MCTd with the severity grade of the keratoconus was evaluated, a trend toward lower values of anterior and posterior AP MCTd were found in those eyes with a more severe stage of the disease (negative correlations). This demonstrates that MCT and apex points become closer in both corneal surfaces with an increased level of severity in keratoconus. This is consistent with the results of morphogeometric analyses performed in keratoconus in previous studies of our research group using different parameters, such as the anterior and posterior apex deviations (mean distance from the Z axis to the highest point of both ACS and PCS), and anterior and posterior minimum thickness point deviations (mean distance in the XY plane from the Z axis to the minimum thickness points in both corneal surfaces) [1,2]. However, it should be considered that the correlations found of anterior and posterior AP MCTd with keratoconus severity grade in our series were limited. Therefore, these parameters may be beneficial to differentiate keratoconus from normal corneas, but possibly are insufficient to be used by clinicians to characterize the level of severity of keratoconus. Future studies should be performed in order to confirm all these trends obtained in the current series.

Finally, we evaluated the correlations between the new morphogeometric parameters and other clinical variables in control and KC groups. In contrast to the lack of significant correlations found in the control groups, several statistically significant correlations of different strength were found in the keratoconus group.

Positive and negative significant correlations of GA AP and AP MCT with a great variety of clinical parameters that have been found previously to correlate also with the severity of the disease were found in our keratoconus group [15,17,31,53]. Specifically, poorer CDVA and higher level of coma like and spherical like corneal aberrations, as well as more negative asphericity values and lower MCT and CCT, were found in those eyes showing higher values of GA AP and AP MCT. This confirms that GA AP and AP MCT are parameters with the ability of characterizing the corneal structural changes occurring in keratoconus with an increasing level of severity. Likewise, significant correlations were found between anterior and posterior corneal asphericities and anterior and posterior AP MCTd. Specifically, higher values of these parameters were found in those eyes with less negative values of asphericity. Therefore, MCT and apex were closer in those eyes with more prolate ACS and PCS, which is associated with the presence of more severe stages of keratoconus [15,17,31,53,54].

This study has some limitations that should be acknowledged. Although the Scheimpflug imaging technology has been shown to provide repeatable geometric and pachymetric measurements in keratoconus eyes [44,45], this consistency of tomographic measurements obtained with this type of technology is poorer than that observed in healthy subjects, especially in terms of posterior corneal shape characterization. Future studies using the same morphogeometric approach but with data obtained using other types of technologies should be performed to confirm these outcomes. Likewise, although the level of interobserver repeatability seems to be low considering that measurements are taken automatically by the device, the observer has an active role and there is a range of acceptable focuses that may lead to variable measurements. For this reason, this factor may be also considered as a potential limitation of the current study and should be addressed in future investigations.

Conclusions

The use of new morphogeometric indices developed considering the position and spatial projection of anterior and posterior corneal apex and MCT points allows a clinical characterization of the 3 D structural alteration occurring in keratoconus. Likewise, this type of analysis may allow the clinician to characterize the level of severity of the disease, with less coincidence in the spatial projection of apex and MCT points of both corneal surfaces, as well as lower separation between these two localizations in each surface in the more advanced stages of keratoconus. These changes, according to the severity of this corneal disease, are consistent with the significant reduction in corneal volume and the significant increase in the area occupied by each corneal surface that is observed. Therefore, besides changes occurring separately in each corneal surface, a significant alteration of the 3 D configuration of the corneal structure is present in keratoconus that should be considered in clinical evaluations and decisions. Future studies should be conducted to evaluate the diagnostic ability of the morphogeometric parameters developed for the detection of subclinical keratoconus, comparing such diagnostic performance with that currently provided by spectral domain optical coherence tomography.

Conflict of interest

The authors have declared no conflict of interest.

Compliance with Ethics Requirements

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation.

tion (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study.

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EMKLAS: A New Automatic-Scoring System for Early and Mild Keratoconus Detection

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Abstract

Purpose: Create a unique predictive model based on a set of demographic-optical-geometric variables with two objectives: classifying Keratoconus (KC) in its first clinical manifestation stages; establishing the probability of having correctly classified each case.

Methods: 178 eyes of 178 subjects were selected (115 males; 64.6%; 63 females, 35.4%). Of these, 74 were “healthy” control subjects, and 104 suffered from KC according to the RETICS grading system (61 early KC, 43 mild KC). Only one eye from each patient was selected, and 27 different parameters were studied (demographic, clinical, pachymetric, geometric). The obtained data were used in an ordinal logistic regression model programmed as a web application, capable of using new patients’ data for real-time predictions.

Results: An early and mild KC classifier (EMKLAS) showed good training performance figures, with global 73% accuracy and a 95% confidence interval of 65%–79%. This is particularly accurate when validated by an independent sample for the Control (79%) and Mild KC (80%) groups. The accuracy of the Early KC group was remarkably lower (69%). The variables included in the model were Age, Gender, CDVA, Q8mm and Posterior Minimum Thickness Point Deviation.

Conclusions: Our web application allows the fast, objective and quantitative assessment of early and mild KC in detection and classification terms, and assists ophthalmology professionals in diagnosing this disease.

Translational Relevance: As no single “gold standard” exists for detecting and classifying pre-clinical KC, using our web application and EMKLAS score may help doctors in their decision-making process.

Introduction

Keratoconus (KC) is a progressive corneal ectasia that manifests itself by a cone-like bulge and reduced corneal thickness¹. Diagnosing KC in its milder forms is accurately made according to clinical evidence and a corneal tomography analysis². However in its more incipient phases, as patients remain clearly asymptomatic^{3,4}, KC detection remains a clinical challenge.

