Universidad de Valladolid

Escuela de Doctorado Universidad de Valladolid

PROGRAMA DE DOCTORADO EN CIENCIAS DE LA VISIÓN

TESIS DOCTORAL:

DESARROLLO DE UNA GUÍA CLÍNICA BASADA EN LA EVIDENCIA PARA LA ADAPTACIÓN DE LENTES DE CONTACTO PERMEABLES AL GAS DE DISEÑO CORNEAL EN QUERATOCONO

DEVELOPMENT OF AN EVIDENCE-BASED CLINICAL PRACTICE GUIDELINE TO FIT CORNEAL GAS PERMEABLE CONTACT LENSES IN KERATOCONUS

Presentada por Dña. Sara Ortiz Toquero para optar al grado de Doctora por la Universidad de Valladolid

Dirigida por:
Dr. Raúl Martín Herranz

Universidad de Valladolid

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Impreso 1T

AUTORIZACIÓN DEL DIRECTOR DE TESIS

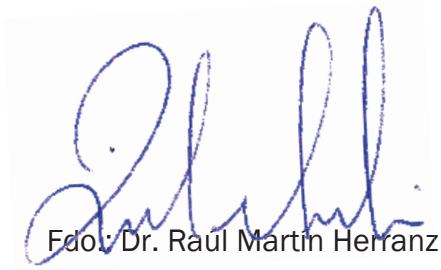
(Art. 7.2 de la Normativa para la presentación y defensa de la Tesis Doctoral en la UVa)

D. RAÚL MARTÍN HERRANZ, con D.N.I. 50.447.910-D, Investigador principal del Grupo de Investigación en Optometría del Instituto Universitario de Oftalmobiología Aplicada de la Universidad de Valladolid (IOBA) y Profesor Contratado Doctor del Departamento de Física Teórica, Atómica y Óptica de la Facultad de Ciencias de la Universidad de Valladolid, con dirección a efecto de notificaciones "Campus Miguel Delibes. Paseo de Belén 7, 47011, Valladolid" y con e-mail "raul@ioba.med.uva.es", como Director de la Tesis Doctoral titulada **"Desarrollo de una guía clínica basada en la evidencia para la adaptación de lentes de contacto permeables al gas de diseño corneal en queratocono"** realizada por Dª Sara Ortiz Toquero, alumna del Programa de Doctorado en Ciencias de la Visión impartido por el IOBA,

AUTORIZA su presentación, considerando que es APTA para su defensa.

Valladolid, 14 de marzo de 2017

El Director de la Tesis,



Fdo: Dr. Raúl Martín Herranz

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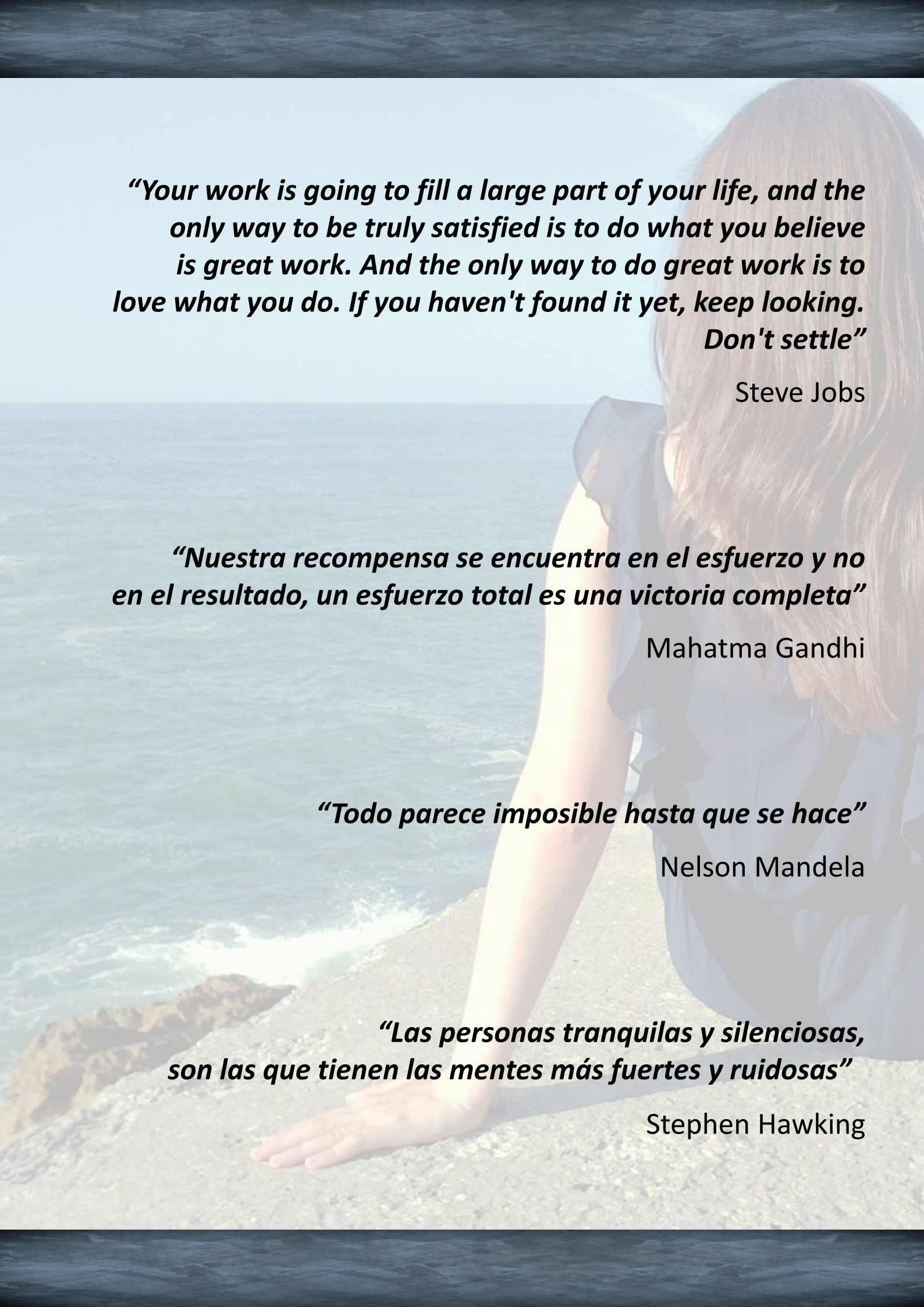
A mi abuela Vicenta

Ahora ya sí que me puedes llamar "doctora"

A mi sobrino Joaquín

No pierdas nunca esa sonrisa que nos ilumina el camino a todos. No hay nada más bonito que redescubrir el mundo a través de tus ojos



“Your work is going to fill a large part of your life, and the only way to be truly satisfied is to do what you believe is great work. And the only way to do great work is to love what you do. If you haven't found it yet, keep looking. Don't settle”

Steve Jobs

“Nuestra recompensa se encuentra en el esfuerzo y no en el resultado, un esfuerzo total es una victoria completa”

Mahatma Gandhi

“Todo parece imposible hasta que se hace”

Nelson Mandela

“Las personas tranquilas y silenciosas, son las que tienen las mentes más fuertes y ruidosas”

Stephen Hawking

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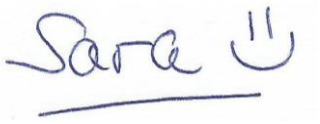

Instituciones participantes

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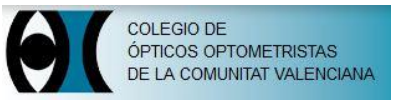
Hospital Universitario Valladolid	**Hospital Clínico Universitario de Valladolid** *Dr. José María Herreras / Dr. David Galarreta (por el diagnóstico y derivación de los pacientes)*
COOCYL Colegio de Ópticos Optometristas Castilla y León	**Colegio de Ópticos Optometristas de Castilla y León** *(por la distribución de la encuesta entre sus colegiados y por su apoyo incondicional)*
Colegio Nacional de Opticos-Optometristas	**Delegaciones Regionales del Colegio Nacional de Ópticos Optometristas (Aragón, Asturias, Canarias, Cantabria, Galicia, País Vasco)** *(por la distribución de la encuesta entre sus colegiados)*
COOOC Col·legi Oficial d'Òptics Optometristes de Catalunya	**Colegio Oficial de Ópticos Optometristas de Cataluña** *(por la distribución de la encuesta entre sus colegiados)*

	**Colegio de Ópticos Optometristas de la Comunidad Valenciana** *(por la distribución de la encuesta entre sus colegiados)*
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	**Universitá del Salento (Italia)** *D. Giancarlo Montani (por la evaluación de la Guía)*
	**Universidade do Minho (Portugal)** *Dr. José M González-Méijome (por la evaluación de la Guía)*
	**Visser Contactlenzen (Holanda)** *D. Henny Otten (por la evaluación de la Guía)*
	**Universidad Complutense de Madrid** *Dr. Gonzalo Carracedo (por la evaluación de la Guía)*
	**Universidad Europea de Madrid** *Dr. César Villa (por la evaluación de la Guía)*
	**Universidad de Alicante** *Dr. David Piñero (por la evaluación de la Guía)*

Currículum Vitae

Sara Ortiz Toquero

- Diplomada en Óptica y Optometría por la Universidad de Valladolid (2010).
- Máster en Optometría y Ciencias de la Visión por la Universidad de Valladolid (2011).
- Máster en Investigación en Ciencias de la Visión por la Universidad de Valladolid (2012).
- Investigadora predoctoral en el Grupo de Investigación en Optometría del Instituto de Oftalmobiología Aplicada (IOBA) - Departamento de Física Teórica Atómica y Óptica de la Universidad de Valladolid (2013-2017).
- Publicaciones: 11 artículos científicos en revistas indexadas, 4 artículos en revistas no indexadas nacionales e internacionales y 3 capítulos de libro.
- Comunicaciones: Más de 30 comunicaciones en congresos nacionales e internacionales.
- Estancias: Plymouth University. Plymouth, Reino Unido (Enero 16 – Abril 16).

- *Degree in Optometry. University of Valladolid. Spain (2010).*
- *Master in Optometry and Vision Sciences. University of Valladolid. Spain (2011).*
- *Master in Research Vision Sciences. University of Valladolid. Spain (2012).*
- *Predoctoral Researcher of the Optometry Research Group of the IOBA Eye Institute and Department of Theoretical Physics, Atomic and Optics of the University of Valladolid (Spain) (2013-2017).*
- *Publications: 11 scientific articles in indexed journals, 4 scientific articles in non-indexed national and international journals and 3 book chapters.*
- *Presentations: More than 30 presentations in national and international congresses.*
- *Predoctoral stays: Plymouth University. Plymouth, UK (Jan 2016 to Apr 2016).*

Difusión de los resultados

Esta tesis doctoral ha dado lugar a diferentes resultados entre los que destacan la transferencia a la industria, publicaciones (artículos y capítulos de libro), presentaciones a congresos, premios y páginas web (que se presentan por orden cronológico).

Propiedad industrial e intelectual

1. Contrato de licencia de explotación del nomograma para el cálculo de los parámetros de la primera lente de prueba con la empresa Conóptica SL (España) como licenciatario. 18 de Febrero de 2015.

2. Registro de la propiedad intelectual Nº VA-321-2016 del *software para la adaptación de lentes de contacto en pacientes con queratocono*. Autores: Sara Ortiz Toquero, Raúl Martín Herranz, Paula Cardeñoso Gigosos, Guadalupe Rodríguez Zarzuelo y Victoria de Juan Herráez. 10 de octubre de 2016.

Publicaciones

1. Ortiz-Toquero S, Rodriguez G, De Juan V, Martin R. *Repeatability of Placido-Based corneal topography in keratoconus*. Optom Vis Sci. 2014; 91: 1467–73. (**Índice de impacto: JCR Q3 – 1,603**).

2. Ortiz-Toquero S, Rodriguez G, De Juan V, Martin R. *Rigid gas permeable contact lens fitting using new software in keratoconic eyes*. Optom Vis Sci. 2016; 93: 286–92. (**Índice de impacto: JCR Q3 – 1,442**).

3. Ortiz-Toquero S, Martin M, Rodriguez G, De Juan V, Martin R. *Success of rigid gas permeable contact lens fitting*. Eye Contact Lens. 2016; In Press. doi: 10.1097/ICL.0000000000000254 (**Índice de impacto: JCR Q3 – 1,466**).

4. Ortiz-Toquero S, Perez S, Rodriguez G, De Juan V, Mayo-Iscar A, Martin R. *The influence of the refractive correction on the Vision-Related Quality of Life in keratoconus patients*. Qual Life Res. 2016; 25: 1043–51. (**Índice de impacto: JCR Q2 – 2,486**).

5. Ortiz-Toquero S, Rodriguez G, De Juan V, Martin R. *Repeatability of wavefront aberration measurements with a Placido-Based topographer in normal and keratoconic eyes*. J Refract Surg. 2016; 32: 338–344. (**Índice de impacto: JCR Q1 – 3,468**).

6. Ortiz-Toquero S, Zuñiga V, Rodriguez G, de Juan V, Martin R. *Agreement of corneal measurements between dual rotation Scheimpflug-Placido system and Placido-based topography device in normal and keratoconus eyes*. J Cataract Refract Surg. 2016; 42: 1198–1206. (**Índice de impacto: JCR Q1 – 3,020**).

7. Ortiz-Toquero S, Martin R. *Fitting gas permeable contact lens in keratoconus, still a challenge?* Ophthalmol Open J. 2016; 1: e9-e12. doi:10.17140/OOJ-1-e004.

8. Ortiz-Toquero S, Martin R. *Keratoconus screening in primary eye care – A general overview*. European Ophthalmic Review, 2016; 10: 80–85.

9. Ortiz-Toquero S, Rodriguez G, De Juan V, Martin R. *New web-based algorithm to improve rigid gas permeable contact lens fitting in keratoconus*. Cont Lens Anterior Eye. 2017; In Press (**Índice de impacto: JCR Q3 – 1,752**).

10. Ortiz-Toquero S, Martin R. *Current optometric practices and attitudes in keratoconus patient management*. Cont Lens Anterior Eye. 2017; In Press (**Índice de impacto: JCR Q3 – 1,752**).

11. Ortiz-Toquero S, Rodriguez G, De Juan V, Martin R. *Gas permeable contact lens fitting in keratoconus: comparison of different guidelines to BOZR calculation*. Cont Lens Anterior Eye. 2017; 1ª revisión.

12. Ortiz-Toquero S, Martin R. *The usefulness of the anterior coma aberration in keratoconus severity classification*. Cont Lens Anterior Eye. 2017; 1ª revisión.

13. JL Garrido, J Gispets, R Martin, S Ortiz, FJ Vivó. *Acuerdo entre expertos en el cálculo de lentes de contacto gas permeables de queratocono*. Gaceta de Optometría y Óptica Oftálmica. 2017; Aceptado.

Comunicaciones en congresos

1. **European Academy of Optometry and Optics´ Annual Conference 2013**. Comunicación en póster: *Number of visits and diagnostic lenses in keratoconus, RGP and soft contact lenses*. Ortiz S, de Juan V, Rodriguez G, Alonso E, Martin R. Málaga (España), 2013.

2. **XXXI European Society of Cataract & Refractive Surgeons (ESCRS) Annual Congress**. Comunicación en póster: *Allegro Topolyzer keratoconus diagnosis with Placido-based corneal topographic indices: repeatability in healthy versus keratoconus eyes*. Ortiz S, de Juan V, Rodriguez G, Galarreta D, Martin R. Ámsterdam (Holanda), 2013.

3. **23 Congreso Internacional de Optometría, Contactología y Óptica Oftálmica - OPTOM 2014**. Comunicación oral: *¿Es posible cambiar la tendencia en la adaptación de lentes de contacto? experiencia en un centro universitario*. G Rodríguez, S Ortiz-Toquero, V De Juan, R Martín. Madrid (España), 2014.

4. **23 Congreso Internacional de Optometría, Contactología y Óptica Oftálmica - OPTOM 2014**. Comunicación en póster: *Repetibilidad del topógrafo Oculus Keratograph® en queratoconos.* S Ortiz-Toquero, G Rodríguez, V De Juan, R Martín. Madrid (España), 2014.

5. **23 Congreso Internacional de Optometría, Contactología y Óptica Oftálmica - OPTOM 2014**. Comunicación oral: *Comparación del número de pruebas y visitas necesarias para adaptar lentes de contacto en queratoconos frente a rígidas permeables al gas convencionales e hidrofílicas*. S Ortiz-Toquero, G Rodríguez, V De Juan, R Martín Herranz. Madrid (España), 2014.

6. **II Congreso Internacional Online de Jóvenes Optometristas - SIYO 2014**. Comunicación en póster: *Calidad de vida en pacientes con queratocono*. S Pérez, S Ortiz-Toquero, R Martín. Valencia (España), 2014.

7. **II Congreso Internacional Online de Jóvenes Optometristas - SIYO 2014**. Comunicación en póster: *Repeatability and agreement of new contact lens fitting software in normal and keratoconus eyes*. S Ortiz-Toquero, G Rodríguez, V De Juan, R Martín. Valencia (España), 2014.

8. **British Contact Lens Association (BCLA) 2015 Clinical Conference**. Comunicación en póster: *Assessment of vision-related quality of life in keratoconus patients: influence of spectacles versus RGP contact lenses wear*. Martin R, Ortiz-Toquero S, Perez S, Rodriguez G, De Juan V. Liverpool (Reino Unido), 2015.

9. **British Contact Lens Association (BCLA) 2015 Clinical Conference**. Comunicación en póster: *Clinical evaluation of new topography-based contact lens-fitting software to predict the contact lens parameters in normal and keratoconus eyes*. Ortiz-Toquero S, Rodriguez G, De Juan V, Martin R. Liverpool (Reino Unido), 2015.

10. **XXXIII Congress of the European Society of Cataract & Refractive Surgeons (ESCRS)**. Comunicación en póster: *Agreement of anterior corneal curvature assesment between Placido topography and Scheimpflug topography in healthy and keratoconus eyes*. Ortiz-Toquero S, Zuniga V, de Juan V, Rodriguez G, Galarreta D, Martin R. Barcelona (España), 2015.

11. **XXXIII Congress of the European Society of Cataract & Refractive Surgeons (ESCRS)**. Comunicación en póster: *Intrasubject repeatability of higher-order aberrations in healthy and keratoconus eyes with Allegro-Topolyzer*. Rodriguez G, Martin R, Ortiz-Toquero S, de Juan V, Galarreta D. Barcelona (España), 2015.

12. **24 Congreso Internacional de Optometría, Contactología y Óptica Oftálmica - OPTOM 2016**. Comunicación oral: *Cálculo y validación de un nuevo nomograma de adaptación de lentes de contacto en queratoconos*. S Ortiz-Toquero, G Rodríguez, V De Juan, R Martín. Madrid (España), 2016.

13. **24 Congreso Internacional de Optometría, Contactología y Óptica Oftálmica - OPTOM 2016**. Comunicación en póster: *Aberraciones de alto orden en ojos con queratocono: repetibilidad y método de clasificación*. S Ortiz-Toquero, G Rodríguez, V De Juan, R Martín. Madrid (España), 2016.

14. **24 Congreso Internacional de Optometría, Contactología y Óptica Oftálmica - OPTOM 2016**. Comunicación en póster: *Estudio del grado de acuerdo entre expertos en el cálculo de lentes de contacto gas permeable de queratocono*. JL Garrido, J Gispets, R Martín, S Ortiz-Toquero, FJ Vivó. Madrid (España), 2016.

15. **24 Congreso Internacional de Optometría, Contactología y Óptica Oftálmica - OPTOM 2016**. Comunicación oral: *Tasa de éxito de la adaptación de lentes de contacto rígidas permeables al gas*. G Rodríguez, S Ortiz-Toquero, M Martín, V De Juan, R Martín. Madrid (España), 2016.

16. **I Galería de Innovación Científica y Tecnológica. ExpoÓptica 2016.** Comunicación en póster: *Calculens. Nomograma para la adaptación de lentes de contacto RPG en córneas con queratocono.* S Ortiz-Toquero, G Rodríguez, V De Juan, R Martín. Madrid (España), 2016.

17. **European Academy of Optometry and Optics´ Annual Conference 2016.** Comunicación en póster: *Improvement GP contact lens fitting in keratoconus eyes using the CL fitting software of Oculus Keratograph*. R Martin, S Ortiz-Toquero, G Rodriguez, V de Juan, I Sanchez. Berlín (Alemania), 2016.

18. **European Academy of Optometry and Optics´ Annual Conference 2016.** Comunicación en póster: *Development of an Open Access App to GP contact lens fitting in keratoconus*. S Ortiz-Toquero, G Rodriguez, V de Juan, I Sanchez, R Martin. Berlín (Alemania), 2016.

19. **I Jornada de Investigadores Predoctorales de la Universidad de Valladolid en Ciencias de la Visión**. Comunicación oral: *Desarrollo de una guía clínica basada en la evidencia para la adaptación de lentes de contacto gas permeable en pacientes con queratocono*. S Ortiz-Toquero. Valladolid (España), 2016.

20. **XXXIV Congress of the European Society of Cataract & Refractive Surgeons (ESCRS)**. Comunicación en póster: *Effect of keratoconus severity and cone location in corneal diameter, anterior chamber depth and anterior chamber volume*. Ortiz-Toquero S, de Juan V, Rodriguez G, Galarreta D, Martin R. Copenhague (Dinamarca), 2016.