Given the unpredictable character of this disease⁴, it is vitally important to correctly identify patients suffering post-surgical iatrogenic ectasia⁵⁻¹¹ as several studies suggest that 2.6% of the patients planning to undergo refractive surgery are suspected of suffering KC¹².

An increasing number of technologies allow researchers to combine different metrics for developing algorithms in ophthalmology¹³, allowing some of them the detection of KC in its early stages^{4,8}. However, these developments present significantly different results as no clear consensus has been reached about the relative importance of indices on which these algorithms are based, and also because there are discrepancies in the criteria that should be used to assess the risk probability associated with the disease developing. This suggests that a practical multi-factor formula capable of discriminating between incipient KC and normal eyes is very much needed.

Cavas et al.^{14,15} recently presented an innovative virtual 3D model of the cornea that registers the geometrical decompensation present during asymmetric disease progression. This model allows the continuous and discreet analysis based on morpho-geometrical variables of the biomechanical instability related to re- collagen fibre orientation in the corneal matrix that is manifested during the disease.

Different disease progression classifications for KC exist and are based on several indices.¹⁶ However, handling profuse available information sometimes makes adequate optical-geometric evaluations complicated. From an optical point of view, patients show a certainly deteriorated spectacle-corrected visual acuity during disease development insofar as their visual performance

worsens when the degree of KC severity progresses. Following this criterion, a KC stages classification has been developed and is known as RETICS grading.^{17,18}

The purpose of this study was to propose a unique predictive model based on a set of demographic-optical-geometric variables for two objectives: classifying KC in its first clinical manifestation stages; establishing the probability of correction after classifying each case.

Materials and methods

Patients

For this observational comparative study, 178 eyes of 178 subjects aged between 15 and 76 years were selected, with 115 males (64.6%) and 63 females (35.4%). Of these, 74 formed the “healthy” control subjects, whose ages ranged from 18 to 63. They were divided into 42 males (56.7%) and 32 females (43.3%) and their average age was 41 ± 23.7 , while 104 were 16-76 years old and had KC, with 73 males (70.1%) and 31 females (29.9%). This second group was distributed again into two subgroups depending on whether their members’ degrees of KC according to the RETICS grading system were I (early KC) or II (mild KC)¹⁸. The “Early KC” group comprised 61 subjects aged from 15 to 59, of whom 45 were males (73.8%) and 16 were females (26.2%), whose average age was 36.0 ± 21.0 . The “Mild KC” group comprised 43 subjects of 17-76 years old, of whom 28 were males (65.1%) and 15 were females (34.9%), and their average age was 46.2 ± 29.2 .

A second dataset was obtained 4 months after recruiting the first set of individuals used for the training process by taking special care so that no patient from the training group was included in the validation one. This new dataset comprised 41 individuals, of whom 19 were healthy, 14 were RETICS grade I and eight were RETICS grade II. This dataset was used to make an independent validation of the ordinal logistic regression model.

All the subjects were recruited at Vissum Corporation Alicante (an institution affiliated to the Miguel Hernández University of Elche, Spain) and formed part of the official “Iberia” database of KC cases generated for the National Network for Clinical Research in Ophthalmology RETICS-OFTARED. All the participants provided their written informed consent and the study,

which followed the tenets of the Declaration of Helsinki (7th revision, October 2013, Fortaleza, Brazil), was approved by the clinic's Ethics Committee for Clinical Research.

In order to avoid undesired biases, any subjects who had undergone previous ocular surgery, had worn contact lenses in the 4-week period running up to the tomographical evaluation, or showed any other ocular comorbidity that could affect the present study outcomes, were eliminated.

The Control group's cases were selected randomly from the refractive procedure's candidates, and the data included in the study were acquired during the patients' pre-surgical consultations, always by the same well-experienced technician.

The procedure followed for both KC group diagnosis and classification was based on state-of-the-art clinical and topographical evaluations (Figure 1), including ultrasonic pachymetry, fundus evaluation, manifest refraction (sphere and cylinder), slit-lamp biomicroscopy, uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA) and Goldmann tonometry.¹⁹ For all cases, clinicians searched for pre-surgical evidence for KC, such as: presence of asymmetric bowtie pattern (with or without skewed axes), Fleischer's ring, Rizzuti's sign, Munson's sign, anterior stromal scar or stromal thinning.

Examination

All the subjects herein included were evaluated by a Sirius System® tomographer (Costruzione Strumenti Oftalmici, Italy) following the validated methodology guidelines previously created by our research group, which has been thoroughly described in preceding works^{14,15}. This methodology has proved its effectiveness in diagnosing¹⁵ and characterising KC¹⁴, and is arranged in two stages: a first three-dimensional virtual modelling one, followed by a morpho-geometrical analysis to finish the process.

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The outcome of the previously described procedure is a personalised 3D corneal model that can be examined to establish morpho-geometric variables, which have already been defined and utilised in previous studies^{14,15}. Of them all, posterior minimum thickness point deviation was that selected to be used in this study, along with the demographic and clinical parameters (Figure 1).

Figure 1.

Statistical analysis

Exploratory and descriptive data analysis

Quantitative variables were summarised using median±interquartile range (IQR) and mean±standard deviation (SD), and qualitative using count and percentage. Normality was tested by the Shapiro-Wilks test and collinearity was measured with the Pearson correlation coefficient. The association between each quantitative variable and the group (healthy individuals, early KC and mild KC) was tested by the Kruskal-Wallis test as most did not pass the normality test. A chi-squared test was used for the qualitative variable gender. p-values lower than 0.05 were considered to be statistically significant.

Model training and fine-tuning

The ordinal logistic regression technique was used to model the multivariate relation between all the available parameters and grade:

$$\log \frac{P(Y \leq j)}{P(Y > j)} = \beta_{j0} - \beta_1 x_1 - \dots - \beta_p x_p \quad (1)$$

where Y is an ordinal outcome with J categories, $P(Y \leq j)$ is the cumulative probability of Y being less than or equal to a specific category $j = 1, \dots, J - 1$, β_{j0} is the intercept for category j , and $\beta_1, \beta_2, \dots, \beta_p$ are the coefficients for each predictor p^{20} . It was assumed that the intercepts differed for each category, but slopes were constant across categories (proportional odds model). A backwards procedure with Akaike information criteria (AIC) was followed to obtain a minimal set of variables containing the largest possible amount of information. Initially, the full model (with all the available parameters) was built. Then each parameter was removed one by one and a new model was built. The AIC values for all these models were calculated using the expression²¹:

$$AIC = -2 \cdot \text{maximized log-likelihood} + 2 \cdot \text{number of parameters} \quad (2)$$

The parameter that brought about the most marked reduction in AIC was definitely removed and the process was repeated until no further reduction in AIC took place. Model proportional odds assumption was tested by the Venables-Ripley likelihood ratio test and the Brant test. Model goodness of fit was assessed using the Hosmer-Lemeshow test adapted for ordinal logistic regression, which examines whether the observed proportions of events are similar to the predicted probabilities of occurrence in subgroups of the data set using a chi-square test. The McFadden pseudo R2 value was also calculated, which is defined as

$$pseudo R2 = 1 - \frac{\ln(fitted model)}{\ln(null model)}$$

where ln indicates the log likelihood value and the null model has only an intercept as predictor.

Model validation

The model was evaluated using accuracy, sensitivity and specificity scores deriving from the corresponding confusion matrix. An internal cross-validation procedure using bootstrap aggregating (bagging) was used²². First of all, a new dataset was generated by sampling with replacement from the original dataset, which was the same in size. Then a new model was trained with these data, and it was later used to make predictions on the cases not included during training. This procedure was repeated 100 times to obtain a set of quality parameters that could be averaged. Confidence intervals were calculated. On average, 63.2% of the original data was used in all 100 training steps, and the remaining 36.8% was employed for validation purposes.

Then a second dataset of 41 patients was obtained 4 months after recruiting the first set of individuals, which was used to make an independent validation of the ordinal logistic regression model.

Programmes and libraries

All the statistical calculations were carried out by R Statistics v3.6.1 (R Foundation for Statistical Computing, Vienna, Austria)²³, and p-values below 0.05 were taken as being statistically significant. Packages dplyr, corrplot, nnet, MASS, generalhoslem, pscl, brant, effects, grid, caret, yarr and ROCR were used for the data pre-processing, analysis and plotting, and also for model calculation and validation. The Shiny (RStudio Inc., Boston, MA)²⁴ and ShinyAuthr (Paul Campbell, Paris, France)²⁵ packages were utilised for web application development and deployment, and also for user authentication. Statistical power analysis was conducted by simulation with the Wald test to estimate the power for each covariate according to sample size, as the literature describes.^{26,27}

Results

Of all the eyes herein considered, 41.5% formed the Ctrl group (74 healthy eyes), 34.3% comprised the Early KC group (61 eyes) and 24.2% made up the Mild KC group (43 eyes). Table 1 summarises all the measured variables, initially for all the patients, who were then segregated into healthy individuals (Ctrl), patients showing Early KC eyes and those with a Mild form of disease development. Some trends of the association between variables and grades were observed, which were further tested by the Kruskal-Wallis test for the quantitative variables, and the chi-squared test for the qualitative variable Gender. All the quantitative variables except for Age, Axis and SphericalAbZ40, showed a significant relation, whereas no significant difference was found for Gender. A non-parametrical test was used because most quantitative variables did not pass the normality test.

Figure 2 reveals how all the variables, save Age, Sphere, Axis, Spherical AbZ40 and Anterior/Posterior minimal thickness point deviations, strongly correlated and, therefore, bore very little information. This suggested that a simple model with a limited amount of variables should be expected when applying the ordinal logistic regression technique with a variable selection algorithm. A minimum set of predictors with the most information was selected by a

stepwise backwards procedure using Akaike information criteria. The final model comprised the variables shown in Table 2, including Age and Gender. To assess this final model's goodness-of-fit, the likelihood ratio test gave a p-value < 0.001, while a p-value < 0.001 was also obtained by the Hosmer-Lemeshow test. The McFadden pseudo R² gave a value of 0.507, which indicates good predictive power.

Figure 2.

Figure 3 shows the effects plot for the included variables, where Age and Gender contribute very little, whereas CDVA, Q8mm and Posterior MTP deviation make an important and apparently homogeneous contribution among groups.

Figure 3.

The model passed all the tests run to check for the proportional odds assumption required for ordinal logistic regression to be valid. The Venables–Ripley test value was 0.180 and the omnibus Brant test value was 0.250. The individual Brant test results for Age, Gender, CDVA, Q8mm and Posterior MTP deviation were 0.307, 0.164, 0.196, 0.393 and 0.575, respectively. Thus no significant deviation of assumption was present.

Figure 4 shows the distribution of the scores for each group, where the prediction score for Ctrl follows a markedly different distribution for the true Ctrl *versus* the true early KC and mild KC individuals. A similar behaviour is observed with the mild KC prediction score for the true mild KC *versus* the true Ctrl and early KC patients. Nonetheless, an early KC prediction score for the true early KC *versus* the true Ctrl and mild KC patients does not show such marked differences, and indicates that the early KC patients lie somewhere in a zone between the other two groups.

Figure 4.