21. **European Academy of Optometry and Optics´ Annual Conference 2017.** Comunicación en póster: *Comparison of the anterior coma aberration in different keratoconus stages to improve the Amsler-Krumeich keratoconus classification*. Martin R, Ortiz-Toquero S. 12-14 de mayo de 2017. Barcelona (España). *Aceptado*

22. **European Academy of Optometry and Optics´ Annual Conference 2017.** Comunicación en póster: *Optometric practice attitudes in keratoconus patient management: UK versus Spain*. Ortiz-Toquero S, Martin R. 12-14 de mayo de 2017. Barcelona (España). *Aceptado*

23. **European Academy of Optometry and Optics´ Annual Conference 2017.** Comunicación en póster: *Comparison of different gas permeable contact lenses fitting guidelines in keratoconus.* Ortiz-Toquero S, Rodriguez G, de Juan V, Martin R. 12-14 de mayo de 2017. Barcelona (España). *Aceptado*

Capítulos de libro

1. Martín R, Ortiz S, Rodríguez G, de Juan V. *Guía Clínica para la Adaptación de Lentes de Contacto.* Pág. 25-48 En Gene A, et al. "**Temas actuales en Optometría**". Ediciones MC. ISBN: 84-943550-5-8. 2016. Valencia (España).

2. Ortiz S, Rodriguez G, de Juan V, Martín R. *Repeatability and agreement of a new contact lens fitting software in normal and keratoconus eyes.* Pág. 15-18 En Gene A, et al. "**Temas actuales en Optometría 2**". Ediciones MC. ISBN: 84-943550-8-2. 2016. Valencia (España).

3. Pérez S, Ortiz S, Martín R. *Calidad de vida en pacientes con queratocono.* Pág. 40-43 En Gene A, et al. "**Temas actuales en Optometría 2**". Ediciones MC. ISBN: 84-943550-8-2. 2016. Valencia (España).

Premios

1. Premio PROMETEO otorgado por la Fundación General de la Universidad de Valladolid por el proyecto: "*Software para la adaptación de lentes de contacto en pacientes con queratocono*". Autores: Sara Ortiz, Paula Cardeñoso, Guadalupe Rodríguez, Victoria de Juan, Raúl Martín. Abril, 2016.

2. Premio a la mejor comunicación oral en la I Jornada de Investigadores Predoctorales de la Universidad de Valladolid en Ciencias de la Visión con la presentación del proyecto de tesis "*Desarrollo de una guía clínica basada en la evidencia para la adaptación de lentes de contacto gas permeable en pacientes con queratocono*". Junio, 2016.

3. Premio a la mejor comunicación oral en el Día del IOBA de la Universidad de Valladolid por la ponencia "*Desarrollo de una guía clínica basada en la evidencia para la adaptación de lentes de contacto gas permeable en pacientes con queratocono*". Diciembre, 2016.

Páginas web

1. Web de acceso libre **www.calculens.com** para facilitar la adaptación de lentes de contacto. Autores: Sara Ortiz, Guadalupe Rodríguez, Victoria de Juan, Raúl Martín. Julio, 2016.

Financiación

Este trabajo de investigación ha contado con la siguiente financiación:

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2. Conóptica S.L. Cesión de las lentes de contacto gas permeable con diseño específico para queratocono utilizadas en este proyecto de investigación.

3. Ayudas por la asistencia a cursos, congresos y jornadas relevantes, para el desarrollo de tesis doctorales de la Universidad de Valladolid. Convocatoria 2013.

4. Ayudas por la asistencia a cursos, congresos y jornadas relevantes, para el desarrollo de tesis doctorales de la Universidad de Valladolid. Convocatoria 2015.

5. Ayudas para estancias breves en el desarrollo de tesis doctorales de la Universidad de Valladolid. Convocatoria 2016.

6. Convocatoria Lanzadera TC 2015. Fundación General de la Universidad de Valladolid.

Capítulo 0

Índice

Organización de la tesis

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Índice

Organización de la tesis

Esta memoria de tesis doctoral se presenta en la modalidad de compendio de publicaciones y opta a la Mención Internacional en el título de Doctor. Por lo tanto, su organización se ajusta a lo requerido por el reglamento aprobado por el Consejo de Gobierno de la Universidad de Valladolid, incluyendo una síntesis general, tanto en castellano como en inglés, donde se justifica la relación temática del trabajo de investigación y se presentan los objetivos alcanzados, la metodología empleada, los resultados y la discusión global del trabajo, seguida de un cuerpo formado por los distintos artículos a los que ha dado lugar y finamente las conclusiones extraídas. Además, cumpliendo la citada normativa, se aporta el certificado de la estancia internacional de tres meses de duración realizada en la School of Health Professions de la Universidad de Plymouth (Reino Unido).

Esta memoria de tesis incluye ocho artículos que han sido publicados o aceptados en revistas científicas indexadas en el Journal Citation Reports con índice de impacto (**Capítulos 3, 4.1, 4.2, 4.3, 5.1, 5.2, 5.3 y 6.1**), así como el borrador de dos artículos que se encuentran en fase de revisión (**Capítulos 5.4 y 6.2**) y finalmente el **Capítulo 7** presenta resultados que se prevé sean publicados igualmente en un futuro. Adicionalmente se han incluido otros dos artículos de revisión que han sido publicados en revistas no indexadas (**Capítulos 4.4 y 5.5**).

La memoria de esta tesis doctoral se ha estructurado en un total de 10 capítulos (Figura 0). Los **Capítulos 1 y 2** están compuestos por la síntesis general de la tesis tanto en castellano como en inglés respectivamente. Cada capítulo incluye además una sección, a modo de introducción general, dedicada al estado actual de la detección y manejo de los pacientes con queratocono.

Tras la síntesis general, los **Capítulos 3, 4, 5 y 6** presentan de forma agrupada en función de su temática los doce artículos a los que la tesis ha dado lugar, indicando los ya publicados o los que se encuentran en fase de revisión y en último lugar el **Capítulo 7** que será preparado en breve. Este orden de presentación persigue facilitar la comprensión del trabajo realizado en esta tesis doctoral que aborda la adaptación de lentes de contacto rígidas permeable al gas (LC RPG) de diseño corneal en pacientes con queratocono. Para facilitar al lector la información presentada en esta tesis se presenta una síntesis del contenido de cada uno de estos capítulos:

- El **Capítulo 3** está formado por un único artículo *(Ortiz-Toquero, et al. The influence of the refractive correction on the vision-related quality of life in keratoconus patients. Qual Life Res; 2016)* en el que se demuestra el impacto que tiene la corrección óptica (uso de gafas o el porte de LC) en la calidad de vida de los pacientes con queratocono comparándolo con un grupo control de sujetos sanos.

- El **Capítulo 4**, está formado por cuatro subcapítulos (4.1, 4.2, 4.3 y 4.4), que analizan el estado actual del proceso de adaptación de LC RPG en pacientes con queratocono. El **Capítulo 4.1** *(Ortiz-Toquero, et al. Success of rigid gas permeable contact lens fitting. Eye & Contact Lens; 2016)* determina la tasa de éxito en la adaptación de LC RPG, tanto en

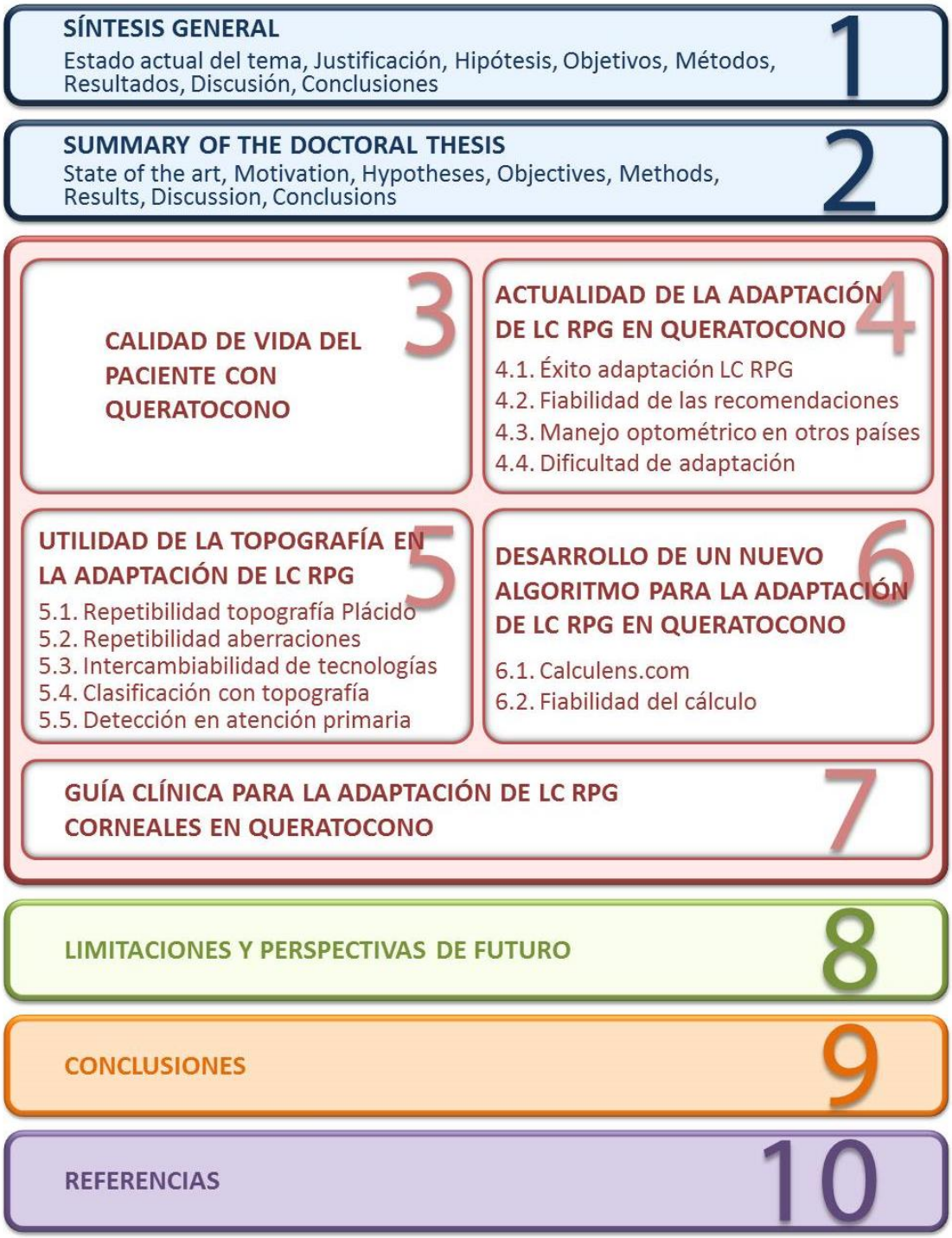

Figura 0. Esquema de la organización de la presente memoria de tesis doctoral.

sujetos sanos, como en pacientes con irregularidades corneales, como el queratocono. Además, en este artículo se define un proceso de adaptación de LC RPG basado en la evidencia en un mínimo de tres visitas. El **Capítulo 4.2** *(Ortiz-Toquero, et al. Rigid gas permeable contact lens fitting using new software in keratoconic eyes. Optom Vis*

Sci; 2016) analiza la precisión y fiabilidad de un software de simulación de la adaptación de LC RPG actualmente comercializado. El **Capítulo 4.3** *(Ortiz-Toquero, et al. Current optometric practices and attitudes in keratoconus patient management. Cont Lens Anterior Eye; 2017)* presenta los resultados del proyecto desarrollado durante la estancia realizada en la Universidad de Plymouth, analizando y comparando el manejo optométrico de los pacientes con queratocono en Reino Unido y en España, empleando una encuesta online distribuida entre los profesionales de ambos países. Por último, el **Capítulo 4.4** *(Ortiz-Toquero, et al. Fitting gas permeable contact lens in keratoconus, still a challenge? Ophthalmol Open J; 2016)* presenta una editorial invitada sobre la dificultad de adaptar LC RPG en pacientes con queratocono.

- El **Capítulo 5**, está constituido por cinco subcapítulos (5.1, 5.2, 5.3, 5.4 y 5.5) con el objetivo global de analizar la fiabilidad de la topografía corneal en pacientes con queratocono y su utilidad en el proceso de adaptación de LC RPG. El **Capítulo 5.1** *(Ortiz-Toquero, et al. Repeatability of Placido-based corneal topography in keratoconus. Optom Vis Sci; 2014)* determina la repetibilidad de la topografía de discos de Plácido en ojos con queratocono, imprescindible para interpretar estos resultados en la práctica clínica. El **Capítulo 5.2** *(Ortiz-Toquero, et al. Repeatability of wavefront aberration measurements with a Placido-Based topographer in normal and keratoconic eyes. J Refract Surg; 2016)* determina la repetibilidad de la medida de las aberraciones corneales obtenida mediante topografía de discos de Plácido en ojos con queratocono. El **Capítulo 5.3** *(Ortiz-Toquero, et al. Agreement of corneal measurements between dual rotation Scheimpflug-Placido system and Placido-based topography device in*

normal and keratoconus eyes. J Cataract Refract Surg; 2016) demuestra las limitaciones a la hora de emplear diferentes tecnologías (discos de Plácido y la topografía de Plácido-Scheimpflug) en la exploración de la topografía corneal en ojos con queratocono y sujetos sanos, de cara a determinar si ambas tecnologías son o no intercambiables en estos casos. El **Capítulo 5.4** *(Ortiz-Toquero, et al. The usefulness of the anterior coma aberration in keratoconus severity classification. Cont Lens Anterior Eye; en 1ª revisión)* propone una nueva clasificación utilizando los valores de coma corneal de la cara anterior para mejorar la actual clasificación de Amsler-Krumeich y ayudar a los profesionales en el seguimiento de esta enfermedad. Por último el **Capítulo 5.5** *(Ortiz-Toquero, et al. Keratoconus screening in primary eye care – A general overview. European Ophthalmic Review; 2016)* presenta una revisión bibliográfica sobre la utilidad de la topografía corneal en atención primaria para la detección y manejo del paciente con queratocono.

- El **Capítulo 6** presenta el desarrollo y validación clínica de un nuevo algoritmo para adaptar LC RPG en ojos con queratocono en dos subcapítulos (6.1 y 6.2). El **Capítulo 6.1** *(Ortiz-Toquero, et al. New web-based algorithm to improve rigid GP CL fitting in keratoconus. Cont Lens Anterior Eye; 2017)* aborda el desarrollo y validación de un nuevo algoritmo para la selección de los parámetros de las LC RPG en queratocono que ha sido íntegramente desarrollado en esta tesis doctoral (disponible en www.calculens.com) y que permite simplificar el proceso de adaptación de LC RPG corneales en queratocono. En el **Capítulo 6.2** *(Ortiz-Toquero, et al. GP CL fitting in keratoconus: comparison of different guidelines to BOZR calculation. Cont Lens*

Anterior Eye; en 1ª revisión) se demuestra que el algoritmo desarrollado (calculens.com) en esta tesis doctoral mejora la propuesta de cálculo del radio base de la primera lente de prueba, empleando nueve guías y/o recomendaciones propuestas en la literatura o por los fabricantes, al encontrar la menor diferencia con el radio finalmente adaptado y mayor tasa de acierto (diferencia menor de 0,05 mm entre el radio propuesto y el finalmente adaptado).

- El **Capítulo 7** aglutina en una Guía Clínica de adaptación de LC RPG corneales todo el conocimiento generado durante el desarrollo de esta tesis doctoral. Esta Guía Clínica ha sido desarrollada y evaluada externamente siguiendo las directrices y recomendaciones del instrumento AGREE II que determina los estándares que debe tener cualquier guía de práctica clínica y a tenor de los resultados encontrados se propone someter este trabajo para su publicación en una revista de impacto.

Finalmente, se ha decidido incluir una serie de capítulos finales que toda tesis doctoral debe contemplar de alguna u otra manera. Así, el **Capítulo 8** describe las principales limitaciones que a juicio de la doctoranda presenta esta tesis doctoral, así como las perspectivas de futuros proyectos de investigación que se plantean con algunos interrogantes, bien no resueltos por esta tesis o bien que se plantean a partir de este trabajo. Seguidamente, se ha considerado oportuno presentar las conclusiones finales de la tesis en el **Capítulo 9** y finalmente, el **Capítulo 10** que incluye las referencias bibliográficas empleadas para la escritura de la presente memoria de tesis doctoral.

Organization of the Doctoral Thesis

This Doctoral Thesis report is presented as a "compendium of publications" and applies for the International-awarded Doctorate Degree. It has been organized under the regulations of the International Doctorate Committee of the University of Valladolid. This memory includes a general summary in both English and Spanish, in which the thematic unit of the work is justified, including the objectives, methodology, results, general discussion, and conclusions. Later, a body formed by the scientific articles are included. This memory also provides a certificate of stay of three months length at the School of Health Professions of the Plymouth University (UK).

Eight articles published or accepted in scientific journals with an impact factor are included (**Chapters 3, 4.1, 4.2, 4.3, 5.1, 5.2, 5.3 and 6.1**). Furthermore, two additional articles under revision (**Chapters 5.4 and 6.2**) and one in preparation which expected are also published in a future (**Chapter 7**) have been also included. In addition, two review articles have been included that have been published in non-indexed journals (**Chapters 4.4 and 5.5**).

This report is organized in ten chapters (Figure 0). **Chapters 1 and 2** are composed of the general summary of the Doctoral Thesis in both Spanish and English respectively. Each chapter also includes a section, as a general

introduction, dedicated to the current state of art of detection and management of patients with keratoconus.

Following the summary, the **Chapters 3, 4, 5 and 6** corresponding to the articles (published or submitted awaiting decision) that reflect different blocks of studies and the **Chapter 7** will be prepared shortly, are included.

This order of presentation aims to facilitate the understanding of the Doctoral Thesis that addresses the development of a Clinical Practice Guidelines to fit corneal gas permeable contact lenses (GP CLs) in keratoconus.

- **Chapter 3** consists of a single article *(Ortiz-Toquero, et al. The influence of the refractive correction on the vision-related quality of life in keratoconus patients. Qual Life Res; 2016)* that demonstrates the impact of optical correction (spectacles or CLs) on the quality of life of keratoconic patients compared to a control group of healthy subjects.

- **Chapter 4** is composed of four sub-sections (4.1, 4.2, 4.3 and 4.4), which analyzed the current state of GP CLs fitting process in keratoconus. **Chapter 4.1** *(Ortiz-Toquero, et al. Success of rigid gas permeable contact lens fitting. Eye & Contact Lens; 2016)* assess the percentage of successful GP CLs fit in healthy subjects and patients with irregular cornea, such as, keratoconus. In addition, this article defines an evidence-based fitting process based on a minimum of three visits. **Chapter 4.2** *(Ortiz-Toquero, et al. Rigid gas permeable contact lens fitting using new software in keratoconic eyes. Optom Vis Sci; 2016)* analyzes the accuracy and reliability of a simulation GP CL software currently commercialized. **Chapter 4.3** *(Ortiz-Toquero, et al. Current optometric practices and attitudes in keratoconus patient*

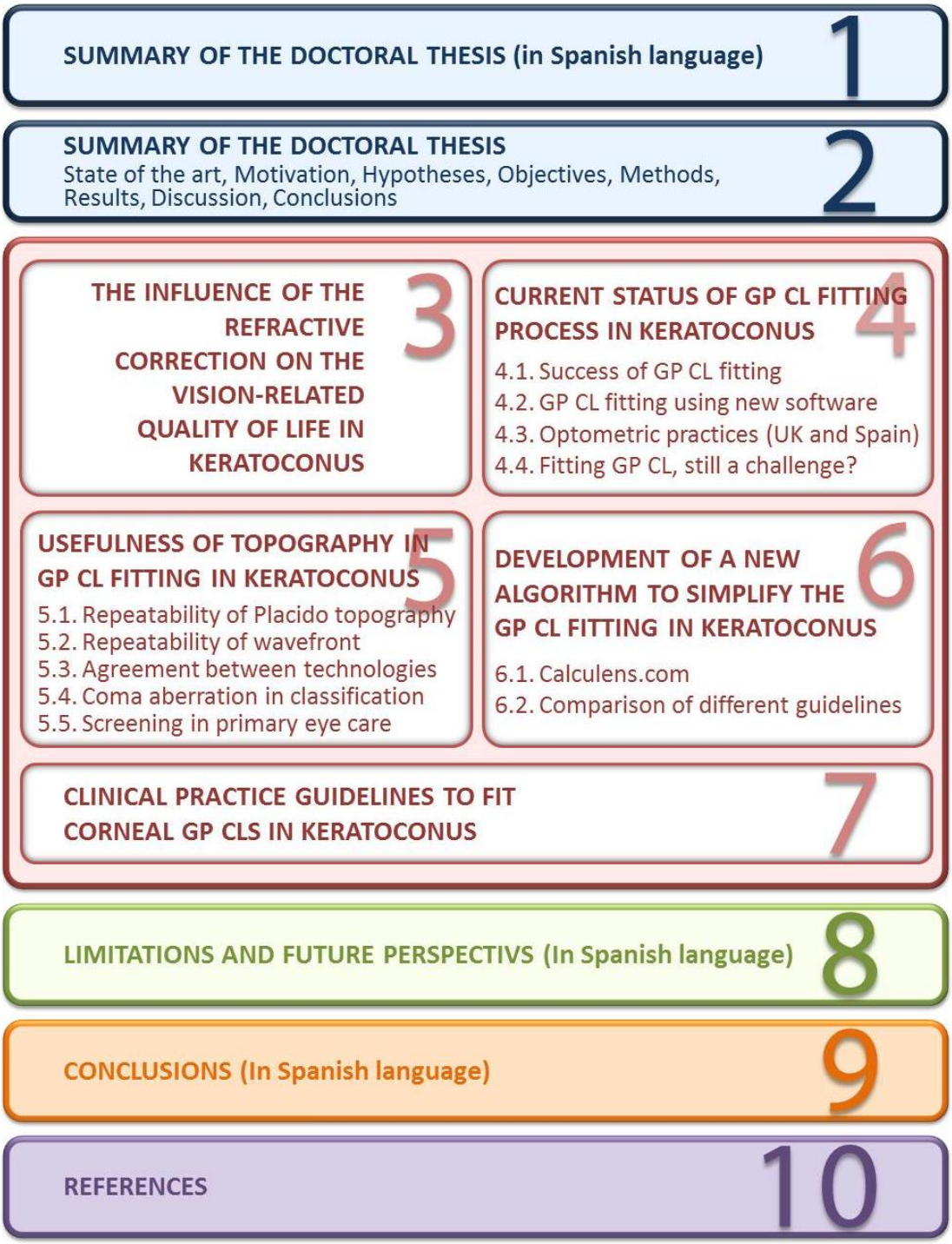

Figure 0. Organization of this Doctoral Thesis report.

management in Spain and UK. Cont Lens Anterior Eye; 2017) presents the results of the project developed during the stay at the University of Plymouth, comparing the optometric management of patients with keratoconus in the UK and Spain, using an online survey distributed among professionals from both countries. Finally, **Chapter 4.4** *(Ortiz-*

Toquero, et al. Fitting gas permeable contact lens in keratoconus, still a challenge? Ophthalmol Open J; 2016) presents a guest editorial on the challenge of GP CLs fittings in keratoconus.