Table 3 shows the corresponding model confusion matrix, where similar results are observed. Table 4 reflects that the balanced accuracy for the Ctrl, early KC and mild KC patients, which are 0.83, 0.70 and 0.83, respectively, with an overall accuracy of 0.73 (95%CI: 0.65–0.79). McNemar’s test yields a p-value of 0.430, which indicates the homogeneity of the results. Only one true mild K patient is predicted as Ctrl and, once again, only one true Ctrl patient is predicted as being mild KC. A higher degree of misclassifying is present among the adjacent groups (Ctrl vs. early KC, or early KC vs. mild KC) with 47 (26.4%) patients incorrectly classified by combining false-positives and false-negatives.

Table 5 provides the inner validation procedure results, where 100 bootstrap resamples with substitution were obtained, which contained the same total number of cases as the original dataset (n=178). For each one, an equivalent ordinal logistic regression model was fitted using the same parameters indicated in Table 2. This fitted model was used to classify the remaining cases, which were those not used in the bootstrap sample. The model’s quality measurements in sensitivity and specificity terms were averaged from these results with their corresponding confidence intervals. We can observe that approximately similar results were obtained, with a slight trade-off between sensitivity and specificity, but with significantly higher values remaining for the Ctrl and Mild KC prediction scores than for Early KC.

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255 Table 6 presents the values of sensitivity, specificity and balanced accuracy for the independent
256 validation database. The obtained figures are slightly lower, but the results generally fall in line
257 with those obtained during the internal bootstrap validation procedure (see Table 5).

258 The power analysis results (Figure 5) indicated that statistical power exceeding 0.80 was
259 achieved for the variables CDVA, Q8mm and Posterior MTP Deviation for those sample sizes
260 over 150 patients, whereas statistical power was around 0.50 for this size for Age and Gender.

261

262 Figure 5.

263

264 Graphics User Interface

265 A web application containing the pre-trained model was created to allow users to instantly
266 estimate the probability of an individual belonging to each modelled group using a minimal set
267 of parameters. This application (Figure 6) was developed with Shiny v1.3.2 (RStudio Inc.,
268 Boston, MA)²⁴ and was deployed within the institutional intranet to prevent accession from
269 unauthorised users using the ShinyAuthr v0.0.99 authentication module (Paul Campbell, Paris,
270 France).²⁵

Figure 6.

The application's landing page (see Figure 6) consisted in a log-in form by adding a secured authentication layer. As registration capabilities were disabled, new users would be added by the system administrator. After logging in, the application exhibits a form composed of five text boxes that correspond to the model predictors, filled by default with typical values for a healthy individual. After inserting any new desired values and pressing the "GET SCORE" button, the application's trained model makes its prediction (Figures 7-9) by providing an Early-Mild KC classification score (named "EMKLAS") as a percentage, and by depicting a typical cornea, including some of the main parameters considered in the prediction.

Figures 7-9 are screen captures of one healthy individual (43-year-old female, OD, CDVA = 1, Q8mm = -0.2, Posterior MTP deviation = 0.1), one of someone with Early KC (36-year-old male, OD, CDVA = 0.9, Q8mm = -0.48, Posterior MTP deviation = 0.9), and one with Mild KC (52-year-old male, OD, CDVA = 0.6, Q8mm = -0.75, Posterior MTP deviation = 0.94),

286 respectively. Each one also includes a 3D image of a typical cornea that represents how
287 different predictors were calculated based on physical measurements.

Figure 7.

Figure 8.

Figure 9.

However, some cases were incorrectly classified by our GUI due to the singularities characterising KC. Figure 10 includes some screenshots from different individuals and represents all the possible model classes. Patients A, B and C are healthy individuals, while D, E and F are Early KC patients and G, H and I are Mild KC patients. Patient A is a correctly classified 43-year-old female, who appears on the lower left end of the score line. Patient B is a 54-year-old male who is incorrectly classified as Early KC. Patient C is a 47-year-old male incorrectly classified as Mild KC. Patient D is a 30-year-old male who is incorrectly classified as healthy. Patient E is a correctly classified 36-year-old male. Patient F is a male aged 28 years and incorrectly classified as Mild KC. Patient G is a male aged 79 years and incorrectly classified as healthy. Patient H is a 57-year-old male incorrectly classified as Early KC. Patient I is male aged 52 and is correctly classified.

In essence, the GUI application has been created using an approachable design that it accessible from any network-connected terminal, no matter what computer, tablet or smartphone is used, it works with most widespread operative systems and does not involve having to install any driver or software, as long as the web browser is up-to-date. It also automatically adjusts the screen

layout to fit different screen sizes and orientations, which makes it more accessible and user-friendly.

Figure 10.

Discussion

Given the multifactorial nature of KC, early KC detection is usually approached by making an optimal evaluation of risk factors². However, the detection of KC in its primary pre-clinical forms remains a clinical challenge as most research works present models based on a wide variety of parameters that strongly depend on the characteristics of the analysed sample⁴. Several robust predictive models have been published in the scientific literature for detecting incipient KC manifestations, although the fact that their standardisation is lacking makes their comparison difficult.

322

323 One of the main problems that ophthalmologists currently encounter is that experts do not reach
324 an agreement about how early corneal ectasia should be characterised⁵⁻¹¹. This is due to the
325 ambiguity surrounding the disease definition in its pre-clinical phase^{4,8}, the size of the samples
326 used for these studies⁴, and the fact that most of the indices employed for disease detection are
327 technology-specific, which renders them non-interchangeable^{4,28}. Hallak and Azar have seen a
328 possible solution to this problem in artificial intelligence (AI), as they consider that “AI will
329 help with screening patients, improving diagnoses, and suggesting personalized treatments.”²⁹

330

331 Therefore, in this study we define a predictive model based on a set of optimal demographic-
332 optical-geometric factors measured by only one technology, which allows to not only assess the
333 current degree of disease development according to the level of patients’ visual limitation, but to
334 also define the probability of correctly classified each case. As far as the authors know, no
335 previous studies have successfully combined demographic, optical, pachymetric and
336 morphogeometric variables in a real-time environment to detect and classify healthy, early KC
337 and mild KC eyes.

338

339 Expressing the probability of correctly classifying a patient as a score involves several benefits.
340 First of all, reducing information from varied parameters of diverse natures in a single and
341 simple one to understand minimises the risk of overlooking important pieces of information. In
342 fact this risk can be quite high as typical analytical reports frequently comprise long lists of
343 different parameters on several pages that need to be read fairly quickly, and they rarely include
344 associated normality intervals.

345

346 This approach also allows the assessment of the joint action of diverse parameters. Detecting the
347 existence of a disease when a key parameter shows a significantly high or low value can be
348 easy, but detection becomes less evident when minor variations of several key parameters are
349 present. In this case, using a score may help ophthalmological professionals in their judgements

because it offers an objective and quantitative scale that ponders all possible parameter relations.

As seen in Table 7, the results of several research works, in which models were obtained by Scheimpflug technologies, fall in line with ours^{6,8,30}. Hwang et al.⁸ proposed an original detection model established by combining five parameters (index height decentration, index vertical asymmetry, pachymetry apex, inferior-superior value, Ambrosio's Relational Thickness Maximum variability) (AUC:0.86, Sensitivity: 83%, Specificity: 83%). Similar results have been obtained by other researchers^{6,30} for the model development phase, depending on the limited metrics of Scheimpflug technology.

Other researchers have relied on multivariate systems to jointly use two different technologies. Saad et al.¹⁰ created a model with 54 variables and six discriminant functions to obtain the model development phase, 93% sensitivity and 92% specificity. It was validated in a posterior study³¹, when its sensitivity and specificity values were 92% and 96%, respectively. These values are slightly better than those we obtained when discerning Ctrl (sensitivity 91%, specificity 80%) and mild KC (sensitivity 97%, specificity 89%), and considerably better than our results for the Early KC group (sensitivity 64%, specificity 80%). However, this model used two different technologies, while ours employs only one.

Other research works have proposed combining a set of different technologies³²⁻³⁴. In these cases however, the authors established a KC suspect profile of suffering KC in a later stage as they included subjects with manifest inferior steepening⁴.

The latest KC severity classification tendencies indicate the use of machine learning-based approaches. Yousefi et al.³⁵ resorted to an unsupervised machine learning analysis over 420 parameters to classify 3,156 eyes with only two eigen-parameters. They reported 97.7% sensitivity and 94.1% specificity. However, these values were obtained in comparison to the CASIA ESI Index, so they cannot be generalised to the parameters generated by other

technologies like Sirius or Pentacam. Moreover, clinical diagnosis labels were not available in their study, hence its accuracy could not be assessed. The same authors have recently taken this study even further, and have proposed a machine-learning model that predicts the likelihood of need for keratoplasty interventions³⁶. Lavric and Valentin³⁷ implemented an algorithm that uses convolutional neural networks to detect the presence of KC with an accuracy of 99.33%, but this method uses topographic pictures of merely the anterior cornea surface and, as the employed device was Pentacam, the results were valid only for this technology.

Our classifier uses an ordinal logistic regression model that combines 27 parameters to obtain an overall accuracy of 73% (95%CI: 65%–79%) in the training phase. This means that the model correctly classifies more than 70% of cases, and is particularly accurate for the Ctrl and Mild KC groups, whose accuracies ranged from 83% to 84%, respectively. The Early KC group presented the lowest accuracy (70%), with 26 cases of 61 incorrectly classified. This can be explained by the difficulty of detecting KC in its early development stages, motivated by the rigidity that corneal structure presents in corneal thickness terms when changing from a healthy scenario to a mild KC one, as the nine examples shown in Figure 10 demonstrate.

It should consider that this early-mild KC classifier has been trained by taking the diagnostics made by ophthalmological professionals as the “gold standard”, which unavoidably implies some undetermined amount of subjective information is taken to be certain. During the fitting procedure, the model attempts to find a generalisation that links predictors with prediction while maximising performance. Nonetheless, some cases may involve certain samples not matching any kind of generalisation given the subjective nature of the training data, which makes it difficult to establish a clear well-defined boundary between groups.

Uncertainty has always been considered consubstantial to medical practice³⁸. Eyes without a clear EMKLAS value for any of the groups (below 95%) could have been classified that way because they present some clinical particularities that make them different. Alternatively, they

may correspond to evolutive cases in which some parameters change more quickly than others. A prospective study of these cases would be necessary to set an accurate decision threshold for considering a case to be “KC-suspect”. In any case, when considering that wrongly classifying KC degrees is less important than classifying a diseased patient (Early or Mild) as healthy, the probabilities of belonging to both KC groups I and II can be summed in those uncertain cases to achieve the best diagnostic accuracy and, in line with the doctor’s criterion, any case suspected of suffering KC should be sent to clinical consultations for be further explored.

Consequently, the presence of certain lack of accuracy is something we can expect, and does not necessarily mean that the model fitting ability fails. Our model quantitatively confirms the difficulty of distinguishing between groups as the degree of misclassification between adjacent groups (Ctrl vs. Early KC, or Early KC vs. Mild KC) reaches 26.4% of incorrectly classified patients when combining false-positives and false-negatives which, thus, confirms the utility of our tool.

In this research, the ordinal detection model area under curve (AUC), specificity and sensitivity attained after the inner validation process suggest high performance, with AUC values of 0.87, 0.69 and 0.94 for the Ctrl, Early and Mild KC groups, respectively. The specificity and sensitivity figures are slightly better than those obtained in the training stage in all cases, except for specificity for the Ctrl group, which slightly lowered (see Table 5).