- **Chapter 5** is composed of five sub-sections (5.1, 5.2, 5.3, 5.4 and 5.5) which overall objective is to analyze the reliability of corneal topography in patients with keratoconus and its usefulness in the GP CLs fitting process. **Chapter 5.1** *(Ortiz-Toquero, et al. Repeatability of Placido-based corneal topography in keratoconus. Optom Vis Sci; 2014)* determines the repeatability of Placido-based disc topography in keratoconic eyes, mandatory to introduce these results in clinical practice. **Chapter 5.2** *(Ortiz-Toquero, et al. Repeatability of wavefront aberration measurements with a Placido-Based topographer in normal and keratoconic eyes. J Refract Surg; 2016*) analyzes the repeatability of the measurement of corneal aberrations obtained by Placido-based disc topography in keratoconus. **Chapter 5.3** *(Ortiz-Toquero, et al. Agreement of corneal measurements between dual rotation Scheimpflug-Placido system and Placido-based topography device in normal and keratoconus eyes. J Cataract Refract Surg; 2016)* demonstrates the limitations of using different technologies (Placido-based and Scheimpflug-Placido topography) in the exploration of corneal topography in keratoconus and healthy eyes, in order to determine the interchangeability of these technologies in these cases. **Chapter 5.4** *(Ortiz-Toquero, et al. The usefulness of the anterior coma aberration in keratoconus severity classification. Cont Lens Anterior Eye; 1st revision)* proposes a new cut-off values using the coma of the anterior corneal surface to improve the current classification of Amsler-Krumeich and to help the professionals in the follow-up of this disease.

Finally, **Chapter 5.5** *(Ortiz-Toquero, et al. Keratoconus screening in primary eye care – A general overview. European Ophthalmic Review; 2016)* presents a review on the usefulness of corneal topography in primary care for the detection and management of keratoconic patients.

- **Chapter 6** shows the development and validation of a new algorithm to fit GP CLs in keratoconic eyes, which is composed by two sub-sections (6.1 and 6.2). **Chapter 6.1** *(Ortiz-Toquero, et al. New web-based algorithm to improve rigid GP CL fitting in keratoconus. Cont Lens Anterior Eye; 2017)* presents the new algorithm that allows simplify the GP CLs fitting process. It has been fully development in this Doctoral Thesis (available in www.calculens.com). **Chapter 6.2** *(Ortiz-Toquero, et al. GP CL fitting in keratoconus: comparison of different guidelines to BOZR calculation. Cont Lens Anterior Eye; 1st revision)* demonstrates that the algorithm (calculens.com) improves the back optic zone radius of GP CLs in keratoconus following other nine guidelines and/or recommendations proposed in the literature or by the manufacturers.

- **Chapter 7** brings together all the knowledge generated in this Doctoral Thesis. This chapter presents an evidence-based Clinical Practice Guidelines to fit corneal GP CLs in keratoconus eyes. This Clinical Practice Guidelines has been developed and evaluated externally following the recommendations of the AGREE II instrument. It is an appraisal tool and validated instrument to provide a framework for assessing quality of clinical practice guideline.

Finally, **Chapter 8** (fully presented in Spanish language) describes the main limitations of this doctoral thesis as well as the perspectives of future research projects that arise with some questions not solved by this thesis or that arise from this work. Next, it was considered opportune to present the final conclusions of the Doctoral Thesis in **Chapter 9** (in Spanish). At last, **Chapter 10** includes the references used for the writing of the present Doctoral Thesis report.

Abreviaturas

AA	Área analizada	Analyzed area
ACP	Potencia corneal media	Average corneal power
AGREE	Appraisal of Guidelines Research and Evaluation	
ALK	Queratoplastia lamelar anterior	Anterior lamellar keratoplasty
ARC	Radio de curvatura anterior	Anterior radius of curvature
AV / VA	Agudeza visual	Visual acuity
BAD	Belin/Ambrósio Display	
BDVA	Mejor agudeza visual en visión lejana	Best distance visual acuity
BIAS	Diseño de lente de contacto biasférica	Contact lens bi-aspheric design
CCI / ICC	Coeficiente de correlación intraclase	Intraclass correlation coefficient
CIM	Medida de irregularidad corneal	Corneal irregularity measurement
CKI	Índice de queratocono central	Center keratoconus index
CLEK	Collaborative Longitudinal Evaluation of Keratoconus	
CLMI	Localización del cono e índice de magnitud	Cone location and magnitude index
CSI	Índice de centro-alrededor	Centre surround index
CV	Coeficiente de variación	Coefficient of variation
CXL	Crosslinking	Cross-linking
D	Dioptría	Dioptre
DALK	Queratoplastia lamelar anterior profunda	Deep anterior lamellar keratoplasty
DSI	Índice de sector diferente	Different sector index
IAI	Índice de astigmatismo irregular	Irregular astigmatism index
IC / CI	Intervalo de confianza	Confidence intervale
ICRS	Segmentos de anillos intraestromales	Intracorneal ring segment
IHA	Índice de asimetría de altura	Index of height asymmetry
IHD	Índice de descentración de altura	Index of height decentration
I-S	Asimetría Inferior-Superior	Inferior-Superior Value
ISV	Índice de variación de la superficie	Index of surface variance

IVA	Índice de asimetría vertical	Index of vertical asymmetry
K	Curvatura corneal	Corneal curvature
KAKC	Diseño de lente para queratocono	Contact lens with design for keratoconus
KCI	Índice de clasificación de queratocono	Keratoconus classification index
KI	Índice de queratocono	Keratoconus index
KISA	Índice de porcentaje de queratocono	Keratoconus percentage index
KPI	Índice de predicción de queratocono	Keratoconus prediction index
KSI	Índice de severidad de queratocono	Keratoconus severity index
KSS	Puntuación de severidad del queratocono	Keratoconus Severity Score
LASIK	Laser in situ keratomileusis	
LC / CL	Lente de contacto	Contact lens
LIO / IOL	Lente intraocular	Intraocular lens
LH	Lámpara de hendidura	Slit-lamp
Mm	Milímetros	Millimetres
MTK	Queratometría tórica media	Mean toric keratometry
NEI-VFQ-25	Cuestionario de Funcionamiento Visual del National Eye Institute	The National Eye Institute-Vision Function Questionnaire
OCT	Tomografía de coherencia óptica	Optical coherence tomography
OSI	Índice de sector opuesto	Opposite sector index
PCA	Agudeza corneal predictiva	Predicted corneal acuity
PK	Queratoplastia penetrante	Penetrating keratoplasty
PLK	Queratoplastia lamelar posterior	Posterior lamellar keratoplasty
PRC	Radio de curvatura posterior	Posterior radius of curvature
PRK	Queratectomía fotorrefractiva	Photorefractive keratectomy
PTK	Queratectomía fototerapéutica	Phototherapeutic keratectomy
RMin	Curvatura sagital mínima	Smallest sagittal curvature
RMS	Valor cuadrático medio	Root Mean Square
RPG / GP	Rígida permeable al gas	Gas permeable
SAI	Índice de asimetría de la superficie	Surface asymmetry index
SD	Desviación estándar	Standard deviation
SimK	Queratometría simulada media	Simulated keratometry
SRAX	Inclinación del eje radial más curvado	Skew of steepest radial axis
SRI	Índice de irregularidad de la superficie	Surface regularity index
µm	Micrómetros	Micrometers

Capítulo 1

Síntesis general

1.1. Estado actual del tema

1.1.1. Definición, evolución y etiología del queratocono

El queratocono (del griego κέρα-ς/-ατος <<córnea>> y del latín cōn(um) <<cono>>) es una enfermedad bilateral, aunque asimétrica, de la córnea que se caracteriza por presentar un adelgazamiento corneal progresivo no inflamatorio con un aumento de curvatura, generando una ectasia o protrusión.[1-6] La curvatura excesiva y anormal de la córnea induce miopía y astigmatismo que a medida que la enfermedad progresa se va haciendo cada vez más irregular provocando una disminución de la visión que no es fácil de corregir con lentes oftálmicas.[1-6]

Se inicia generalmente en la adolescencia, y progresa lentamente hasta la tercera o cuarta década de la vida, momento en el que suele estabilizarse,[1-6] aunque recientemente se ha descrito su progresión en pacientes mayores de 30 años.[7] Su prevalencia varía en función de los estudios, aceptándose que se sitúa entre 50 y 230 casos de cada 100.000 habitantes, o dicho de otra manera una de cada 2000 personas,[1, 3, 8] si bien, estudios recientes elevan esta prevalencia hasta un caso por 375 habitantes.[9]

La etiología del queratocono es desconocida aunque se acepta un origen multifactorial, que combina factores genéticos, bioquímicos, biomecánicos y ambientales.[1, 3] Los factores de riesgo para padecer queratocono son

síndrome de Down, familiares con queratocono, alergias oculares, factores étnicos (origen asiático o arábico), factores mecánicos (como el frote vigoroso de los ojos o pacientes con el síndrome del párpado flácido -floppy eyelid syndrome-), atopia, desórdenes del tejido conectivo (síndrome de Marfan), síndrome de Ehlers-Danlos, o amaurosis congénita de Leber.[1, 3]

1.1.2. Diagnóstico del queratocono

El diagnóstico del queratocono se realiza fundamentalmente a partir de los signos clínicos y topográficos característicos de esta enfermedad (Tabla 1). Destaca la disminución de la agudeza visual que en estadios moderados y/o avanzados no puede ser compensada con gafas, presencia de astigmatismo irregular a favor de regla, reflejo "en tijeras" durante la realización de la retinoscopía, presencia de miras queratométricas irregulares, patrón topográfico característico (Figura 1), o hallazgos mediante biomicroscopía de polo anterior (Figura 2), como depósitos de hierro epiteliales (anillo de Fleischer), estrías estromales finas, verticales y profundas (estrías de Vogt), nervios corneales prominentes, cicatrices epiteliales y estromales, abombamiento del párpado inferior en la mirada hacia abajo (signo de Munson), además de adelgazamiento estromal, o hidrops corneal en estadios muy avanzados.[1-6]

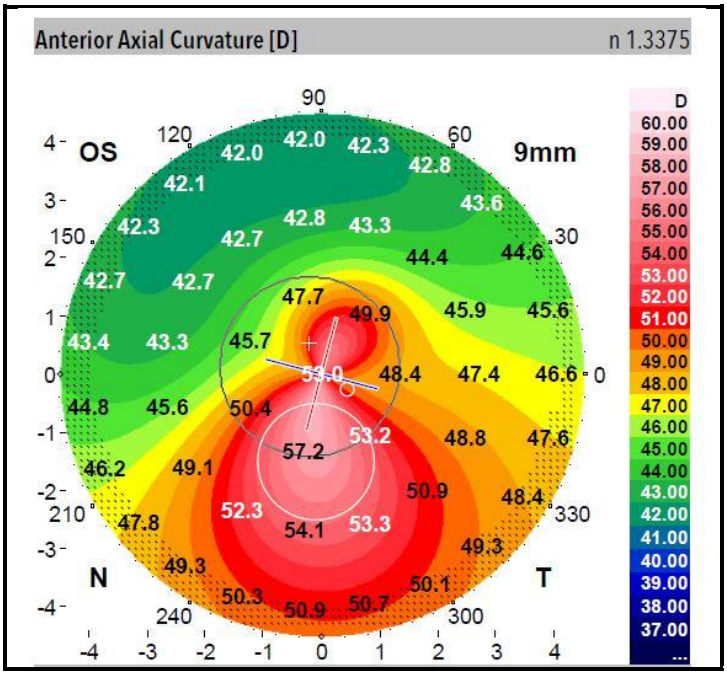

Figura 1. Patrón topográfico de curvatura axial anterior característico de una córnea con queratocono.

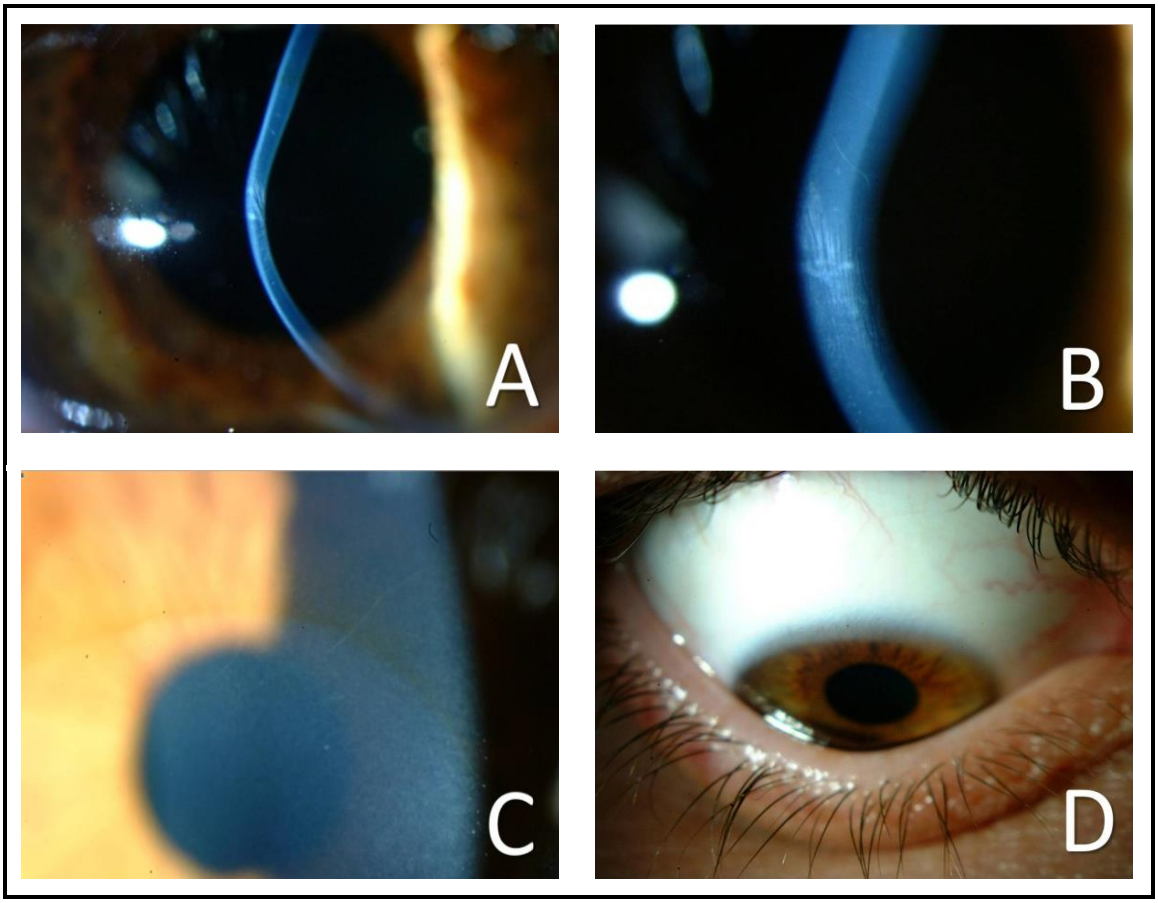

Figura 2. Signos clínicos en queratocono. A: Sección óptica de una córnea con queratocono; B: Estrías de Vogt; C: Anillo de Fleischer y nervios corneales; D: Signo de Munson.

Indicadores refractivos:

- Miopía y astigmatismo irregular (generalmente a favor de regla u oblicuo).
- Disminución de agudeza visual con gafa tanto de lejos como de cerca.
- Cambios en el componente cilíndrico (eje y potencia).
- Diplopía monocular e imágenes fantasma.

Signos en la retinoscopía, queratometría y oftalmoscopía:

- Reflejo irregular o en "tijeras" en la retinoscopía.
- Miras queratométricas distorsionadas.
- Visualización del cono en el reflejo rojo pupilar durante la oftalmoscopía (signo de "gota de aceite" de Charleaux).

Signos en biomicroscopía de polo anterior:

- Nervios corneales prominentes.
- Estrías de Vogt.
- Anillo de Fleischer.
- Cicatrices corneales.
- Adelgazamiento corneal.
- Signo de Munson.
- Hidrops corneal (en estados avanzados).
- Signo de Rizzuti (brillo luminoso reflejado en la zona nasal del limbo al iluminar temporalmente la córnea).

Signos topográficos:[10-12]

- Zona delimitada con curvatura y potencia excesiva, rodeada por zonas de potencia decreciente.
- Patrón topográfico en forma de pajarita.
- Astigmatismo corneal >1,50 D.
- Ápex del cono situado en la zona media inferior (central, nasal o temporal).
- Potencias corneales mayores de 47,2 D.
- Asimetría de potencia corneal (en 3,0 mm de diámetro) inferior-superior ≥ 1,4 D.
- Ángulo de torsión del patrón topográfico del astigmatismo en pajarita > 20º.
- Patrón de elevación en la cara posterior (superior a 35 µm).
- Aumento en las aberraciones corneales topográficas (especialmente el coma).

Otros signos:[10, 13-15]

- Espesor corneal central 494 µm (queratocono central) o 503 µm (no central).
- Alteración de la biomecánica corneal.
- Diferencias de paquimetría central entre ambos ojos >10 µm.

Tabla 1. Signos clínicos y topográficos para la detección de queratocono.

1.1.3. Topografía corneal

Aunque el diagnóstico clínico del queratocono en estadios moderados y/o avanzados no es muy problemático debido al patrón topográfico y a los signos clínicos característicos que presenta la enfermedad cuando progresa (Tabla 1), su diagnóstico en estadios iniciales puede ser complicado. La detección temprana y el diagnóstico del queratocono requieren un análisis exhaustivo de la córnea, existiendo para ello diferentes técnicas disponibles en la actualidad entre las que destaca la topografía/tomografía corneal.[10, 16] La topografía corneal de reflexión es una de las herramientas más comunes y utilizadas en la práctica clínica, especialmente en atención primaria, tanto en la detección como en el manejo del queratocono. Esta técnica basada en el análisis de la imagen de varios discos de Plácido reflejada en la córnea, permite detectar esta enfermedad con el análisis de la topografía de la cara anterior.[10, 17-23] Sin embargo, actualmente se considera que el análisis pormenorizado de la superficie posterior de la córnea, es necesario para completar el diagnóstico de esta enfermedad, sobre todo en estadios iniciales.[1, 24] Concretamente, la presencia de un patrón de elevación en la cara posterior se ha propuesto como un signo importante de la enfermedad, proponiéndose valores de sospecha elevaciones entre 29-35 µm (queratocono subclínico) o diagnósticos entre 35-51 µm. Si bien, estos valores pueden variar en función del equipo empleado en el análisis de la morfología corneal posterior.[10, 12, 25, 26]

Entre los equipos que analizan la cara anterior y posterior corneal destacan los tomógrafos corneales (Scheimpflug o dispositivos mixtos de

Scheimpflug-Placido)[27-30] y los tomógrafos de coherencia óptica de segmento anterior (AS-OCT).[31, 32]

Recientemente se han propuesto dispositivos que analizan las propiedades biomecánicas y morfológicas de la córnea [33-35] si bien, existe mucha controversia aún sobre los valores diagnósticos (cut-off),[1] aunque algunos equipos como el Corvis, muestran altos valores de sensibilidad y especificidad.[36]

Por otra parte, el análisis de las aberraciones corneales también ha demostrado ser una herramienta eficaz para detectar córneas con queratocono, ya que se han reportado mayores valores de coma vertical (<-0,116 µm)[37] y de RMS coma-like (>1,50 µm)[38] en pacientes con diagnóstico o sospecha de queratocono.[37-43]

También se han desarrollado varios índices topográficos para detectar la presencia de irregularidades corneales intentando introducir objetividad en el diagnóstico, detección y seguimiento del queratocono.[3, 10, 16, 44-47] Dependiendo del análisis topográfico realizado se diferencian índices individuales (Tabla 2) o índices multivariantes que combinan varios índices individuales (Tabla 3). Sin embargo, estos índices presentan como principal problema una alta dependencia del topógrafo corneal o dispositivo para el que se han desarrollado, y además, en numerosos casos utilizan un gran número de variables que dificultan su aplicación en la práctica clínica.[16]

Índice	Descripción	Valor normal
K central	*Queratometría central*[11, 48] Media de la potencia corneal distribuida entre los anillos de diámetro 2, 3 y 4 mm.	<47,2 D
SimK	*Queratometría simulada*[46, 49] Media de las potencias corneales de los meridianos principales (más y menos potente; anillos de 3 a 9 mm).	-
I-S	*Asimetría Inferior-Superior*[11, 48] Diferencia de potencia entre cinco puntos del hemisferio inferior y cinco puntos del hemisferio superior de la córnea separados 30 ° (anillo 3 mm).	<1,4 D
SRAX	*Ángulo de torsión (Skewed Radial Axes)*[44] Expresión numérica del astigmatismo irregular.	<20º
SAI	*Índice de asimetría de la superficie*[49, 50] Valor medio de las diferencias de potencia entre puntos espacialmente situados a 180° en 128 meridianos equidistantes.	0,10 a 0,42 D
SRI	*Índice de irregularidad de la superficie*[49, 51] Variación de la potencia en 256 semimeridianos regularmente espaciados en los 4,5 mm centrales.	<1,55 D
CIM	*Medida de irregularidad corneal*[16, 49] Desviación estándar entre la superficie corneal y la superficie de referencia de mejor ajuste.	0,03 a 0,68 µm
MTK	*Queratometría tórica media*[16, 52] Elevación corneal calculada mediante el mejor ajuste a una superficie de referencia tórica.	43,1 a 45,9 D
CLMI	*Localización del cono e índice de magnitud (Cone location and magnitude index)*[45] Detección de la presencia de un patrón de queratocono determinando la ubicación y magnitud del cono.	<45%
PCA[a]	*Agudeza corneal predictiva*[16, 53] Calidad óptica de la córnea en los 3 mm centrales en escala Snellen.	-
SDSD	**Desviación estándar de la desviación estándar** del radio de curvatura de cada anillo.[22, 49]	-
ACP	*Potencia corneal media*[16, 47] Valor de potencia promedio de varios puntos en la región central de la córnea.	40,5 a 46,7 D
AA	*Área analizada*[16, 47] Valor del área corneal cubierta por los anillos de Plácido que se puede analizar.	-

Índice	Descripción	Valor normal
CSI	*Índice de centro-alrededor*[16, 47] Diferencia entre la media de potencia del área central (3 mm) y de un área anular de 3 mm alrededor del área central (3 a 6 mm).	-0,28 a 0,80 D
DSI	*Índice de sector diferente*[16, 47] Diferencia máxima entre la potencia media corneal entre 8 sectores que subtienden un ángulo de 45º.	0,21 a 3,51 D
OSI	*Índice de sector opuesto*[16, 47] Diferencia máxima de potencia media entre dos sectores opuestos que subtienden un ángulo de 45º.	-0,55 a 2,09 D
IAI	*Índice de astigmatismo irregular*[16, 47] Variación de potencia entre cada anillo a lo largo de un mismo meridiano.	0,19 a 0,49 D
ISV_b	*Índice de variación de la superficie*[10, 49] Irregularidad de la curvatura de la superficie corneal anterior.	<37
IVA_b	*Índice de asimetría vertical*[10, 49] Asimetría entre la curvatura corneal superior e inferior.	<0,28
KI_b	*Índice de queratocono*[10, 49] Calculado a partir de otros índices topográficos (DSI, OSI, CSI, SAI, IAI, AA, SimK1 y SimK2).	<1,07
CKI_b	*Índice de queratocono central*[10, 49] Calculado para detectar queratoconos centrales.	<1,03
IHA_b	*Índice de asimetría de altura*[10, 49] Diferencia entre la elevación media de la córnea superior y e inferior.	<19
IHD_b	*Índice de descentración de altura*[10, 49] Grado de descentración vertical de los datos de elevación corneal.	<0,014
$Rmin_b$	*Curvatura sagital mínima*[10, 49] Curvatura sagital menor en los 8 mm centrales.	>6,71 mm

Tabla 2. Algunos de los índices topográficos utilizados para la detección del queratocono.

[a]Topógrafos EyeVision [b]Topógrafos Oculus (Pentacam; Keratograph; Easygraph)

Índice	Descripción	Valor de corte
KISA%	Combinación 4 índices topográficos: potencia corneal paracentral, asimetría inferior-superior, astigmatismo corneal y SRAX.[44]	60%-100% Sospecha >100% queratocono
KPI	***Keratoconus Prediction Index***[46, 47] Obtenido de 8 índices queratométricos (SimK1, SimK2, OSI, CSI, DSI, SAI, IAI, y AA).	0,23
KCI%	***Keratoconus classification index (Klyce/Maeda)***[47] Derivado de KPI y otros 4 índices topográficos (DSI, OSI, CSI y SimK2) que proporciona la probabilidad (en tanto por ciento) de tener queratocono.	>0%
KSI	***Keratoconus severity index (Smolek/Klyce)***[46] Derivado de 10 índices topográficos diferentes. Diseñado para clasificar el grado de severidad del queratocono.	30%
Rabinowitz & McDonell	Combinación de los índices topográficos I-S, K central y diferencia de K central entre ambos ojos.[48]	I-S > 1,4 D K > 47,2 D Dif > 1 D
Chastang[a]	Árbol de decisión topográfico que combina SDSD y asfericidad.[22, 49]	Índices fuera de valores normales
PathFinder Corneal Analysis[b]	Módulo topográfico que combina varios índices (CIM, MTK, factor de forma) para detectar irregularidades corneales.[10, 54]	Índices fuera de valores normales
BAD III[c]	***Belin/Ambrósio Enhanced Ectasia Display III***[55] Módulo que analiza 9 índices distintos y proporciona una evaluación final global basado en el análisis de regresión de cada índice analizado.	Índices fuera de valores normales

Tabla 3. Algunos de los principales índices multivariantes que combinan diversos índices topográficos para la detección del queratocono y sus valores de corte para el diagnóstico.

[a]Topógrafo EyeSys 2000 (EyeVision) [b]Topógrafo Atlas (Carl Zeiss) [c]Topógrafo Pentacam (Oculus)

1.1.4. Clasificación y progresión del queratocono

La clasificación del queratocono en diferentes estadios permite mejorar tanto el diagnóstico como la monitorización de la progresión de la enfermedad. Sin embargo, no existe una clasificación clínicamente aceptada que permita a los profesionales distinguir claramente entre una

córnea sana y una córnea afectada por queratocono (especialmente en las primeras etapas de la enfermedad) o distinguir claramente entre sus diferentes estadios, lo que sería de gran utilidad en el seguimiento clínico tanto de los casos sospechosos (forma frustra) como en casos ya diagnosticados.[1, 16] Generalmente, para la clasificación del queratocono se suelen emplear criterios que combinan datos clínicos tanto refractivos, biomicroscópicos, paquimétricos como topográficos.

Clásicamente, la forma o localización del cono identificada mediante topografía corneal se ha empleado para clasificar el queratocono en varias categorías. En función de la forma o localización del cono se pueden diferenciar varias clasificaciones como: el tipo *pezón o central* (con diámetro del cono <5 mm), *oval o temporal* inferior (con diámetro del cono >5 mm) o *global o tipo generalizado* (cuando el cono comprende más del 75% de la córnea).[20, 56] También puede clasificarse como central o paracentral,[20, 56] sin que estas clasificaciones parezcan tener un efecto significativo en el proceso de adaptación de un tipo u otro de lente de contacto (LC) rígida permeable al gas (RPG).[20]

Las clasificaciones más aceptadas para gradar la severidad del queratocono son la de Amsler-Krumeich (Tabla 4),[57, 58] modificada posteriormente por Alió et al. introduciendo valores de aberraciones de cara anterior[38] y las empleadas por el Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study basadas en la queratometría (incipiente <45 D, moderado 45-52 D, avanzado >52 D)[59] o en varios factores clínicos y topográficos (KSS: Keratoconus Severity Score; Tabla 5).[56]

Pero estas clasificaciones fueron propuestas hace bastante tiempo y no incorporan información reciente y los avances tecnológicos disponibles en

la actualidad para la exploración de la córnea, lo que hace necesario un nuevo método o criterio de clasificación.[1, 16] Recientemente se ha desarrollado una nueva escala para detectar y gradar la severidad y progresión del queratocono, denominada escala ABCD de Belin-Ambrosio ("A" del inglés "anterior surface"; "B" de "back Surface", "C" de "corneal thickness" y "D" de "distance visual acuity") implementándose únicamente en los nuevos equipos Pentacam (Tabla 6).[60, 61]

Grado I	Encorvamiento periférico Miopía y/o astigmatismo >5,00 D Lectura queratométrica central <48,00 D Estrías de Vogt, ausencia de cicatrices corneales *Coma-Like RMS 1,50 a 2,50 µm
Grado II	Miopía y/o astigmatismo entre 5,00-8,00 D Lectura queratométrica central <53.00 D Ausencia de cicatrices Espesor corneal mínimo ≥400 µm *Coma-Like RMS >2,50, ≤3,50 µm
Grado III	Miopía y/o astigmatismo entre 8,00-12,00 D Lectura queratométrica central >53,00 D Ausencia de cicatrices Espesor corneal mínimo entre 200-400 µm *Coma-Like RMS >3,50, ≤4,50 µm
Grado IV	Refracción no medible Lectura queratométrica central >55,00 D Cicatrices corneales centrales Espesor corneal mínimo <200 µm *Coma-Like RMS >4,50 µm

Tabla 4. Clasificación de Amsler-Krumeich. *Modificación introducida por Alió et al.[38]

0	**No afectado – Topografía Normal** Ausencia de cicatrices corneales Sin signos clínicos en la exploración con lámpara de hendidura (LH) Patrón topográfico axial normal Potencia corneal media ≤47,75 D RMS de alto orden ≤0,65
1	**No afectado – Topografía atípica** Ausencia de cicatrices corneales Sin presencia de signos clínicos en la exploración con LH Patrón topográfico axial atípico (patrón irregular, pajarita asimétrica superior, pajarita asimétrica inferior o región inferior de mayor curvatura, aunque no más de 3 D en relación a la potencia corneal central media). Potencia corneal media ≤48 D RMS de alto orden ≤1 µm
2	**Topografía sospechosa** Ausencia de cicatrices corneales Sin presencia de signos clínicos en la exploración con LH Patrón topográfico axial con área aislada de mayor curvatura, patrón de encorvamiento inferior o patrón de encorvamiento central Adicionalmente: - Potencia corneal media ≤49 D - RMS de alto orden >1,00, ≤1,50 µm
3	**Queratocono - Leve** Ausencia de cicatrices corneales Puede presentar signos clínicos en la exploración con LH Patrón topográfico axial típico de queratocono Adicionalmente: - Potencia corneal media ≤52 D - RMS de alto orden >1,50, ≤3,50 µm
4	**Queratocono - Moderado** Debe presentar signos clínicos en la exploración con LH Patrón topográfico axial típico de queratocono Adicionalmente: - Potencia corneal media >52D, ≤56 D - RMS de alto orden >3,50, ≤5,75 µm - Cicatrices corneales en estroma (≤ grado 3 en la escala CLEK)
5	**Queratocono - Severo** Debe presentar signos clínicos en la exploración con LH Patrón topográfico axial típico de queratocono Adicionalmente: - Potencia corneal media >56 D - RMS de alto orden >5,75 µm - Cicatrices corneales en estroma (≥grado 3,5 en la escala CLEK)

Tabla 5. Clasificación propuesta por el estudio CLEK[56] para diferenciar la severidad del queratocono [Clasificación KSS (Keratoconus Severity Score)].

	A	B	C	D	
Criterios ABCD	ARC (zona 3 mm)	PRC (zona 3 mm)	Paquimetría en el punto más delgado	BDVA	Cicatrices corneales
Grado 0	>7,25 mm (<46,5 D)	>5,90 mm (<57,25 D)	>490 µm	≥20/20 (≥1,0)	-
Grado 1	>7,05 mm (<48 D)	>5,70 mm (<59,25 D)	>450 µm	<20/20 (<1,0)	-, +, ++
Grado 2	>6,35 mm (<53 D)	>5,15 mm (<65,5 D)	>400 µm	<20/40 (<0,5)	-, +, ++
Grado 3	>6,15 mm (<55 D)	>4,95 mm (<68,5 D)	>300 µm	<20/100 (<0,2)	-, +, ++
Grado 4	<6,15 mm (>55 D)	<4,95 mm (>68,5 D)	≤300 µm	<20/400 (<0,05)	-, +, ++

Tabla 6. Clasificación ABCD. ARC=Radio de curvatura anterior en los 3mm centrados sobre el punto con menor espesor corneal; PRC=Radio de curvatura posterior en los 3mm centrados sobre el punto con menor espesor corneal; BDVA=mejor agudeza visual en visión lejana; Cicatrices: - ausencia; + presencia, pero se puede ver el iris a su través; ++ presencia sin observación de iris a su través.

Recientemente se han propuesto una serie de criterios para definir la progresión clínica del queratocono que requiere que se cumplan, al menos, dos de estos tres supuestos:[1]

a) aumento de la curvatura corneal anterior,
b) aumento de la curvatura corneal posterior, o
c) aumento del adelgazamiento corneal.

Esto implica que la medida o detección de la progresión de la enfermedad depende directamente de la precisión y fiabilidad del dispositivo o dispositivos utilizados en la evaluación de la córnea del paciente.[1]

1.1.5. Manejo del queratocono

El manejo del paciente con queratocono puede realizarse con opciones quirúrgicas y no quirúrgicas (Figura 3), siendo las opciones no quirúrgicas la primera elección.[1, 3, 8] En estadios precoces, se puede corregir el defecto refractivo, generalmente miopía y/o astigmatismo, con gafas o con LC blandas o hidrofílicas de diseños tóricos[3, 62] o LC RPG con diseño estándar.[20, 59, 63] Sin embargo, cuando el queratocono progresa, aumentan las irregularidades corneales que inducen aberraciones de alto orden que no pueden ser corregidas con lentes oftálmicas tradicionales, disminuyendo la visión de los pacientes.[3, 62, 64]

Las LC RPG representan la primera y mejor opción en el manejo de los pacientes con queratocono,[1, 8, 18, 20, 62, 65-69] porque permiten reducir la distorsión visual de origen corneal, debido a que la lágrima que queda entre la LC RPG y la cara anterior de la córnea permite una "homogenización", ópticamente hablando, de la mayor parte de las irregularidades corneales inducidas por el queratocono, proporcionando así un dioptrio formado por la superficie anterior de la córnea, la lágrima y la LC RPG que proporciona una superficie anterior ópticamente regular que permite corregir la mayor parte de las aberraciones de alto orden[70-72] mejorando la visión en la mayoría de los casos.[20, 62, 64, 65]

Cuando no se consigue una adaptación adecuada de LC RPG corneal, bien porque la enfermedad esté muy avanzada o porque el porte de LC RPG no es satisfactorio, existen otras alternativas, como son la combinación de varias LC como ocurre con el piggy-back (adaptando una LC hidrofílica sobre la que se adapta la LC RPG),[73] o la adaptación de diseños específicos de LC[62, 64] entre los que destacan las lentes híbridas (LC con centro RPG y

periferia hidrofílica),[74, 75] o la adaptación de LC RPG de mayor diámetro. En este último grupo en función de la zona de apoyo de la lente, se distinguen las lentes corneo-esclerales o semiesclerales que reparten su apoyo entre la córnea y la esclera (hasta 3 mm mayores que el diámetro de iris visible del paciente, generalmente entre 12,9-14,9 mm) o de apoyo completo en la esclera, como son las lentes miniesclerales (entre 3-6 mm mayores que el diámetro de iris visible del paciente, generalmente entre 15-18 mm) o esclerales (más de 6 mm mayores que el diámetro de iris visible del paciente, generalmente entre 18,1-25 mm).[76-78]

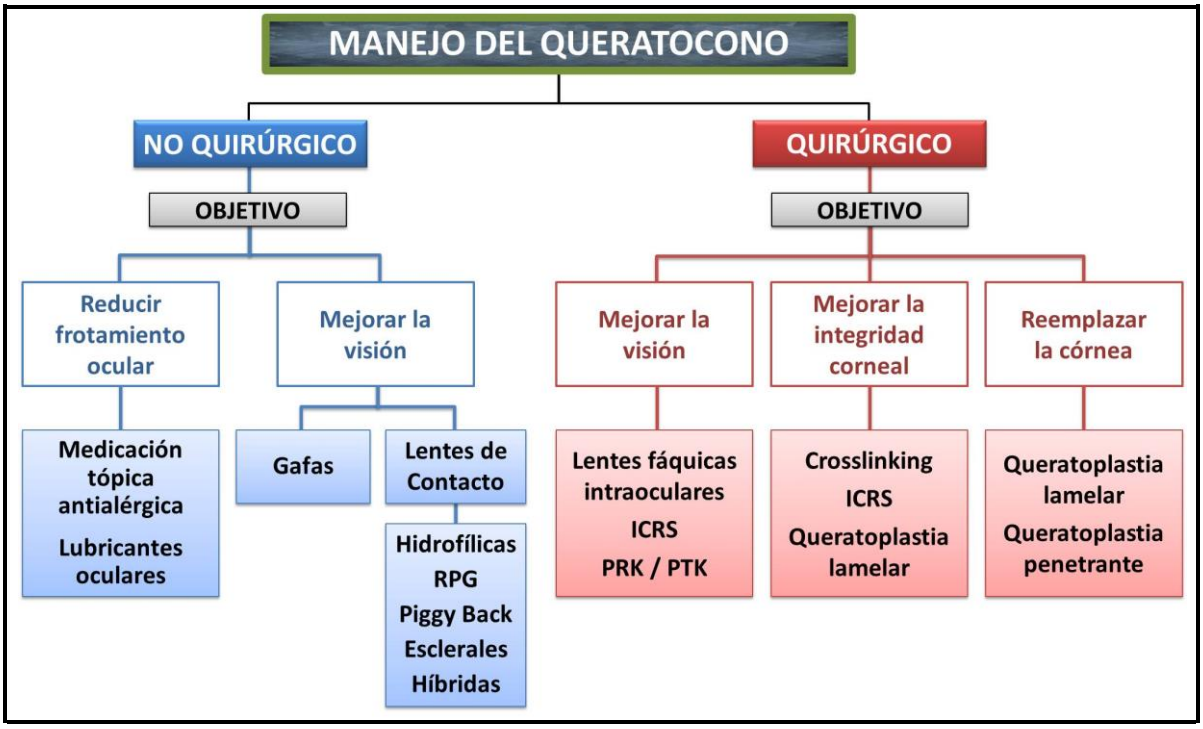

Figura 3. Opciones quirúrgicas y no quirúrgicas en el manejo del paciente con queratocono.

Además, se han propuesto diversas opciones quirúrgicas para manejar a los pacientes con queratocono, con distintos objetivos, como puede ser frenar la progresión de la enfermedad, mejorar la visión y/o mejorar la integridad corneal cuando existe intolerancia al porte de las LC o la visión es insatisfactoria (Figura 3, 4).[1, 3, 8]

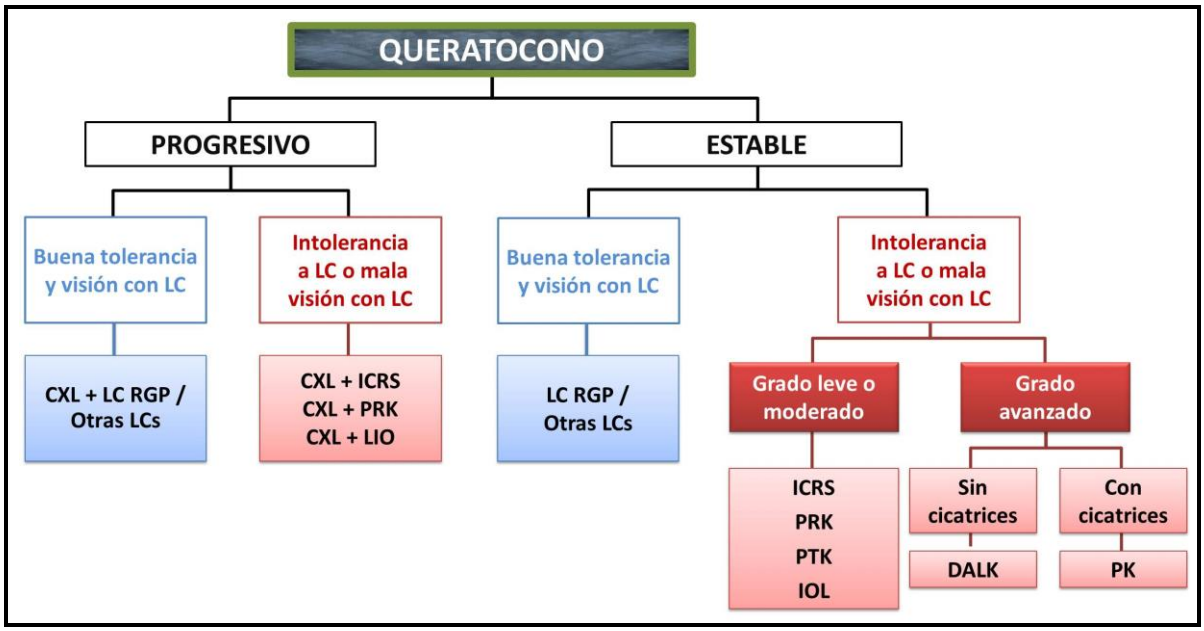

Figura 4. Manejo del paciente con queratocono en función de la evolución y/o progresión de la enfermedad.[1, 8]

Cuando existe progresión de la enfermedad o se pretende evitar su progresión, está indicado realizar la técnica del crosslinking (CXL),[1, 79] que consiste en aplicar radiación ultravioleta en conjunción con riboflavina, que actúa sobre las fibras de colágeno del estroma corneal[1, 79] para aumentar la rigidez corneal y mejorar la estabilidad biomecánica corneal con el objetivo de frenar el avance del queratocono.[80] El CXL no está indicado en córneas con espesores menores a 400 µm,[79, 81] siendo poco frecuente su realización en pacientes mayores de 40 años.[1]