The independent validation of the ordinal logistic regression model showed an overall accuracy of 71% (95% CI: 55% – 84%), which suggests that even though the obtained quality figures were slightly lower (with accuracies of 79%, 69% and 80% for the Ctrl, Early and Mild KC groups, respectively), the results generally fall in line with those obtained in the internal bootstrap validation procedure, as Table 6 shows. This indicates that the model’s validated performance is fairly good, even though the decisions based on the ordinal logistic regression model should be made cautiously, and it would be advisable to repeat the model’s training process with a bigger independent sample to validate the results.

Our study also presents some limitations. Apart from the previously mentioned subjectivity induced by using the diagnostics made by ophthalmological professionals for model training as a “gold standard”, sample size was also limited by our inclusion criteria because we preferred to ensure that evaluated eyes were truly subclinical KC ones. It should also be taken into account that clinical metrics strongly depend on the technology used for their measure²⁸, thus our results can be considered valid only for those eyes tested using the Sirius tomographer (CSO, Italy).

In conclusion, in this work we have developed a GUI based on an ordinal logistic regression model that assesses the current degree of KC development, and defines the probability of correctly classifying each case. Our model correctly classified more than 70% of cases, and was particularly accurate for the Ctrl (79%) and Mild KC (80%) groups, while the accuracy of the Early KC group was considerably lower (69%). Thus by repeating the training process with a bigger sample using different data should be considered to improve the results. Although ordinal logistic regression is a widely used state-of-the-art tool in biomedical data research, other techniques, such as deep learning, can be used to improve the quality of the obtained results.

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Figures

Figure 1: Methodology proposed for generating the Early-Mild Keratoconus Classifier.

Figure 2: Correlation plot for quantitative variables. Colour indicates a positive or negative correlation.

Figure 3: Effects plot of the variables included in the ordinal logistic regression model. Age and Gender make a very small contribution, whereas BICAV, Q8mm and Posterior MTP deviation make an important and homogeneous contribution among groups.

Figure 4: Distribution of the scores generated by the ordinal logistic regression model over all the training set individuals. Each plot corresponds to the predicted group score, while each bean in a plot corresponds to a reference group. Beans show approximate distribution, and boxes indicate median and 25th and 75th quartiles. Each point corresponds to a patient.

Figure 5: Power analysis results for CDVA, Q8mm Posterior MTP Deviation, Age and Gender.

Figure 6: Application landing page showing the login form with a secured authentication layer.

Figure 7. Screenshot of a healthy individual (Ctrl) with the typical 3D virtual corneal model schematic representation.

Figure 8. Screenshot of an early KC individual (RETICS) with the typical 3D virtual corneal model schematic representation.

Figure 9. Screenshot of a mild KC individual (RETICS) with the typical 3D virtual corneal model schematic representation.

Figure 10. Screenshots representing all the possible classes in the model. The top row corresponds to true healthy individuals, predicted as healthy (A), early KC (B), and mild KC (C). The middle row corresponds to the true early KC individuals predicted as healthy (D), early KC (E), and mild KC (F). Finally, the bottom row refers to the true mild KC individuals predicted as healthy (G), early KC (H), and mild KC (I).