La implantación de anillos intraestromales (ICRS) en pacientes con queratocono es controvertida[1] aceptándose cuando el paciente no alcanza buena visión con LC o presenta intolerancia al porte de LC con la intención de mejorar su visión. Esta técnica consiste en insertar uno o dos anillos de material sintético en el estroma corneal[1, 82-84] siendo los diseños más utilizados Intacs (Addition technologies) y Kerarings (Mediphacos).[82-84] El objetivo de esta técnica es regularizar la geometría corneal, disminuyendo el astigmatismo irregular, para mejorar la visión y aumentar la tolerancia al

porte de las LC.[82, 83] Se recomiendan para tratar casos leves y moderados de queratocono, ya que se requiere un espesor corneal mínimo de 450 µm en la zona de la incisión y ausencia de cicatrices corneales, especialmente en la zona central.[3, 83, 85]

Sin embargo, existe una limitada evidencia científica que abale la eficacia de estas técnicas (ICRS y CXL) por la falta de ensayos clínicos bien diseñados (incluyendo enmascaramiento y randomización).[8] Además la falta de acuerdo en la definición de la severidad y progresión del queratocono, también dificulta conocer la fiabilidad y seguridad de estas técnicas, porque aunque la mayor parte de los estudios reportan como variable de efectividad el cambio producido en la agudeza visual (AV), en la topografía corneal, en las aberraciones de alto orden o en la refracción (esfera y/o cilindro),[8] existe una falta de consenso en los criterios de éxito que dificulta la comparación de resultados y pueden cuestionar su eficacia, al no compararse, por ejemplo con la AV obtenida con LC RPG. Además, tras estos procedimientos, en una mayoría de los casos sigue siendo necesaria la adaptación de LC RPG para conseguir una buena visión.[8]

Otras técnicas propuestas para mejorar la visión en casos de intolerancia o mala visión con LC, implican el uso de procedimientos ablativos, como el LASIK[86] o la queratectomía fotorrefractiva (PRK) junto a CXL,[87, 88] la queratectomía fototerapéutica (PTK) con láser excimer utilizada para regularizar la superficie corneal y eliminar opacidades,[89, 90] o la inserción de lentes intraoculares fáquicas de cámara anterior o posterior,[91, 92] si bien son poco frecuentes con un uso mucho más limitado.[1, 8]

Finalmente, en estadios avanzados de la enfermedad en los que no se consigue buena visión y/o tolerancia al uso de LC, está indicado el

trasplante de córnea o queratoplastia. El término queratoplastia se refiere a la sustitución parcial o total de la córnea de un paciente por la obtenida de un donante. Así, se diferencian varias técnicas quirúrgicas, si bien no todas están indicadas en los pacientes con queratocono.[1, 93] Por ejemplo, la Queratoplastia Lamelar Anterior Superficial (ALK del inglés Anterior Lamellar Keratoplasty) está indicada en los trastornos corneales que afectan a las 300 µm superficiales de la córnea y la Queratoplastia Lamelar Posterior (PLK del inglés Posterior Lamellar Keratoplasty) está indicada en trastornos del estroma profundo, membrana de Descemet y endotelio, por ejemplo, en distrofias endoteliales o lesiones iatrogénicas; por tanto estas dos técnicas no estarían indicadas en pacientes con queratocono.[94] Sin embargo, la Queratoplastia Lamelar Anterior Profunda (DALK del inglés Deep Anterior Lamellar Keratoplasty) está indicada en pacientes con queratocono que presenten córneas transparentes sin compromiso en la membrana de Descemet y endotelio, que se mantienen intactos, reduciendo la posibilidad de rechazo, y como última instancia, el reemplazo de la córnea en su totalidad mediante la Queratoplastia Penetrante (PK del inglés Penetrating Keratoplasty) que estaría indicada en los casos que se acompañen de disfunción endotelial, cicatrices corneales profundas o hidrops corneal.[1, 93, 94] Se estima que el 12% de los pacientes con queratocono terminan siendo sometidos a una queratoplastia penetrante.[95]

1.1.6. Uso de LC RPG en queratocono

El uso de LC RPG en queratocono supone la primera opción de manejo de estos pacientes y su rehabilitación visual.[1, 8, 18, 62, 65-69] El proceso de adaptación de LC RPG tiene como objetivo mejorar la visión del paciente,

con la máxima comodidad posible y respeto de la fisiología ocular,[62, 64] de manera que se pueda evitar o retrasar la necesidad de recurrir a una opción quirúrgica.[8, 63] Encontrar los parámetros adecuados de la LC RPG que mejor se adapte a la forma de la córnea es de gran importancia para conseguir el éxito en la adaptación.[62, 64] En casos de adaptaciones en queratocono, buscar el equilibrio entre visión, comodidad y respeto de la fisiología ocular hacen que en muchas ocasiones este tipo de adaptaciones sean consideradas por los profesionales como un reto o desafío, que requiere más lentes de prueba y más visitas del paciente para conseguir una adaptación óptima que las necesarias en una adaptación de LC RPG estándar.[17, 18, 20, 21, 62, 65, 67]

Clásicamente, se han descrito tres diferentes filosofías de adaptación[96] de LC RPG corneales en queratocono: *levantamiento apical*, *toque apical* o *toque de tres puntos o de apoyo dividido*, considerándose esta última adaptación como la más segura y recomendable en estos casos.[68, 96, 97] (Tabla 7; Figura 5).

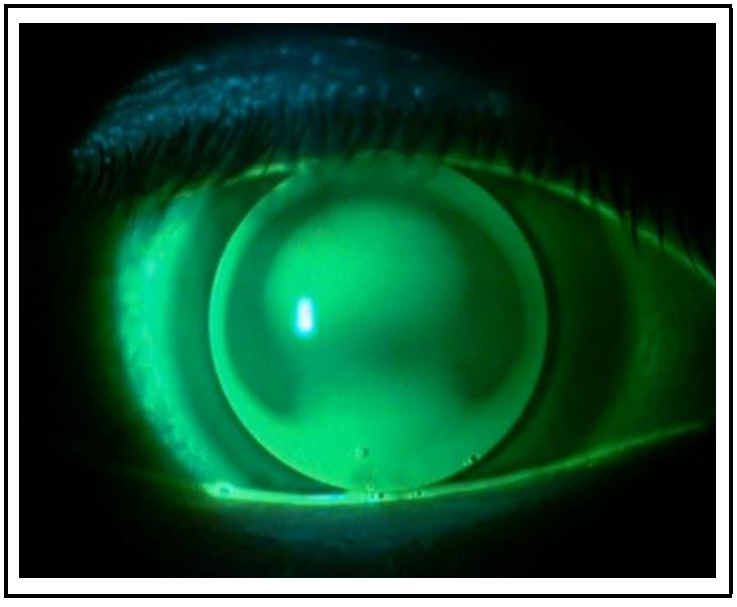

Figura 5. Fluorograma óptimo siguiendo la técnica del *toque en tres puntos* o *apoyo dividido*.

	Levantamiento apical	Toque apical	Toque de tres puntos
VENTAJAS	Menor probabilidad de cicatrices en el ápex Menor edema Menor incidencia de queratitis central	Adaptación más sencilla Mejor AV	Mayor zona de distribución de presión y peso de la lente Adaptación más sencilla que en levantamiento apical Menor probabilidad de cicatrices que con toque apical
DESVENTAJAS	Menor intercambio lagrimal Dimple veiling Moldeo corneal paracentral Peor AV	Moldeo corneal Mayor probabilidad de abrasiones corneales Posibles cicatrices en la zona del ápex	Necesidad de revisar las zonas de toque de la LC periódicamente

Tabla 7. Ventajas y desventajas de las distintas filosofías de adaptación de las LC RPG corneales en queratocono.

Los fabricantes de LC RPG generalmente proporcionan lentes específicamente diseñadas para ser adaptadas en córneas con queratocono, tanto con diseños corneales, corneo-esclerales, semiesclerales o esclerales; siendo las lentes corneales la primera opción a adaptar[1, 8, 18, 20, 62, 65-67] reservando los otros diseños para los casos en los que éstas LC fracasan. Las LC RPG corneales suelen incorporar un mayor número de curvas periféricas, diferente diámetro de zona óptica o bandas periféricas asféricas, con la intención de proporcionar un diseño que se adecue a la morfología de la córnea irregular característica del queratocono.[98]

Lógicamente, las LC RPG corneales específicamente diseñadas para ser adaptadas en córneas con queratocono requieren unos criterios, pautas o guías de adaptación diferentes a las empleadas con sujetos sanos con córnea regular que requieran LC RPG estándar, por lo que los fabricantes suelen dar unas instrucciones generales para seleccionar (o calcular) los parámetros de las LC. Estas recomendaciones suelen centrarse en el cálculo del radio base o radio de la zona óptica de la LC, generalmente a partir de los valores de curvatura corneal anterior (queratometría). Una vez calculado el radio de la primera lente de prueba se suele escoger la LC de la caja de pruebas con el radio elegido y adaptarla durante unos minutos para realizar su valoración clínica (movimiento, centrado, y fluorograma, principalmente). Otros fabricantes recomiendan el cálculo de los parámetros a partir de la topografía corneal de manera que puede pedirse al fabricante la primera lente de prueba sin necesidad de usar caja de pruebas. Esta manera de trabajar suele aumentar el tiempo de adaptación al ser necesario pedir al fabricante cada cambio en los parámetros de la lente hasta encontrar la lente adecuada.

Lamentablemente, es muy frecuente que se necesiten varios cambios en los parámetros de la primera lente de prueba, sobre todo en el radio y el diámetro, hasta encontrar una lente adecuada, lo que aumenta el número de lentes probadas y pedidas para estos pacientes[17, 18, 65, 68, 69, 99] comparado con una adaptación estándar en ojos sanos. Esto se traduce en procesos de adaptación relativamente largos y complejos, especialmente en córneas muy irregulares (estadios moderados o avanzados), o en los casos que muestren complicaciones relacionadas con el queratocono y su evolución, lo que hace que adaptar LC RPG en queratocono se considere un proceso difícil de realizar.[17, 18, 20, 21, 62, 65, 67]

1.2. Justificación

En conclusión, está ampliamente descrito en la literatura que la adaptación de LC RPG corneales es la primera opción en el manejo de los pacientes con queratocono, [1, 8, 18, 62, 65-69] ya que, aunque no frenan la progresión de la enfermedad,[8] está demostrado que su uso ayuda a retrasar la necesidad de cirugía[8, 63] en estos pacientes mejorando su calidad de vida.[100, 101]

Sin embargo, la adaptación de este tipo de lentes en estos pacientes está considerada como un proceso largo y complicado, que requiere numerosos cambios tanto de lentes de prueba como de lentes pedidas al fabricante, además de numerosas visitas consumiendo mucho tiempo, tanto para el paciente como para el profesional.[17, 18, 20, 21, 62, 65, 67-69, 99] Aunque algunos autores han propuesto el uso de softwares específicos basados en el análisis de la topografía corneal para calcular los parámetros de las LC RPG,[17, 18] estos no han demostrado una reducción relevante en el número de lentes de prueba[17] y sin embargo suponen una dependencia tecnológica de un modelo o topógrafo específico, lo que puede limitar su uso generalizado por parte de los profesionales de la visión.

Finalmente, algunos trabajos clásicos[102] proponen que casi el 70% de los pacientes con queratocono que acuden a una consulta especializada para realizar un trasplante de córnea pueden ser correctamente manejados con

LC RPG, lo que indica claramente que es necesario simplificar y mejorar el proceso de adaptación de LC RPG para proporcionar el mejor manejo a los pacientes con queratocono, disminuyendo el número de pacientes que tengan que recurrir a una opción quirúrgica invasiva[8, 103] que se puede asociar con mayores complicaciones y coste tanto para los pacientes como para los sistemas de salud.[104]

Por tanto, esta tesis pretende desarrollar una guía clínica basada en la evidencia que permita:

- Estandarizar el proceso de adaptación de LC RPG corneales en pacientes con queratocono identificando las visitas necesarias para completar la adaptación y los criterios para seleccionar y modificar los parámetros de la LC RPG corneal, que pueda ser aplicado por cualquier profesional de la visión.
- Simplificar el proceso de adaptación proporcionando un método robusto para el cálculo de los parámetros de la primera lente de prueba que reduzca la diferencia entre los parámetros de la lente probada y los de la lente finalmente adaptada.
- Disminuir el tiempo necesario para completar la adaptación, tanto para el profesional como para el paciente, reduciendo el número de LC, ya sean de prueba como las LC pedidas al fabricante, necesarias para completar la adaptación de la LC RPG adecuada en cada caso.
- Proporcionar la mejor rehabilitación visual a los pacientes con queratocono de una forma segura y eficaz minimizando el impacto de la enfermedad en su calidad de vida.

1.3. Hipótesis

Es posible estandarizar el proceso de adaptación de LC RPG en pacientes con queratocono mediante el desarrollo de una guía clínica basada en la evidencia que simplifique el proceso de adaptación y ayude al profesional a calcular los parámetros de las lentes de prueba, reduciendo la diferencia entre los parámetros de la primera lente de prueba y los de la lente finalmente adaptada, disminuyendo el tiempo de adaptación, para proporcionar la mejor rehabilitación visual a los pacientes con queratocono de una forma segura y eficaz.

1.4. Objetivos

Objetivo general:

Desarrollar una guía clínica basada en la evidencia que permita estandarizar y simplificar el proceso de adaptación de LC RPG corneales en pacientes con queratocono de una forma segura y eficaz.

Objetivos específicos:

1. Cuantificar la calidad de vida de los pacientes con queratocono relacionada con el método de corrección (gafas o LC RPG corneales) mediante el cuestionario NEI-VFQ-25 identificando la mejor opción para la rehabilitación visual de estos pacientes. ***Capítulo 3***

2. Estandarizar el proceso de adaptación de LC RPG corneales, identificando las visitas necesarias para completar la adaptación y los criterios para seleccionar y modificar los parámetros de la LC RPG a adaptar, determinando la tasa de éxito en la adaptación de LC RPG corneales en sujetos sanos y con queratocono. ***Capítulo 4.1***

3. Determinar las posibles diferencias entre el radio de la LC RPG calculado siguiendo las recomendaciones actuales del fabricante con el radio finalmente adaptado. ***Capítulos 4.2 y 6.3***

4. Analizar la práctica clínica optométrica en el manejo del paciente con queratocono en España y Reino Unido. ***Capítulo 4.3***

5. Determinar la fiabilidad y utilidad de la topografía corneal en la adaptación de LC RPG en ojos con queratocono cuantificando la repetibilidad (topografía de reflexión) tanto de los valores topográficos como de la medida de las aberraciones corneales de la cara anterior y evaluando la intercambiabilidad de distintas tecnologías topográficas (Plácido versus Plácido-Scheimpflug). ***Capítulo 5***

6. Proponer nuevos valores de las aberraciones corneales para mejorar los criterios empleados en la detección y clasificación de ojos con queratocono. ***Capítulo 5.4***

7. Desarrollar y validar un nuevo nomograma para la selección de los parámetros de las LC RPG en ojos con queratocono que permita simplificar el proceso de adaptación reduciendo la diferencia entre los parámetros de la primera lente probada y los de la lente finalmente adaptada. ***Capítulo 6.1***

8. Elaborar y validar una guía de adaptación de LC RPG corneales en queratocono bajo los estándares del consorcio AGREE-II que permita disminuir el tiempo necesario para completar la adaptación, tanto para el profesional como para el paciente, reduciendo el número de LC, tanto de prueba como pedidas al fabricante, necesarias para completar la adaptación de la LC RPG adecuada en cada caso. ***Capítulo 7***

1.5. Material y métodos

A continuación se describe de forma generalizada la parte metodológica empleada en este proyecto de investigación. Para una descripción en detalle del material y métodos usados en cada uno de los estudios que componen esta tesis doctoral es necesario consultar los **Capítulos 3, 4, 5, 6 y 7** de esta memoria en la que se presenta detalladamente cada publicación a las que ha dado lugar este trabajo de investigación.

1.5.1. Sujetos y pacientes

Este proyecto de investigación fue aprobado por el Comité Ético de Investigación Clínica de la Universidad de Valladolid (Anexo 2), y todos los voluntarios y pacientes que han participado fueron tratados acorde con la declaración de Helsinki y demás legislación aplicable a la investigación biomédica, especialmente la referente a materia de protección de datos y privacidad de los pacientes (Ley 14/2007 de investigación biomédica; Ley 41/2002 básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica; Ley Orgánica 15/1999, de Protección de Datos de Carácter Personal). Los pacientes con queratocono decidieron libremente participar en esta investigación después de recibir una hoja con la información que describía

la naturaleza del estudio, los detalles de su participación, etc. y tras recibir respuesta a todas sus preguntas por parte del equipo investigador firmaron el consentimiento informado (Anexo 3).

En términos generales, en este proyecto de investigación han participado 74 pacientes con queratocono, 115 sujetos sanos, 464 profesionales (optometristas/contact lens opticians) y 9 expertos en adaptar LC en córneas irregulares por queratocono. Además se han revisado retrospectivamente más de 500 historias clínicas de adaptaciones de LC realizadas por la Unidad de Optometría del IOBA.

En el grupo de pacientes con queratocono (grupo de estudio) se han incluido pacientes diagnosticados de queratocono por especialistas en superficie ocular tanto del IOBA como del Hospital Clínico Universitario de Valladolid, tras un examen ocular completo. Se excluyeron a todos aquellos pacientes que hubieran sido sometidos a algún tipo de cirugía ocular, así como cualquier otra patología ocular activa o uso de medicación que pudiera afectar la fisiología ocular. Además, para los estudios descritos en los **Capítulos 3, 4.1, 4.2 y 6.2** los pacientes con queratocono además debían ser usuarios de LC RPG corneales y no presentar ningún tipo de contraindicación para el uso de LC.

Como grupo control, se han incluido sujetos sanos sin ningún tipo de patología ocular. Se excluyeron a aquellos sujetos con enfermedades activas de la superficie ocular, opacidades de la córnea, glaucoma, uso de medicación que pudiese afectar a la fisiología ocular o antecedentes de cualquier tipo de cirugía ocular. Además, en los estudios descritos en el **Capítulo 3** los sujetos sanos debían ser portadores de cualquier tipo de LC (RPG o hidrofílica); en el **Capítulo 4.1** debían ser usuarios de LC (RPG o

hidrofílica) o haber iniciado al menos un proceso de adaptación de LC RPG mientras que en los **Capítulos 4.2 y 6.1** debían ser usuarios de LC RPG corneales.

El **Capítulo 4.1** recoge un análisis retrospectivo que incluyó 232 adaptaciones de cualquier tipo de LC (RPG o hidrofílica) iniciadas y completadas por la Unidad de Optometría del IOBA (desde 2010 hasta 2014).

En el **Capítulo 4.3** se incluyeron 464 profesionales de la visión ejercientes en Reino Unido (126 Optometrists y Contact lens opticians) y en España (338 optometristas colegiados) que completaron el cuestionario diseñado para este estudio.

Finalmente, el **Capítulo 7** recoge el proceso de elaboración y validación de la guía clínica para la adaptación de LC RPG corneales en la que ha participado un equipo de 9 expertos ajenos al equipo de investigación pertenecientes a diferentes universidades nacionales (Universidad Complutense de Madrid, Universidad Europea de Madrid y Universidad de Alicante) e internacionales [Universidad de Plymouth (Reino Unido), University of New South Wales, Sydney (Australia), University of Minho (Portugal) y Universitá del Salento (Italia)] así como de centros profesionales no universitarios [Hospital Oftalmar (España), Novolent-Novovisión (España), Visser Contactlenzenpraktijk (Holanda) y Orriss & Low Optometrists (Reino Unido)]. Para el desarrollo y validación de esta guía se han empleado las recomendaciones del consorcio AGREE-II para la elaboración de guías clínicas.[105]

La tabla 8 resume el número de ojos, sujetos y pacientes incluidos en cada uno de los estudios que conforman este proyecto de investigación.

Capítulo	Sanos	Queratoconos
3	25 sujetos	25 pacientes
4.2	40 ojos (40 sujetos)	40 ojos (22 pacientes)
5.1	25 ojos (25 sujetos)	25 ojos (25 pacientes)
5.2	36 ojos (36 sujetos)	36 ojos (36 pacientes)
5.3	56 ojos (56 sujetos)	56 ojos (33 pacientes)
5.4	70 ojos (70 sujetos)	77 ojos (45 pacientes)
6.1	50 ojos (50 sujetos)	85 ojos (49 pacientes)
6.2	-	81 ojos (46 pacientes)

Tabla 8. Número de ojos, sujetos y/o pacientes incluidos en cada capítulo.

1.5.2. Lentes de contacto

En este proyecto de investigación se han utilizado varios diseños de LC RPG en función de la naturaleza de cada estudio y pueden resumirse en:

- **Lente KAKC** [Conóptica (España) / Hecht Contaclinsen (Alemania)]: LC RPG corneal con diseño específico para queratocono (esférica pentacurva) (Tabla 9). Solo se incluyeron lentes esféricas de manera que los casos que precisaron diseños tóricos o periferia individual fueron excluidos. Este diseño de LC se ha utilizado en los estudios descritos en los **Capítulos 3, 4.1, 4.2, 6.1 y 6.2.**

- **Lente BIAS-S** [Conóptica (España) / Hecht Contaclinsen (Alemania)]: LC RPG corneal biasférica de rotación simétrica (Tabla 9) utilizada en los sujetos del grupo control en los estudios descritos en los **Capítulos 4.1, 4.2 y 6.1.**

	KAKC	BIAS- S
Fabricante	Conóptica-Hecht Contactlinsen	
Diseño	Esférica pentacurva	Biasférica de rotación simétrica
Potencia (D)	±30,00 D (pasos de 0,25)	±30,00 D (pasos de 0,25)
Radio base (mm)	4,80 a 8,90 (pasos de 0,05)	6,50 a 10,00 (pasos de 0,05)
Diámetro total	8,40 a 12,20 (pasos de 0,10)	7,00 to 12,20 (pasos de 0,10)
Diámetro estándar	9,20	9,60
Material	Boston ES/EQ/EO/XO/XO2	

Tabla 9. Descripción general de las LC RPG utilizadas en este proyecto (KAKC para ojos con queratocono; BIAS-S para ojos sanos).

1.5.3. Equipamiento

Los principales equipos utilizados en este proyecto han sido los siguientes:

- **Topógrafo corneal Allegro Topolyzer** (WaveLight Technologie AG, Laboratorios Alcon, Erlangen, Alemania) / comercializado por Oculus bajo el nombre **Oculus Keratograph** (Oculus Optikgeräte GmbH, Wetzlar, Alemania) [Software de datos de pacientes versión 6.02r24; Software de examen versión 1.75r11]. Es un topógrafo de discos de Plácido que consta de 22 anillos concéntricos que proporcionan medición de 22.000 puntos de la cara anterior de la córnea. Este dispositivo se ha utilizado en los **Capítulos 4.2, 5.1, 5.2, 5.3, 5.4, 6.1 y 6.2.**

- **Módulo de adaptación y simulación de LC RPG APEX®** (versión 1.1.0.6) diseñado por Hecht-Contactlinsen en colaboración con Oculus y comercializado en España por Conóptica (Barcelona). Este módulo de adaptación utiliza la topografía corneal obtenida con el topógrafo Oculus Keratograph y muestra un patrón de fluoresceína simulado del diseño RPG especificado para ayudar en la adaptación y selección de

parámetros de las LC RPG. Este software de simulación se ha utilizado en los **Capítulos 4.2, 6.1 y 6.2.**

- **Topógrafo/Tomógrafo Galilei G4** (Ziemer, Port, Suiza) (Software versión V6.0.3) comercializado en España por BLOSS Group (Barcelona). Equipo mixto que combina discos de Plácido con dos cámaras de Scheimpflug ubicadas a 180º una de la otra. Este dispositivo permite analizar 122.000 puntos del segmento anterior del ojo en un modelo tridimensional, que permite analizar tanto la cara anterior como posterior de la córnea. Este topógrafo se ha utilizado en los **Capítulos 5.3 y 6.1.**

- **Topógrafo Orbscan II** (Bausch & Lomb, Rochester, Nueva York, EEUU). Dispositivo que funciona por escaneo mediante barrido de hendidura en combinación con discos de Plácido para proporcionar un análisis exhaustivo de la cara anterior y posterior de la córnea. Este equipo se ha utilizado en el **Capítulo 6.1.**

- **Queratómetro de Helmholtz** (OM-4, Topcon, Japón). Este dispositivo permite medir los radios de curvatura de los meridianos principales de la cara anterior de la córnea de forma simultánea (en milímetros o dioptrías) utilizando un sistema de miras fijas y de doblaje móvil. Este tipo de queratómetro se ha usado en los **Capítulos 4.1, 6.1 y 6.2.**

1.5.4. Cuestionarios

Se han utilizado distintos cuestionarios en este proyecto de investigación para llevar a cabo diferentes estudios:

- **Cuestionario de Funcionamiento Visual (VFQ-25) del National Eye Institute.**[106] Este instrumento permite evaluar el impacto que tiene un problema visual en la calidad de vida, basándose en la percepción subjetiva de los sujetos afectados. Consta de 25 preguntas de fácil comprensión y respuesta, orientadas a evaluar 11 dominios dependientes de la visión y uno de salud general, entre los que se incluyen: salud general, dolor ocular, actividades en visión próxima, actividades en visión lejana, función social, salud mental, visión general, dificultades de rol, dependencia, conducción, visión del color y visión periférica. Este cuestionario se ha utilizado en el **Capítulo 3** para evaluar la calidad de vida de los pacientes con queratocono con el porte de LC RPG y gafas.

- **Cuestionario sobre la práctica optométrica en el manejo del paciente con queratocono**. Se ha diseñado un cuestionario online específico para el estudio descrito en el **Capítulo 4.3** que evalúa las actitudes y práctica profesional en el manejo del paciente con queratocono. Este cuestionario se elaboró en español y en inglés, y fue validado por profesionales españoles y británicos para garantizar el mismo significado y objetivo de ambas versiones previamente a su difusión entre profesionales (optometristas y adaptadores de LC) ejercientes en Reino Unido y en España que se realizó por diferentes medios electrónicos (en Reino Unido: General Optical Council, British Contact Lens Association, Optometry Today; y en España: Colegios y Delegaciones Regionales del Colegio Nacional de Ópticos-Optometristas).

- **Instrumento AGREE II (evaluación de guías de práctica clínica).**[105] Este instrumento y su cuestionario específico ha sido utilizado en el

Capítulo 7 tanto para elaborar como evaluar la guía clínica basada en la evidencia para adaptar LC RPG corneales en queratoconos propuesta en esta tesis doctoral. Esta herramienta sirve para evaluar el rigor metodológico y la transparencia con la que se desarrolla una guía de práctica clínica. Para ello, presenta una serie de recomendaciones para la elaboración de la guía y para su evaluación por un mínimo de 4 expertos utilizando un cuestionario específico compuesto por seis dominios diferentes con 23 ítems en total. Cada ítem debe ser clasificado en una escala de 7 puntos (siendo 1: muy en desacuerdo; y 7: muy de acuerdo). Para cada uno de los seis dominios incluidos en AGREE II se calcula una puntuación de calidad, obteniendo una puntuación global final con la respuesta de los expertos que proporciona el valor de la calidad metodológica de la guía propuesta.

1.5.5. Análisis estadístico

El análisis estadístico de este proyecto de investigación se ha llevado a cabo con el programa SPSS versión 15.0 (SPSS, Chicago, EEUU) para Windows. Además, en el **Capítulo 3** se realizó un Rasch Analysis empleando el algoritmo de Massof para el análisis del cuestionario de calidad de vida (VFQ-25).[107]

En todos los estudios que se recogen en esta memoria se determinó la normalidad de las variables mediante la prueba de Kolmogorov-Smirnov, tomando un valor de $p>0,05$ como distribución normal de la muestra para emplear el contraste de hipótesis más adecuado en función de las variables a analizar.

Cada capítulo de esta memoria describe en detalle el análisis estadístico utilizado, identificando los test empleados tanto para el análisis descriptivo (presentación de media, desviación estándar, intervalo de confianza al 95%, rango máximo y mínimo, mediana, moda, rango intercuartílico, etc.) como inferencial (identificando el test empleado y su significancia estadística para determinar correlaciones, diferencias, establecer modelos, etc.) así como otros métodos matemáticos empleados como el análisis de Bland-Altman, coeficiente de variación, repetibilidad, precisión, coeficiente de correlación intraclase, etc.

CAPÍTULO	NÚMERO	LC	EQUIPAMIENTO	CUESTIONARIO
3. Impacto de la corrección con LC RPG en la calidad de vida	25 sujetos sanos 25 pacientes queratocono	KAKC en queratocono Cualquiera en sanos	----	NEI-VFQ-25
4.1. Éxito de adaptación a LC RPG	232 adaptaciones	Cualquiera	Queratómetro	----
4.2. Fiabilidad de las recomendaciones actuales para adaptar LC RPG	40 ojos sanos 40 ojos queratocono	KAKC BIAS-S	Oculus Keratograph / Allegro Topolyzer Software APEX	----
4.3. Manejo optométrico de los pacientes con queratocono	126 Reino Unido 338 España	----	----	Específico diseñado para este estudio
5.1. Repetibilidad de la topografía en queratocono	25 ojos sanos 25 ojos queratocono	----	Oculus Keratograph / Allegro Topolyzer	----
5.2. Repetibilidad de la medida de las aberraciones corneales en queratocono	36 ojos sanos 36 ojos queratocono	----	Oculus Keratograph / Allegro Topolyzer	----
5.3. Intercambiabilidad de tecnologías (Plácido versus Scheimpflug) en queratocono	56 ojos sanos 56 ojos queratocono	----	Oculus Keratograph / Allegro Topolyzer Galilei G4	----
5.4. Clasificación de la severidad del queratocono con topografía corneal	70 ojos sanos 77 ojos queratocono	----	Oculus Keratograph / Allegro Topolyzer	----
6.1. Nuevo algoritmo para mejorar la adaptación de LC RPG en queratocono	50 ojos sanos 85 ojos queratocono	KAKC BIAS-S	Oculus Keratograph / Allegro Topolyzer Orbscan II; Galilei G4; Queratómetro	----
6.2. Fiabilidad del proceso de cálculo de la primera a adaptar en queratocono	81 ojos queratocono	KAKC	Oculus Keratograph / Allegro Topolyzer Queratómetro	----
7. Guía Clínica adaptación LC RPG en queratocono	----	----	----	AGREE II

Tabla 10. Esquema del material y métodos utilizado en este proyecto de investigación.

1.6. Resultados

En este apartado se resumen los principales resultados encontrados en cada uno de los estudios que forman parte de esta tesis doctoral. Para una descripción más detallada de los resultados encontrados es preciso consultar el capítulo correspondiente a cada uno de los estudios que conforman esta memoria.

Capítulo 3. Impacto de la corrección con LC RPG en la calidad de vida de los pacientes con queratocono

Este capítulo ha encontrado que los pacientes con queratocono tienen peor calidad de vida cuando usan las gafas como medio corrector que la que tienen sujetos sanos portadores de gafas, al mostrar una menor puntuación en todas las subescalas y en la puntuación global del cuestionario NEI-VFQ-25 ($p<0,01$).

Sin embargo, cuando portan LC RPG, aunque la puntuación que muestran los pacientes con queratocono sigue siendo menor que la obtenida por los sujetos sanos usuarios de LC, la diferencia entre ambos grupos es mucho menor y sólo fue estadísticamente significativa ($p<0,04$) en cuatro subescalas (actividades en visión lejana, salud mental, visión del color y visión periférica). Incluso en la subescala de visión general, los pacientes

con queratocono muestran mayor puntuación que la presentada por los sujetos sanos (p=0,38). Esta reducción en las diferencias entre pacientes con queratocono y sujetos sanos es un claro indicador del impacto que tiene la corrección con LC RPG en la calidad de vida de los pacientes con queratocono.

Al comparar la puntuación del grupo de queratoconos usando gafas o LC RPG se encontró una mejor calidad de vida (mayor puntuación) con el porte de sus LC RPG en todas las subescalas y en la puntuación final global ($p \leq 0,01$), excepto en dos subescalas; la de dolor ocular ($p<0,01$) y la salud mental (p=0,25), que presentaron mejores valores con la gafa.

Por último, los pacientes con queratocono más avanzado (clasificación de Amsler-Krumeich) presentaron peor calidad de vida (menor puntuación) que los pacientes con queratoconos leves o moderados al usar sus gafas ($p<0,01$ Kruskal-Wallis), mientras que con el porte de LC RPG no se encontraron diferencias significativas entre los distintos grados de severidad de la enfermedad (p=0,06 Kruskal-Wallis).

Capítulo 4. Estado actual del proceso de adaptación de LC RPG en pacientes con queratocono

4.1. Éxito de adaptación a LC RPG

Este estudio encontró un mayor porcentaje de éxito a la adaptación de LC RPG en pacientes con córnea irregular (tasa del 96,7%) que en sujetos sanos (tasa del 69,3%), tras analizar retrospectivamente la adaptación de LC en 232 sujetos (61,2% mujeres y 38,8% hombres) de las cuales el 71,6% (n=166; 68,7% mujeres y 31,3% hombres) se realizaron por razones

refractivas (miopía, hipermetropía, astigmatismo y/o presbicia) y el 28,4% restante (n=66; 42,4% mujeres y 57,6% hombres) por razones terapéuticas en pacientes con algún tipo de patología (queratocono, degeneración marginal pelúcida, afaquia, etc.), astigmatismo irregular secundario a procedimientos de cirugía refractiva o traumatismos o tratamientos de ortoqueratología.

Adaptaciones refractivas

De las 166 adaptaciones con fines refractivos, las LC RPG fueron la opción de primera elección en el 53% de los casos (n=88), seguido de las LC hidrofílicas de hidrogel de silicona (31,9%, n=53) y las LC hidrofílicas de hidrogel convencional (15,1%, n=25).

De los 88 sujetos que iniciaron la adaptación con LC RPG, el 69,3% (n=61) se adaptó a las LC RPG, mostrando un porte confortable de 7,61 ± 1,54 horas al día, sin complicaciones relevantes en la superficie ocular. La experiencia previa de uso de LC no pareció mostrar un impacto clínicamente relevante en la tasa de adaptación ya que los nuevos usuarios que nunca habían usado LC, mostraron una tasa de adaptación del 72%, similar a la encontrada en los usuarios previos de LC hidrofílicas, que mostraron una tasa del 62%, mientras que los usuarios previos de LC RPG mostraron una tasa mayor, del 92,3%.

Adaptaciones terapéuticas

En el grupo de adaptaciones terapéuticas (56,1% queratocono, 28,8% ortoqueratología, 4,5% post cirugía refractiva o queratoplastia y el 10,6% restante por otras causas) la LC RPG fue la primera elección en el 92,4% de los casos (n=61). De estos 61 casos (42 con córnea irregular y 19 con

ortoqueratología) 59 de ellos se adaptaron con éxito al porte de las LC RPG (96,7%) y únicamente en 2 pacientes con queratocono avanzado no pudo completarse la adaptación de LC RPG corneales.

4.2. Fiabilidad de las recomendaciones actuales para adaptar LC RPG

En este estudio se encontró que el software de adaptación de LC APEX® presenta una alta repetibilidad en el valor del radio base propuesto de la LC RPG tanto en ojos sanos (CV=0,32%) como en ojos con queratocono (CV=0,51%). Sin embargo, este software propone un radio base estadísticamente ($p<0,01$) más plano que el radio de la LC RPG finalmente adaptada tanto en ojos sanos (diferencia media de +0,07 ± 0,05 mm; límites de acuerdo -0,03 a +0,17 mm; $R^2 = 0,852$, $p<0,01$) como en ojos con queratocono (diferencia media de +0,11 ± 0,15 mm; límites de acuerdo -0,19 a +0,41 mm; $R^2 = 0,969$, $p<0,01$).

Las diferencias entre el radio propuesto por el software APEX® y la lente finalmente adaptada pueden reducirse ajustando el radio propuesto por el software mediante ecuaciones de regresión lineal tanto en ojos sanos [diferencia media de -0,01 ± 0,05 mm con el ajuste (Radio_APEX® (mm)*1,06 – 0,53)] como en ojos con queratoconos [diferencia media de -0,01 ± 0,14 mm con el ajuste (Radio_APEX® (mm)*0,88 + 0,77)]. Igualmente, estas diferencias se reducirían con ecuaciones específicas para cada grado de severidad; en queratocono grado 1 a +0,01 ± 0,04 mm con el ajuste (Radio_APEX® (mm)*0,81 + 1,38); en grado 2 a +0,03 ± 0,10 mm con el ajuste (Radio_APEX® (mm)*0,84 + 1,07); y en grado 3 a +0,02 ± 0,16 mm con el ajuste (Radio_APEX® (mm)*0,93 + 0,28).

4.3. Manejo optométrico de los pacientes con queratocono en Reino Unido y España

En este estudio se ha encontrado una práctica profesional muy similar entre profesionales en Reino Unido y en España a la hora de manejar los pacientes con queratocono tanto en el diagnóstico, adaptación de LC RPG o derivación al oftalmólogo a pesar de las diferencias que presenta el ejercicio profesional de la Optometría en ambos países.

Un total de 464 profesionales (126 en Reino Unido y 338 en España) contestaron a un cuestionario online específicamente diseñado para este estudio, encontrando que sólo el 38,1% de los profesionales de Reino Unido disponen de topógrafo en su práctica habitual, frente al 59,8% reportado en España, siendo más proclives los profesionales con topógrafo a prescribir mayor número de LC RPG, detectar mayor número de nuevos casos de queratocono y co-manejar un mayor número de casos con un oftalmólogo.

Predominantemente en ambos países, los encuestados detectaron menos de 5 nuevos casos de queratocono por año (65,1% en Reino Unido y 65,7% en España, p=0,21). La mayoría de los profesionales (79,4% en Reino Unido y 75% en España, p=0,68) consideraron que es necesaria una combinación de múltiples factores en la detección de los pacientes con queratocono (historia clínica, agudeza visual, reflejos en tijeras durante la retinoscopía, queratometría manual, topografía corneal y signos biomicroscópicos de polo anterior).

En general, los profesionales respondieron que el uso de clasificaciones para gradar la severidad del queratocono es relevante en la práctica clínica (67,5% en Reino Unido y 70,7% en España, p=0,50), sin embargo, sólo el

7,1% en Reino Unido y el 17,8% en España (p=0,01) utilizan algún tipo de clasificación de queratocono de forma habitual.

Los encuestados, en su gran mayoría, consideraron que la adaptación de LC RPG en ojos con queratocono es más complicada que en ojos sanos (79,4% en Reino Unido y 80,5% en España; p=0,79), utilizando de media 3,2 ± 1,4 lentes de prueba los profesionales británicos y 3,4 ± 1,2 lentes de prueba los optometristas españoles (p=0,72) para adaptar LC RPG en queratoconos.

En cuanto a la derivación y co-manejo de los pacientes con queratocono, la mitad de los encuestados remitió a estos pacientes al oftalmólogo en el momento del diagnóstico inicial (50% en Reino Unido y 50% España; p=1,00), y la gran mayoría no trabaja de manera conjunta con el oftalmólogo después de que el paciente sea sometido a algún tipo de técnica quirúrgica (60,3% en Reino Unido y 72,8% en España; p=0,01).

Capítulo 5. Fiabilidad y utilidad de la topografía corneal en el proceso de adaptación de LC RPG en queratocono

5.1. Repetibilidad de la topografía de discos de Plácido en queratocono

Este capítulo demuestra que el topógrafo Allegro Topolyzer / Oculus Keratograph basado en discos de Plácido es repetible (coeficiente de variación (CV) <1% para la mayoría de las variables analizadas) al explorar tanto ojos sanos como ojos con queratocono [encontrando diferencias estadísticamente significativas entre los principales datos topográficos (potencia máxima y mínima corneal, punto de máxima potencia corneal, excentricidad, diámetro corneal, ISV, IVA, KI, Rmin y coeficiente de

aberraciones) con menores valores en ojos sanos que en ojos con queratocono ($p<0,02$), excepto para el índice Rmin que fue mayor en los ojos sanos].

El análisis pormenorizado de la repetibilidad en cada una de las variables topográficas analizadas mostró una alta repetibilidad tanto en ojos sanos como en ojos con queratocono para la potencia máxima (CV=0,21% y 0,47%, respectivamente); potencia mínima (0,19% y 0,36%); punto de máxima potencia corneal (0,22% y 0,77%); diámetro corneal (0,27% y 0,33%); ISV (4,82 y 3,10%); IVA (7,05% y 3,80%); KI (0,29% y 0,72%); Rmin (0,53% y 0,78%), y coeficiente de aberraciones (0% y 4,00%), excepto en el valor de la excentricidad corneal que presentó peor repetibilidad (CV=5,79% y 14,53%, respectivamente).

5.2. Repetibilidad de la medida de las aberraciones corneales en queratocono

Este estudio encontró una mejor repetibilidad en la medida de las aberraciones corneales de alto orden con el topógrafo Allegro Topolyzer / Oculus Keratograph en ojos con queratocono [CV entre el 2,06% (RMS total) y 25,82% (tetrafoil), y un intervalo de correlación intraclase (ICC) entre 0,839 (RMS 8º orden) y 0,996 (coma-like)] que en ojos sanos (CV entre el 6,49% (aberración esférica) y 37,18% (astigmatismo secundario) y un ICC entre 0,227 (RMS 7º orden) y 0,982 (coeficiente Z^{+1}_{3})]. Todos los coeficientes de Zernike analizados fueron significativamente mayores en los ojos con queratocono que en sanos ($p\leq0,03$), excepto en los coeficientes Z^{+1}_{3}, Z^{+3}_{3}, Z^{-4}_{4}, Z^{+4}_{4} en los que no se encontraron diferencias significativas ($p>0,30$).

Al analizar la repetibilidad de la medida de las aberraciones en queratocono por grado de severidad según la clasificación de Amsler-Krumeich, se obtuvo una tendencia a encontrar mejor repetibilidad para los coeficientes de Zernike a medida que aumenta la severidad de la enfermedad, siendo el coma el que presentó mejores valores de repetibilidad.

5.3. Intercambiabilidad de tecnologías topográficas (Plácido *versus* Scheimpflug) en queratocono

En este estudio se encuentra un mejor acuerdo en las medidas topográficas de cara anterior proporcionadas por la topografía de discos de Plácido y la topografía de Placido-Scheimpflug en ojos sanos (límites de acuerdo al 95%: queratometría simulada media o SimK -0,13 a +0,40 D; potencia corneal máxima -0,30 a 0,59 D; potencia corneal mínima -0,29 a +0,51 D; astigmatismo -0,60 a +0,64 D; J_0 -1,15 a +1,13 D; J_{45} -1,10 a +1,20 D; punto de máxima potencia corneal -0,70 a +1,17 D; diámetro corneal -0,96 a +0,76 mm) que en ojos con queratocono (límites de acuerdo al 95%: SimK -2,84 a +4,55 D; potencia máxima -2,80 a +5,21 D; potencia mínima -3,68 a +4,70 D; astigmatismo -1,90 a +2,95 D; J_0 -2,85 a +3,20 D; J_{45} -3,21 a +3,05 D; punto de máxima potencia corneal -7,00 a +4,51 D; diámetro corneal -1,00 a +0,88 mm) que podría permitir el uso intercambiable de ambos equipos con cautela en ojos sanos, pero lo desaconseja en casos de queratocono.