Median ± IQR	Total	Healthy	Early KC	Mild KC	p	p
Mean ± SD	N = 178	n = 74	n = 61	n = 43	Normality	Association
Age (years)	38.0 ± 22.3	41.0 ± 23.7	36.0 ± 21.0	46.2 ± 29.2	< 0.001	0.208
	39.6 ± 16.2	37.5 ± 14.9	40.5 ± 15.5	44.8 ± 19.2		
Gender: male (%)	63 (35.4)	32 (43.2)	16 (26.2)	15 (34.9)	-	0.120
female (%)	115 (64.6)	42 (56.8)	45 (73.8)	28 (65.1)		
Sphere	-0.51 ± 3.50	0.00 ± 3.56	-0.08 ± 2.01	-1.00 ± 3.13	< 0.001	0.018
	-1.82 ± 4.30	-0.86 ± 3.51	-0.81 ± 2.38	-2.53 ± 3.67		
Cylinder	-1.88 ± 2.50	-0.50 ± 1.00	-2.25 ± 2.14	-2.63 ± 1.64	< 0.001	< 0.001
	-2.02 ± 1.91	-0.65 ± 0.86	-2.24 ± 1.60	-2.95 ± 1.29		
Axis	75.8 ± 81.1	80.1 ± 88.7	85.0 ± 65.0	75.8 ± 60.8	< 0.001	0.117
	74.9 ± 55.3	66.8 ± 60.7	83.3 ± 50.9	84.4 ± 48.5		
CDVA	0.94 ± 0.37	1.00 ± 0.00	0.96 ± 0.09	0.72 ± 0.19	< 0.001	< 0.001
	0.80 ± 0.29	1.01 ± 0.05	0.95 ± 0.11	0.74 ± 0.11		
PIO	12.0 ± 4.0	15.9 ± 3.6	11.5 ± 1.0	12.8 ± 3.0	< 0.001	< 0.001
	13.3 ± 2.8	15.6 ± 2.8	11.7 ± 1.7	13.1 ± 2.0		
Total RMS	2.39 ± 2.88	0.81 ± 0.55	2.39 ± 1.58	3.38 ± 1.38	< 0.001	< 0.001
	3.02 ± 2.79	0.94 ± 0.69	2.55 ± 1.32	3.62 ± 1.65		
High-order	1.12 ± 1.96	0.41 ± 0.14	1.42 ± 1.18	2.04 ± 0.50	< 0.001	< 0.001
	1.88 ± 2.09	0.41 ± 0.11	1.46 ± 0.78	2.17 ± 0.86		
Astigmatism	1.59 ± 2.14	0.69 ± 0.65	1.61 ± 1.73	2.26 ± 1.41	< 0.001	< 0.001
	2.18 ± 2.06	0.79 ± 0.74	1.94 ± 1.32	2.77 ± 1.67		
Coma Z31	0.74 ± 1.78	0.25 ± 0.12	0.77 ± 1.16	1.66 ± 0.71	< 0.001	< 0.001
	1.54 ± 1.89	0.27 ± 0.12	1.09 ± 0.72	1.86 ± 0.84		
Spherical AbZ40	0.19 ± 0.32	0.21 ± 0.08	0.21 ± 0.34	0.10 ± 0.44	< 0.001	0.161
	0.01 ± 0.76	0.22 ± 0.06	0.14 ± 0.32	0.09 ± 0.24		
Coma-like	1.05 ± 1.98	0.32 ± 0.16	1.29 ± 1.20	1.93 ± 0.57	< 0.001	< 0.001
	1.72 ± 1.94	0.32 ± 0.12	1.33 ± 0.76	2.06 ± 0.83		
Spherical-like	0.43 ± 0.47	0.22 ± 0.08	0.49 ± 0.34	0.61 ± 0.34	< 0.001	< 0.001
	0.64 ± 0.82	0.23 ± 0.05	0.55 ± 0.30	0.59 ± 0.27		
Q8mm	-0.48 ± 0.81	-0.26 ± 0.21	-0.43 ± 0.76	-0.74 ± 0.79	< 0.001	< 0.001
	-0.61 ± 0.65	-0.27 ± 0.19	-0.44 ± 0.62	-0.71 ± 0.47		
Central thickness	507 ± 73	547 ± 46	500 ± 48	468 ± 51	0.081	< 0.001
	499 ± 58	545 ± 31	499 ± 34	480 ± 34		
Temporal	543 ± 65	585 ± 43	534 ± 58	515 ± 51	0.188	< 0.001
	544 ± 48	578 ± 32	351 ± 38	524 ± 34		
Nasal	577 ± 65	617 ± 50	566 ± 61	562 ± 34	0.709	< 0.001
	579 ± 45	612 ± 36	563 ± 39	568 ± 37		
Superior	588 ± 72	632 ± 42	585 ± 59	560 ± 39	0.031	< 0.001
	589 ± 48	625 ± 36	574 ± 42	573 ± 32		
Inferior	560 ± 60	597 ± 51	553 ± 63	553 ± 29	0.265	< 0.001
	559 ± 53	596 ± 34	543 ± 41	547 ± 33		
Volume	24.4 ± 2.7	26.2 ± 2.1	23.9 ± 1.17	23.5 ± 1.6	0.069	< 0.001
	24.7 ± 1.9	25.9 ± 1.5	24.1 ± 1.46	23.9 ± 1.2		
Anterior area	43.2 ± 0.4	43.1 ± 0.2	43.3 ± 0.3	43.3 ± 0.2	0.005	< 0.001
	43.2 ± 0.5	43.1 ± 0.1	43.3 ± 0.2	43.3 ± 0.2		
Posterior area	44.5 ± 0.6	44.3 ± 0.3	44.6 ± 0.5	44.7 ± 0.5	0.063	< 0.001
	44.7 ± 0.8	44.3 ± 0.3	44.5 ± 0.3	44.7 ± 0.3		
Anterior apex deviation	7.4e-5 ± 6.5e-3	0.0 ± 0.0	2.4e-4 ± 3.2e-3	2.3e-3 ± 1.2e-2	< 0.001	< 0.001
	7.4e-3 ± 1.4e-2	2.7e-4 ± 8.8e-4	3.3e-3 ± 6.5e-3	8.1e-3 ± 0.1e-2		
Posterior apex deviation	0.12 ± 0.12	0.07 ± 0.03	0.14 ± 0.09	0.17 ± 0.11	< 0.001	< 0.001
	0.15 ± 0.09	0.07 ± 0.02	0.16 ± 0.08	0.19 ± 0.08		
Anterior minimal thickness point deviation	0.90 ± 0.38	0.83 ± 0.30	0.97 ± 0.41	1.01 ± 0.52	< 0.001	0.003
	0.95 ± 0.36	0.86 ± 0.30	1.01 ± 0.39	1.05 ± 0.34		
Posterior minimal thickness point deviation	0.83 ± 0.35	0.77 ± 0.27	0.88 ± 0.37	0.92 ± 0.47	< 0.001	0.002
	0.87 ± 0.33	0.80 ± 0.28	0.94 ± 0.36	0.98 ± 0.32		

581

582 Table 1. Demographic, clinical and morphogeometric parameters segregated into healthy (Ctrl) and early
583 KC and mild KC patients. The corresponding p-values for a Kruskal-Wallis univariate association test for
584 each variable between groups are also shown.

	Coef.	Std. error	t	p	OR (95% CI)
Age	-0.009	0.011	-0.834	0.404	0.099 (0.970 – 1.013)
Gender	0.361	0.350	1.033	0.302	1.435 (0.073 – 2.872)
CDVA	-15.059	2.150	-7.005	< 0.001	2.88e-7 (3.02e-9 – 1.47e-5)
Q8mm	-1.491	0.444	-3.360	0.001	0.225 (0.091 – 0.523)
Posterior MTP deviation	2.511	0.663	3.787	< 0.001	12.32 (3.59 – 48.52)

Table 2. Ordinal logistic regression model summary showing the remaining variables after applying a backward stepwise procedure using the Akaike information criterion (AIC): CDVA, Q8mm and Posterior MTP deviation, plus age and gender. Coefficients, corresponding standard error, t and p values, and odds ratios with 95% confidence intervals for each variable, are included.

Predicted	Ctrl	Early KC	Mild KC
Ctrl	63	18	1
Early KC	10	35	11
Mild KC	1	8	31

Table 3. Training confusion matrix corresponding to the ordinal logistic regression model.

	Ctrl	Early KC	Mild KC
Sensitivity	0.85	0.57	0.72
Specificity	0.82	0.82	0.93
Balanced accuracy	0.83	0.70	0.83

Table 4. Ordinal logistic regression model training the sensitivity, specificity and balanced accuracy results. Overall accuracy is 73%, with a 95% confidence interval of 65%-79%. McNemar's test indicates homogeneous results (p=0.430).

	Ctrl	Early KC	Mild KC
AUC	0.87 ± 0.04	0.69 ± 0.06	0.94 ± 0.03
Sensitivity	0.91 ± 0.06	0.63 ± 0.12	0.97 ± 0.04
Specificity	0.80 ± 0.08	0.80 ± 0.12	0.89 ± 0.04

Table 5. Inner validation scores in terms of the sensitivity and specificity obtained using 100 bootstrap samples. AUC: Area Under Curve

	Ctrl	Early KC	Mild KC
Sensitivity	0.84	0.57	0.63
Specificity	0.73	0.82	0.97
Balanced accuracy	0.79	0.69	0.80

Table 6. Ordinal logistic regression model independent external validation scores in terms of the sensitivity, specificity and balanced accuracy obtained from 41 new samples (19 healthy individuals, 14 RETICS grade I and 8 RETICS grade II). Overall accuracy is 71%, with a 95% confidence interval of 55%-84%. McNemar's test indicates homogeneous results (p = 0.112).

Studies by and Year	Sample size (eyes)		Technology used & degree of KC detected / classified	Total parameters considered / Best parameters used	Area Under Curve	Sensitivity %	Specificity %
	KC group	Control group					
Current study	74	104	Sirius Scheimpflug Tomography + Geometric Modelling. Detects Early and Mild KC Classifies according to RETICS scale (Grade I to grade IV+),	Combination of 27 demographic, clinical, pachymetric and geometric parameters. Age, Gender, CDVA, Q _{8mm} and Posterior MCT Point Deviation.	Healthy 0.87 (Training) Early KC 0.69 (Training) Mild KC 0.94 (Training)	Healthy 84 Early KC 57 Mild KC 63	Healthy 73 Early KC 82 Mild KC 97
Hwang <i>et al</i> 2018 ⁸	30	60 (Post-LASIK)	Pentacam Scheimpflug Tomography and spectral-domain (SD) OCT imaging Detects asymmetric KC eyes (pre-clinical) No classification.	Combines 9 Tomography with 15 OCT variables 5 Scheimpflug variables 13 variables from both Scheimpflug and SD-OCT devices	Not mentioned 83 100	83 100	
Shajari <i>et al</i> 2018 ³⁰	27 (unilateral KC in fellow eye)	50	Pentacam Scheimpflug Tomography Detects asymptomatic Early KC No classification.	18 variables from Scheimpflug device Index of height decentration (IHD) and index of vertical Asymmetry (IHA)	0.79 (IHD) 0.72 (IHA)	Not mentioned	Not mentioned
Saad <i>et al</i> 2010 ¹⁰ 2012 ³¹	40 FFKC + 31 KC	72	Orbscan IIz and OPD-Scan Detects FFKC (Early) and KC (Mild) No classification.	54 variables and 6 discriminant functions	N vs. FFKC 0.98 N vs. KC 0.99	N vs. FFKC 93 N vs. KC 97	N vs. FFKC 0.92 N vs. KC 100
Qin <i>et al</i> 2013 ³²	84	67	RTVue Fourier-domain OCT Detects clinical KC No classification.	5 pachymetric variables Logistic regression formula	0.98	90.5	95.0
Rabinowitz <i>et al</i> 2014 ³³	46 moderate 54 early 7 FFKC 16 suspect	180	TMS-4 videokeratographer, RTVue Fourier-domain OCT and Hartmann-Shack aberrometer. Detects and classifies Normal, FFKC, Suspect, Early and Moderate KC	A combination of videokeratography and OCT indices (I-S value and Minimum pachymetry) and PA/I-S index	Not mentioned	Moderate 100 Early 100 FFKC 100 Suspect 63	Moderate 100 Early 100 FFKC 97 Suspect 98
Silverman <i>et al</i> 2017 ³⁴	30	111	Pentacam Scheimpflug Tomography and Artemis very-high-frequency ultrasound. Detects clinical KC	105 Artemis and 96 Pentacam variables Combination of 3 Artemis and 4 Pentacam parameters.	>0.99	97	100
Yousefi <i>et al</i> 2018 ³⁵	796 FFKC 390 KC	1970	Casia OCT. Detects FFKC (Early) and KC (Mild) Four clusters according to the Casia ESI index and diagnostic labelling convention	420 parameters Two eigen-parameters.	Not mentioned	N vs. KC 97	N vs. KC 96

605

606 Table 7. Comparison of the current study with previous published studies as regards sample size,
607 technology used, degree of detected KC, number of parameters considered, best diagnostic parameter(s)
608 and sensitivity/specificity values.

609 **N**= Normal, **KC**= Keratoconus, **OCT**= Optical Coherence Tomography, **CDVA**= Corrected distance visual acuity, **MCT**=
610 minimum corneal thickness, **FFKC**= Forme fruste keratoconus, **ESI**= Ectasia Status Index, **PAI-S** =
611 Pachymetry/Asymmetry Index, **I-S**= inferior-superior keratometric difference, **RETICS**= Thematic Network for Co-
612 Operative Research in Health