El topógrafo de discos de Plácido proporcionó un valor medio menor en todas las variables comparadas que el topógrafo Placido-Scheimpflug en ojos sanos (excepto J_{45} y diámetro corneal) y en ojos con queratocono (excepto J_0, J_{45}, punto de máxima potencia corneal y diámetro corneal).

Todas las medidas fueron significativamente diferentes ($p<0,05$) entre los dos dispositivos tanto en ojos sanos (excepto la potencia del astigmatismo, J_0, J_{45} y diámetro corneal; $p\geq0,10$) como en ojos con queratocono (excepto la potencia corneal mínima, J_0, J_{45} y diámetro corneal; $p\geq0,08$).

5.4. Clasificación de la severidad del queratocono con topografía corneal

Este estudio propone mejorar la clasificación de Amsler-Krumeich incluyendo el valor del coma (de la cara anterior corneal, obtenido con topografía de discos de Plácido) identificando nuevos valores de corte para diferenciar entre ojos sanos y ojos con queratocono (el punto de corte de 0,377 µm mostró un 100% de sensibilidad y un 100% de especificidad) y para diferenciar entre los grados de severidad del queratocono 1 y 2 con un punto de corte de 1,466 µm, con 90% de sensibilidad, y 100% de especificidad y entre los grados 2 y 3 con un punto de corte de 2,790 µm, con 92% de sensibilidad, y 83,3% de especificidad.

Así pues, se encontró que el valor del coma en la muestra analizada fue significativamente mayor ($p<0,01$) en ojos con queratocono (2,294 ± 0,137 µm; intervalo de confianza (IC) 95% 2,020 a 2,567 µm) que en sanos (0,173 ± 0,009 µm; IC95% 0,154 a 0,193 µm) y se encontraron diferencias significativas entre los grados de severidad del queratocono ($p<0,01$) (grado 1: 0,948 ± 0,069 µm, IC95% 0,803 a 1,093 µm; grado 2: 2,062 ± 0,103 µm, IC95% 1,853 a 2,273 µm; grado 3: 3,646 ± 0,135 µm, IC95% 3,368 a 3,925 µm).

Capítulo 6. Desarrollo de un nuevo algoritmo para simplificar la adaptación de LC RPG en queratocono

6.1. Nuevo algoritmo para mejorar la adaptación de LC RPG en ojos con queratocono

Este estudio muestra el desarrollo y posterior validación clínica de un nuevo nomograma o algoritmo para seleccionar los parámetros de la primera lente de prueba en adaptaciones de LC RPG de diseño corneal en ojos con queratocono. Este algoritmo permite reducir las diferencias entre la primera lente probada (calculada por el nuevo algoritmo) y la lente finalmente adaptada y simplificar el proceso de adaptación con un número de lentes de prueba (1,6 ± 0,8 versus 1,3 ± 0,5; p=0,02), lentes pedidas al fabricante (1,4 ± 0,6 versus 1,1 ± 0,3; p<0,01) o de visitas (3,4 ± 0,7 versus 3,2 ± 0,4; p=0,08) ligeramente superior al empleado en adaptaciones de LC RPG refractivas en sujetos sanos, lo que hace que, empleando el nuevo algoritmo, ambos procesos de adaptación sean clínicamente similares.

El cálculo del nuevo algoritmo se realizó con un estudio retrospectivo de 35 adaptaciones previas de LC RPG corneales en ojos con queratocono tras realizar un análisis de regresión múltiple por pasos (stepwise) para determinar la ecuación de mejor ajuste entre el radio final adaptado y las diferentes variables clínicas y topográficas analizadas (edad, refracción, potencia corneal, astigmatismo corneal, excentricidad, punto de máxima potencia, espesor corneal central, esfera de mejor ajuste anterior y posterior y queratometría manual) presentando una buena correlación entre el radio base de la lente propuesta y el radio finalmente adaptado (R^2=0,825; p<0,01). Este algoritmo se incluyó en la web de libre acceso (www.calculens.com).

Por su parte, el nomograma se validó prospectivamente en una nueva muestra de 38 pacientes (50 ojos) con queratocono, realizando 50 nuevas adaptaciones de LC RPG de diseño corneal (KAKC, Conóptica España) en las que el radio de la lente propuesto por Calculens.com mostró menor diferencia con el radio finalmente adaptado (diferencia de -0,01 ± 0,12 mm, p=0,65) que la mostrada por el radio propuesto siguiendo las indicaciones que proporciona el fabricante (diferencia de +0,12 ± 0,22 mm, p<0,01) y el radio de la lente propuesto por el software APEX® (diferencia de -0,14 ± 0,16 mm, p<0,01).

Empleando el nuevo algoritmo (Calculens.com) las diferencias entre el radio de la lente propuesto y el finalmente adaptado fueron iguales o menores a 0,05 mm (denominando a esta diferencia como tasa de acierto) en el 58% de los casos; mientras que siguiendo las recomendaciones del fabricante esta tasa de acierto solo se consiguió en el 26% de los casos y utilizando el software de simulación APEX® la tasa de acierto fue del 34%.

6.2. Fiabilidad del proceso de cálculo de la primera lente de prueba a adaptar en queratocono

Este capítulo demuestra que el radio base de la LC RPG corneal propuesto por el algoritmo desarrollado en esta tesis doctoral (Calculens.com) muestra menos diferencias con el radio finalmente adaptado que el radio calculado siguiendo otras 9 guías o recomendaciones que proponen diferentes fabricantes o autores para calcular el radio base de la primera lente de prueba a adaptar en ojos con queratocono.

Solo tres recomendaciones (Calculens.com; pauta propuesta por el Centre of Contact Lens Research (University of Waterloo, Canadá)[98] y la elección del radio como K medios) no mostraron diferencias estadísticamente

significativas (p<0,05 T-Student para datos pareados) con el radio finalmente adaptado. Sin embargo, el algoritmo desarrollado en esta tesis (Calculens.com) mostró la menor diferencia (0,00 ± 0,12 mm) y mayor tasa de acierto (un 50,6%) que las otras dos recomendaciones con diferencias de +0,03 ± 0,17 mm (tasa de acierto del 26,3%) y +0,03 ± 0,18 mm (tasa de acierto del 34,6%) respectivamente. Incluso alguna de las recomendaciones[67] presentó diferencias de -0,38 ± 0,22 mm con el radio finalmente adaptado y una tasa de acierto de sólo el 3,8%.

Capítulo 7. Guía clínica para la adaptación de LC RPG en queratocono

En este capítulo se presenta la guía clínica basada en la evidencia que se ha desarrollado en esta tesis para adaptar LC RPG corneales en queratocono siguiendo las recomendaciones propuestas por el Consorcio Agree (Instrumento Agree II)[105] que ha sido evaluada por 9 expertos externos, tanto nacionales como internacionales, con amplia experiencia en la adaptación de LC. La guía propuesta ha obtenido unos resultados satisfactorios en todos los dominios del Instrumento Agree II (alcance y objetivo 89%, participación de los implicados 74%, rigor en la elaboración 84%, claridad de la presentación 89%, aplicabilidad 72% e independencia editorial 88%) y en la evaluación global (calidad general de la guía 85%) lo que permite su recomendación para el manejo de los pacientes con queratocono con LC RPG de diseño corneal.

1.7. Discusión

En este apartado se presenta una sucinta discusión de los principales hallazgos de esta tesis doctoral de manera global. Una discusión pormenorizada se incluye en cada uno de los capítulos en los que se detallan los diferentes estudios que se han incluido en este proyecto de investigación.

Está ampliamente descrito en la literatura que las LC RPG suponen la primera opción de manejo de los pacientes con queratocono.[1, 8, 18, 62, 65-69] Como se ha demostrado en el **Capítulo 3**, la calidad de vida de estos pacientes es mucho mayor con el porte de estas lentes que con sus gafas, siendo similar a la de sujetos sanos sin ninguna patología. Estos resultados, aparte de evidenciar los beneficios que supone el uso de LC RPG en la calidad de vida de los pacientes con queratocono, subrayan la importancia de distinguir el método corrector del defecto refractivo (gafas o LC) en la metodología de los estudios de calidad de vida que se hacen en estos pacientes o en los que se evalúa la eficacia de alguna técnica en base a la agudeza visual alcanzada, ya que es habitual incluir pacientes con cualquier tipo de corrección o mostrar resultados sin especificar la corrección refractiva utilizada,[100, 101, 108-113] lo que resta objetividad y dificulta la comparación de los resultados.

Por su parte, la adaptación de este tipo de LC en estos pacientes está considerada como un proceso largo y complicado (**Capítulo 4.4**).[17, 18, 20, 21, 62, 65, 67-69, 99] Esta premisa está en la línea de los resultados del **Capítulo 4.3**, en el que tanto los profesionales británicos como los españoles encuestados consideran la adaptación de LC RPG en queratocono como un proceso más complicado que en sujetos sanos, constatando que no hay criterios definidos sobre cómo manejar a estos pacientes. Por ello, parece no haber grandes diferencias en la práctica optométrica en el manejo de estos pacientes, pese a las diferencias que ambos modelos profesionales podrían presentar (principalmente en el uso de fármacos diagnósticos y la colaboración con el sistema público de salud más desarrollados en Reino Unido que en España).

Los fabricantes de las LC RPG corneales con diseño específico para queratocono proporcionan pautas de adaptación para seleccionar la primera lente de prueba en estos casos o incluso se comercializan diferentes softwares de simulación con la intención de ayudar en el proceso de adaptación. Sin embargo, la lente calculada siguiendo estas indicaciones suele estar alejada de la finalmente adaptada[17, 18] (**Capítulo 4.2**) lo que hace que en vez de simplificar el proceso de adaptación, en ocasiones pueda producirse el efecto contrario, y que se necesiten más lentes, ya sean de prueba o pedidas al fabricante, traduciéndose en más visitas y más tiempo consumido durante la adaptación.

Otra de las cuestiones planteadas, es la importancia del uso de la topografía corneal en el proceso de adaptación de LC RPG. La topografía corneal es de especial utilidad en la detección temprana y seguimiento del queratocono,[10, 16] y concretamente, la topografía basada en discos de Plácido es una de las herramientas más comunes y utilizadas en la práctica

clínica, especialmente en atención primaria (**Capítulo 5.5**).[49, 114, 115] En los **Capítulos 5.1** y **5.2** se ha demostrado que la topografía corneal de discos de Plácido proporciona medidas repetibles de las principales variables topográficas, así como de las aberraciones corneales, especialmente útiles en la detección y gradación de la severidad del queratocono[37, 38] (**Capítulo 5.4**) por lo que son equipos de gran utilidad en el manejo de estos pacientes. Sin embargo, al comparar dos técnicas diferentes de topografía/tomografía (Plácido versus Plácido-Scheimpflug) las medidas entre ambos equipos en córneas con queratocono no son intercambiables, debido a la diferencia que existe entre las medidas proporcionadas (**Capítulo 5.3**). Por tanto, aunque disponer de topógrafo es de gran utilidad en el manejo de estos pacientes, el protocolo de adaptación de LC RPG no debería de ser topográfico-dependiente en estos casos, debido a la falta de acuerdo que existe entre diferentes tecnologías, resultando de gran utilidad pautas de adaptación de LC RPG independientes de los equipos topográficos de los que disponga cada profesional.

Para ello, se ha definido un protocolo de adaptación de LC RPG estructurado con 3 tipos de visitas (inicial, adaptación, y dispensación), que ha demostrado que aproximadamente 7 de cada 10 sujetos sanos y 9 de cada 10 pacientes con irregularidad corneal, se adaptan con éxito al porte de LC RPG (**Capítulo 4.1**). Además, se ha desarrollado y validado clínicamente un nuevo algoritmo para seleccionar la primera LC RPG de prueba (con diseño específico para queratocono, KAKC) (**Capítulo 6.1**) que ha mostrado mejores resultados de validación que otras recomendaciones existentes, al mostrar menor diferencia entre el radio base de la lente propuesta con el de la lente finalmente adaptada (**Capítulo 6.2**) ayudando a simplificar este proceso de adaptación.

Este nuevo algoritmo se ha incorporado en una página web (www.calculens.com) de libre acceso para ayudar a que cualquier profesional interesado en la adaptación de LC RPG pueda incorporarlo en su práctica profesional. Con el uso de Calculens.com y el protocolo de adaptación definido en esta tesis doctoral, aproximadamente tres cuartas partes de las adaptaciones de LC RPG corneales en queratocono se realizan en el número mínimo de visitas definido por el protocolo (3 visitas) y, además, la diferencia entre el radio que propone el algoritmo y el que finalmente se adapta es igual o menor a 0,10 mm en el 74% de las adaptaciones realizadas en esta tesis.

Por último, con el objetivo final de facilitar la diseminación de los resultados de esta tesis doctoral, se ha desarrollado una guía clínica basada en la evidencia para adaptar LC RPG corneales en ojos con queratocono (**Capítulo 7**) que aglutina el conocimiento generado en este proyecto de investigación. Además, se ha querido evaluar la guía bajo los estándares del instrumento AGREE II.[105] Este instrumento permite evaluar la calidad de guías clínicas propuestas en cualquier especialidad, proporcionando estrategias metodológicas tanto para su desarrollo como para su evaluación que debe hacerse obligatoriamente por expertos externos, además de establecer que información debe incorporar la guía y como debe presentarla para garantizar su calidad. El instrumento AGREE II ha sido traducido a numerosos idiomas y utilizado en más de 400 publicaciones considerándose una herramienta robusta para garantizar la calidad de una guía clínica. En esta tesis se ha contado con expertos que dominan el castellano y el inglés por lo que se ha empleado el instrumento AGREE II en ambos idiomas sin necesidad de traducirlo (tanto en su descripción, instrucciones o cuestionario de evaluación) lo que garantiza

que no se han cometido errores de interpretación en la lectura de este instrumento. Sin embargo, la guía clínica se redactó en inglés y no se optó por incluir una versión en castellano en esta tesis para evitar errores en la interpretación del equipo investigador a la hora de traducir la guía. Este aspecto puede tener un mínimo impacto en la evaluación de la guía ya que los expertos castellano hablantes tienen un dominio del inglés profesional que garantiza su capacidad como evaluador.

Finalmente, la guía propuesta muestra un razonable grado de acuerdo y aceptación por los profesionales encuestados que permite ser optimistas sobre su futuro uso por parte de los profesionales de la visión que adaptan LC RPG en pacientes con queratocono.

1.8. Conclusiones

Las conclusiones que se pueden extraer de esta tesis doctoral son las siguientes:

1. Los pacientes con queratocono tienen mejor calidad de vida (cuestionario estandarizado NEI-VFQ-25) cuando usan LC RPG corneales que cuando usan gafas.

2. El proceso de adaptación de LC RPG corneales siguiendo un protocolo estandarizado y basado en la evidencia, permite obtener una alta tasa de éxito en la adaptación al uso o porte de LC RPG tanto en sujetos sanos (7 de cada 10) como con queratocono (9 de cada 10).

3. Las recomendaciones actuales que ofrecen los fabricantes y algunos autores para adaptar LC RPG corneales en queratocono presentan diferencias clínicamente relevantes entre el radio de la LC RPG propuesto y el radio finalmente adaptado que obligan a realizar varios cambios de lente de prueba hasta identificar el radio adecuado.

4. La práctica clínica optométrica entre profesionales de Reino Unido y España es similar en el manejo del paciente con queratocono, siendo la adaptación en estos pacientes más complicada que en ojos sanos.

5. La topografía corneal basada en discos de Plácido proporciona medidas repetibles en ojos con queratocono, pero existe una falta de acuerdo entre la topografía de Placido y la de Placido-Scheimpflug que impide que las medidas topográficas sean intercambiables en pacientes con queratocono.

6. El uso de indicadores de aberraciones corneales, concretamente del coma con un valor de corte de 0,377 µm permite discriminar entre ojos sanos y ojos con queratocono lo que podría ser de gran utilidad en la detección y clasificación de los ojos con queratocono.

7. El nuevo nomograma para la selección de los parámetros de las LC RPG en ojos con queratocono (Calculens.com) permite simplificar el proceso de adaptación, reduciendo la diferencia entre los parámetros de la lente probada y los de la lente finalmente adaptada.

8. La guía de adaptación de LC RPG corneales en queratocono, desarrollada bajo los estándares del consorcio AGREE-II, permite estandarizar y simplificar el proceso de adaptación, reduciendo el número de LC, ya sean de prueba o pedidas al fabricante, necesarias para completar la adaptación de la LC RPG corneal adecuada en cada caso.

Capítulo 2

Summary of the Doctoral Thesis

2.1. State of the art

2.1.1. Definition, evolution and aetiology of keratoconus

Keratoconus (from the Greek κέρα-ς/-ατος <<cornea>> and from the Latin cōn(um) <<cone>>) is a progressive and non-inflammatory thinning corneal disorder that is characterized by a thinning and steepening of the central and paracentral cornea, leading to protrusion.[1-6] This is a bilateral and asymmetric ectatic condition,[1-6] that causes high myopia and irregular astigmatism, affecting patients' visual quality.[1-6] Keratoconus commonly appears during puberty, in the second decade of life, and it progresses until the fourth decade of life, and then generally it stabilizes,[1-6] however its progression has recently been described in patients older than 30 years.[7] The incidence of keratoconus varies from 50 to 230 per 100,000 in the general population (approximately 1 in 2,000 people),[1, 3, 8] although a recent study raises this prevalence up to one case per 375 habitants.[9]

The aetiology of this disease is uncertain but is likely to be multifactorial, involving a combination of genetic, biochemical, biomechanical and/or environmental factors.[1, 3] It is found to be more common in patients with Down syndrome, ocular allergy, ethnic factors (Asian and Arabian), mechanical factor (eye rubbing or floppy eyelid syndrome), atopy,

connective tissue disorders (Marfan syndrome), Ehlers-Danlos syndrome and Leber congenital amaurosis.[1, 3]

2.1.2. Diagnosis of keratoconus

There are several ocular symptoms and signs of keratoconus that are important in the diagnosis of this disease (Table 1), for example, significant loss of visual acuity which cannot be compensated with spectacles, increasing with-the-rule astigmatism, appearance of "scissor" shadows while performing retinoscopy, distortion of keratometry mires, characteristic topographic image pattern (Figure 1) or presence of biomicroscopy findings (Figure 2) such as Fleischer's ring, Vogt's striae, corneal scarring, focal thinning, Munson's sign or corneal hydrops in late stages.[1-6]

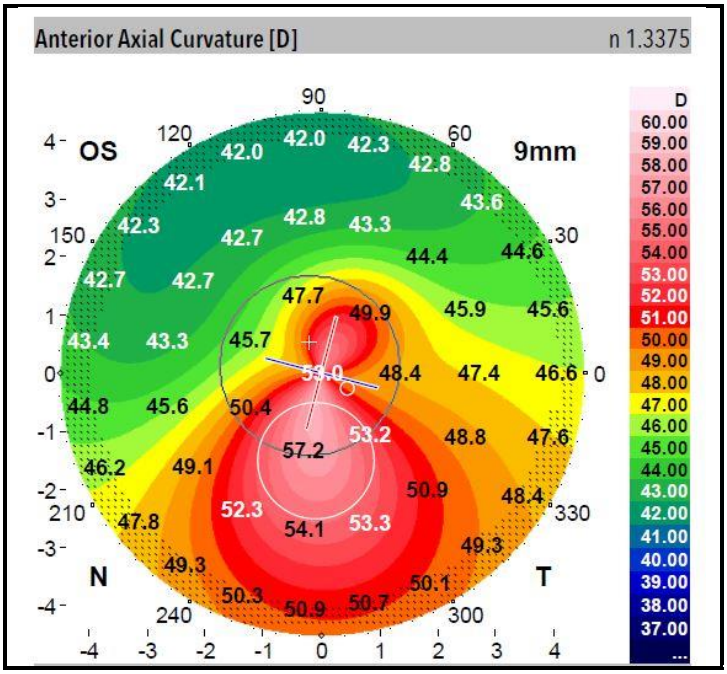

Figure 1. Typical appearance of the keratoconic topographic map.

Refractive indicators:

- Myopia and irregular astigmatism (usually with-the-rule or oblique).
- Reduction of spectacle-corrected visual acuity at distance and near.
- Change in cylinder axis and power of astigmatic correction.
- Monocular diplopia and image ghosting.

Keratometry, ophthalmoscopy and retinoscopy signs:

- Irregular or scissoring retinoscopic reflex.
- Distortion of keratomety mires.
- Visualization of the shadow of the cone in the red reflex within the pupil area during ophthalmoscopy (Charleaux's oil droplet sign).

Biomicroscopy signs:

- Prominent corneal nerves.
- Vogt's striae, which disappear transiently on digital pressure.
- Fleischer's ring (iron ring).
- Corneal scarring.
- Focal thinning.
- Munson Sign, inferior displacement of the lower lid on down gaze.
- Corneal hydrops (late stages), a breakdown in endothelial function causing acute epithelial corneal oedema followed by scarring.
- Rizzuti's sign, a bright reflection on the nasal area of the limbus when light is directed to the limbus temporal area.

Topographic signs:[10-12]

- Focal steepening located in the cone protrusion zone surrounded by concentric decreasing power zones.
- Characteristic topographic image pattern (bowtie pattern).
- Corneal astigmatism >1.50 D.
- Cone vertex displaced toward the lower midperipheral region in either the nasal or temporal quadrant.
- Dioptric values > 47.2 D.
- Inferior-superior asymmetry (in 3.0 mm zone) ≥ 1.4 D.
- Angling of the hemi meridians in the bowtie pattern > 20º.
- Elevation of the posterior corneal surface (greater than 35 µm).
- Larger values of corneal aberration (especially coma value).

Other signs:[10, 13-15]

- Central corneal thickness < 494 µm (central keratoconus) or 503 µm (non-central).
- Corneal biomechanics changes.
- Asymmetry of central corneal thickness between both eyes >10 µm.

Table 1. Clinical and topographical signs in keratoconus detection.

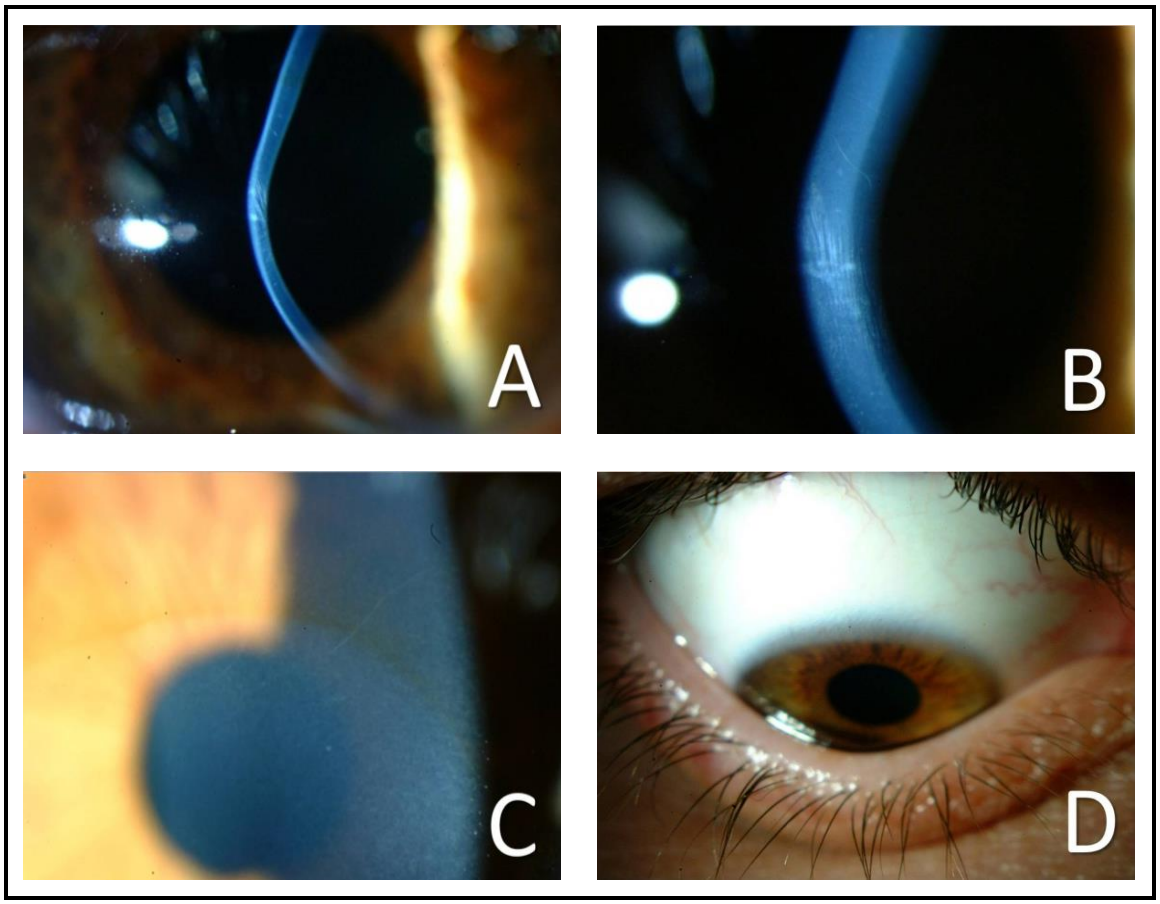

Figure 2. Clinical signs of keratoconus. A: Optical section of a cornea with keratoconus; B: Vogt's striae; C: Fleischer's ring and corneal nerves; D: Munson's sign.

2.1.3. Corneal topography

Although the clinical diagnosis of keratoconus in moderate or advanced stages is not difficult due to the typical topographic pattern and the characteristic clinical signs that this disease shows (Table 1); the diagnosis in early stages can be a challenge. Keratoconus early detection requires an in-deep corneal analysis with different techniques available (topography/tomography).[10, 16] One of the most important tools in detecting and managing keratoconus is videokeratography (Placido-based topographers), especially in primary care, because these devices are one of the most extensively used in clinical practice.[10, 17-23] However,

at present, it is considered that a detailed analysis of the posterior surface of the cornea is compulsory to complete the diagnosis of this disease, especially in early stages.[1, 24] Specifically, the elevation of the posterior corneal surface has been proposed as an important sign of the keratoconus, with cut-off values between 29-35 µm for subclinical keratoconus and 35-51 µm for keratoconus diagnosis. Although these cut-off values may vary depending on the device used in the analysis of posterior corneal morphology.[10, 12, 25, 26]

Among the devices that analyze the anterior and posterior corneal surface highlight the corneal tomographers (Scheimpflug or mixed devices combining Placido disk with Scheimpflug tomography)[27-30] and optical coherence tomographers of anterior segment (AS-OCT).[31, 32]

Recently, biomechanical and morphological properties of the cornea have been proposed to detect the presence of keratoconus.[33-35] However there is still controversy about cut-off values used,[1] although several devices, such as Corvis, show high values of sensitivity and specificity.[36]

In the other hand, the analysis of corneal aberrations has also been shown to be an effective tool for detecting keratoconus, as higher values of vertical coma (<-0.116 microns)[37] and RMS coma-like (>1.50 µm)[38] have been reported in keratoconus suspect and diagnosis.[37-43]

Also, several topographic indices have also been developed to detect the presence of corneal irregularities to introduce objectivity in the diagnosis, detection and follow-up of keratoconus.[3, 10, 16, 44-47] There are numerous indices proposed to conduct the diagnosis of keratoconus, which are classified as univariate (single index; table 2) or multivariate (combination of indices; table 3) detection indices. However, the main

disadvantage of these indices is the high dependence of the corneal topographer from which it has been developed. In addition, in many cases these indices used large number of variables that hinder their application in clinical practice.[16]

Index	Description	Normal Value
K central	*Central Keratometry*[11, 48] Average value of corneal power for the rings with diameters of 2, 3 and 4 mm.	<47.2 D
SimK	*Simulated keratometry*[46, 49] Mean of the corneal powers of the of the flattest and most curved meridians (ring diameters between 3 and 9 mm).	-
I-S	*Inferior-Superior Value*[11, 48] Power difference between five points of the inferior hemisphere and five points of the superior hemisphere at spatial intervals of 30° (3 mm central ring).	<1.4 D
SRAX	*Skew of steepest radial axis*[44] Angle between the steepest semi-meridians situated above and below the horizontal meridian in the same direction.	<20º
SAI	*Surface asymmetry index*[49, 50] Average value of the power differences between the points spatially located at 180° from128 equidistant meridians.	0.10 a 0.42 D
SRI	*Surface regularity index*[49, 51] Power gradient differences between successive pairs of rings in 256 equidistant semi-meridians (4.5 mm central).	<1.55 D
CIM	*Corneal irregularity measurement*[16, 49] Standard deviation between the corneal surface and the best-fit reference toric surface.	0.03 to 0.68 µm
MTK	*Mean toric keratometry*[16, 52] Elevation values of the cornea calculated by means of the best adjustment to a toric reference surface.	43.1 to 45.9 D
CLMI	*Cone location and magnitude index*[45] Presence or absence of keratoconic patterns and determining the location and magnitude of the curvature of the cone.	<45%
PCA[a]	*Predicted corneal acuity*[16, 53] Optical quality in Snellen units in the central zone of the cornea with 3 mm diameter.	-
SDSD	**Standard deviation of standard deviation** of the radii of curvature of each ring.[22, 49]	-

Index	Description	Normal Value
ACP	***Average corneal power***[16, 47] Average power value of various points in the central corneal region.	40.5 to 46.7 D
AA	***Analyzed area***[16, 47] Corneal area covered by the rings that can be analysed.	-
CSI	***Centre surround index***[16, 47] Difference in the average area-corrected corneal power between the central corneal zone (3 mm) and a 3 mm annulus surrounding the central area (3 to 6 mm).	-0.28 to 0.80 D
DSI	***Different sector index***[16, 47] Average power difference between sectors of 45° (8 equal sectors) with the highest and lowest power.	0.21 to 3.51 D
OSI	***Opposite sector index***[16, 47] Average power difference between opposing sectors of 45°.	-0.55 to 2.09 D
IAI	***Irregular astigmatism index***[16, 47] Variation of keratometric power between each ring along a given meridian.	0.19 to 0.49 D
ISV_b	***Index of surface variance***[10, 49] Irregularity of curvature of the anterior corneal surface.	<37
IVA_b	***Index of vertical asymmetry***[10, 49] Degree of asymmetry between the curvature of the superior cornea and the inferior cornea.	<0.28
KI_b	***Keratoconus index***[10, 49] Calculated from other indices previously described in Placido topography (DSI, OSI, CSI, SAI, IAI, AA, SimK1 and SimK2).	<1.07
CKI_b	***Center keratoconus index***[10, 49] Calculated to detect central keratoconus.	<1.03
IHA_b	***Index of height asymmetry***[10, 49] Difference between the mean elevation of the superior cornea and the mean elevation of the inferior cornea.	<19
IHD_b	***Index of height decentration***[10, 49] Degree of vertical decentration of corneal elevation data.	<0.014
$Rmin_b$	***Smallest sagittal curvature***[10, 49] Smallest sagittal curvature radius in the entire measurement range.	>6.71 mm

Table 2. Topographic indices used for the detection of keratoconus.

[a]EyeVision devices [b]Oculus devices (Pentacam; Keratograph; Easygraph)

Index	Description	Cut-off value
KISA%	Derived from four indices: Central K, SIMK, I-S and SRAX.[44]	60%-100% suspect >100% keratoconus
KPI	***Keratoconus prediction index***[46, 47] Combination of 8 topographic indices (SimK1, SimK2, OSI, CSI, DSI, SAI, IAI and AA).	0.23
KCI%	***Keratoconus classification index (Klyce/Maeda)***[47] Derived from KPI and other four indices (DSI, OSI, CSI y SimK2) which provides the probability (in percent) of presence of keratoconus.	>0%
KSI	***Keratoconus severity index (Smolek/Klyce)***[46] Based on a neural network with 10 topographic indices. Designed to calculate the severity of keratoconus.	30%
Rabinowitz & McDonell	Derived from I-S, K central and asymmetry of K central between both eyes.[48]	I-S > 1.4 D K > 47.2 D Dif > 1 D
Chastang[a]	Combines SDSD and Asphericity indices, developing a primary decision tree.[22, 49]	Index outside of normal limits
PathFinder Corneal Analysis[b]	System which combines three indices (CIM, MTK, shape factor) to detect the presence of corneal irregularities.[10, 54]	Index outside of normal limits
BAD III[c]	***Belin/Ambrósio Enhanced Ectasia Display III***[55] System which analyzes 9 indices and provides an overall final evaluation based on the regression analysis of each index.	Index outside of normal limits

Table 3. Systems based on multivariate indices which combine different topographic indices for the detection of keratoconus and the cut-off values for diagnosis.

[a]EyeSys 2000 (EyeVision) [b]Atlas (Carl Zeiss) [c]Pentacam (Oculus)

2.1.4. Classification and progression of keratoconus

The classification of keratoconus in different stages improves the diagnosis and the monitoring of the progression of the disease. However, there is no clinically accepted classification that allows to clearly distinguish between a healthy cornea and a cornea affected by keratoconus (especially in the early stages) or between different stages

of the disease.[1, 16] Generally, in the classification of keratoconus is often used the combination of refractive clinical data, biomicroscopical signs, corneal thickness and corneal topographic measurements.

Classically, the shape or location of the cone identified by corneal topography has been used to classify keratoconus into several categories. Based on the shape of the cone, keratoconus has been classified as round or nipple type (cone diameter <5 mm), oval type (cone diameter >5 mm) or globus type (cone diameter greater than 75% of the cornea).[20, 56] Also, it can be classified into central or paracentral, based on the location of the cone,[20, 56] however this classification has non-significant effect on the fitting of gas permeable (GP) contact lens (CL).[20]

The most accepted classifications for grading keratoconus severity are the Amsler-Krumeich classification (Table 4),[57, 58] modified by Alió et al.[38] with the introduction of corneal higher order aberrations; and the classifications developed by the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) based on keratometry readings (mild <45 D, moderate 45-52 D and severe >52 D)[59] or based on clinical and topographical factors (KSS: Keratoconus Severity Score; Table 5).[56]

These classifications were proposed a few years ago and do not incorporate the technological advances currently available for corneal assessment.[1, 16] Recently, a new tomographic method of classifying keratoconus has been developed, called the ABCD Grading System scale of Belin-Ambrosio ("A" for "anterior surface"; "B" for "back Surface", "C" for "corneal thickness" and "D" for "distance visual acuity") only available in Pentacam devices (Table 6).[60, 61]

Stage I	Eccentric steepening Myopia and/or astigmatism < 5.00 D Mean central K readings < 48.00 D Vogt's striae, no corneal opacities *RMS Coma-Like 1.50 to 2.50 µm
Stage II	Myopia and/or astigmatism from 5.00-8.00 D Mean central K readings < 53.00 D Absence of scarring Minimum corneal thickness ≥ 400 µm *RMS Coma-Like >2.50, ≤3.50 µm
Stage III	Myopia and/or astigmatism from 8.00-12.00 D Mean central K readings > 53.00 D Absence of scarring Minimum corneal thickness from 200-400 µm *RMS Coma-Like >3.50, ≤4.50 µm
Stage IV	Refraction not measurable Mean central K readings > 55.00 D Central corneal scarring Minimum corneal thickness < 200 µm *RMS Coma-Like >4.50 µm

Table 4. Amsler-Krumeich classification. *Modified by Alió et al.[38]

0	**Unaffected – normal topography** No corneal scarring consistent with keratoconus No slit-lamp signs for keratoconus Typical axial pattern Average corneal power (ACP) ≤47.75 D Higher-order RMS error ≤0.65
1	**Unaffected – atypical topography** No corneal scarring consistent with keratoconus No slit-lamp signs for keratoconus Atypical axial pattern (irregular pattern; or asymmetric superior or inferior bowtie; or inferior or superior steepening <3.00 D steeper than ACP) ACP ≤48 D Higher-order RMS error ≤1 µm
2	**Suspect topography** No corneal scarring consistent with keratoconus No slit-lamp signs for keratoconus Axial pattern with isolated area of steepening (inferior, superior or central steep pattern) Additional features: - ACP ≤49 D - Higher-order RMS error >1.00 and ≤1.50 µm
3	**Affected – mild disease** Axial pattern consistent with keratoconus May have positive slit-lamp signs No corneal scarring consistent with keratoconus Additional features: - ACP ≤52 D - Higher-order RMS error >1.50 and ≤3.50 µm
4	**Affected – moderate disease** Axial pattern consistent with keratoconus Must have positive slit-lamp signs Additional features: - ACP >52D and ≤56 D - Higher-order RMS error >3.50 and ≤5.75 µm - Corneal scarring and overall CLEK grade up to 3.0
5	**Affected – severe disease** Axial pattern consistent with keratoconus Must have positive slit-lamp signs Additional features: - ACP >56 D - Higher-order RMS error >5.75 µm - Corneal scarring CLEK grade 3.5 or greater overall

Table 5. Keratoconus Severity Score Ranking Scheme proposed by CLEK.[56]

	A	B	C	D	
ABCD Criteria	ARC (3 mm zone)	PRC (3 mm zone)	Thinnest pachymetry	BDVA	Scarring
Stage 0	>7.25 mm (<46.5 D)	>5.90 mm (<57.25 D)	>490 µm	≥20/20 (≥1.0)	-
Stage 1	>7.05 mm (<48 D)	>5.70 mm (<59.25 D)	>450 µm	<20/20 (<1.0)	-, +, ++
Stage 2	>6.35 mm (<53 D)	>5.15 mm (<65,5 D)	>400 µm	<20/40 (<0.5)	-, +, ++
Stage 3	>6.15 mm (<55 D)	>4.95 mm (<68.5 D)	>300 µm	<20/100 (<0.2)	-, +, ++
Stage 4	<6.15 mm (>55 D)	<4.95 mm (>68.5 D)	≤300 µm	<20/400 (<0.05)	-, +, ++

Table 6. ABCD Keratoconus classification. ARC=Anterior radius of curvature in the 3 mm zone centered on the thinnest area; PRC= Posterior radius of curvature in the 3 mm zone centered on the thinnest area; BDVA=Distance best-corrected; Scarring: - no scarring; + scarring, iris details visible; ++ scarring, iris obscured.

Currently, a criterion has been proposed to define the clinical progression of keratoconus consisting of change in at least 2 of the following parameters:[1]

a) steepening of the anterior corneal surface,
b) steepening of the posterior corneal surface, or
c) thinning of corneal thickness.

This assumes that the measurement or detection of disease progression depends directly on the accuracy and reliability of the devices used in evaluating of the keratoconic cornea.[1]

2.1.5. Management of keratoconus

Management of keratoconic patient can be performed with surgical and non-surgical options (Figure 3), being non-surgical options the first choice in these patients.[1, 3, 8] In early stages of the disease, keratoconic patients often achieve acceptable vision with spectacle correction, soft CL with toric design[3, 62] or GP CL with standard design.[20, 59, 63] However, when keratoconus progresses, an increase of irregular astigmatism and corneal irregularities appears that cannot be corrected with traditional ophthalmic lenses.[3, 62, 64] For this reason, GP CLs with specific design to keratoconic eyes are the first option in keratoconic patient management,[1, 8, 18, 20, 62, 65-69] because the tear layer between the CL and the anterior corneal surface reduces visual distortion and forms a new regular optical surface,[70-72] thereby improving patients' visual acuity.[20, 62, 64, 65]

Alternative option for fitting patients with advanced stages of keratoconus or who have failed with GP CLs design for keratoconus have been documented: these include piggy-back,[73] hybrid CLs[74, 75] or large diameter GP CLs designs such as corneal-scleral or semi-scleral (between 3.0 to 6.0 mm larger than horizontal visible iris diameter or 12.9-14.9 mm), mini-scleral (up to 6 mm larger than horizontal visible iris diameter or 15-18 mm) or scleral (more than 6 mm larger than horizontal visible iris diameter or 18.1-25 mm).[76-78]

Surgical procedures in keratoconus are performed either for optical reasons or to provide tectonic support to the cornea or a combination of these when patients develop CL intolerance, unsatisfactory vision with any type of CL or progression of the disease (Figure 3 and 4).[1, 3, 8]

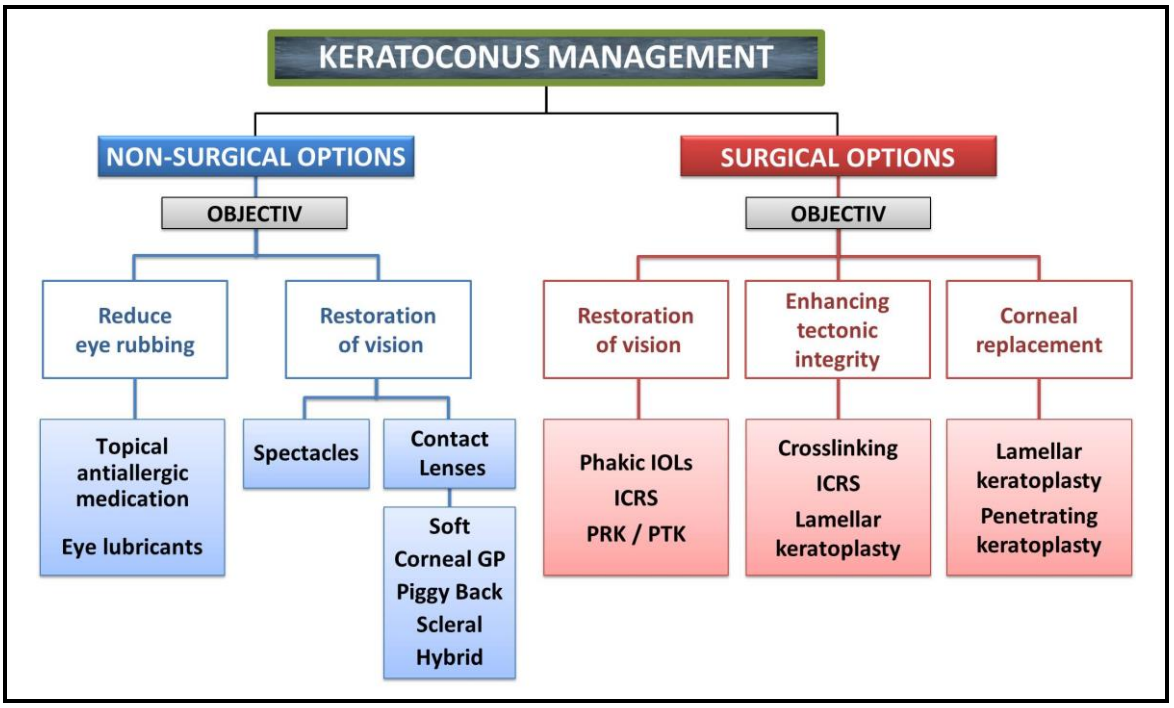

Figure 3. Surgical and non-surgical options in keratoconus management.

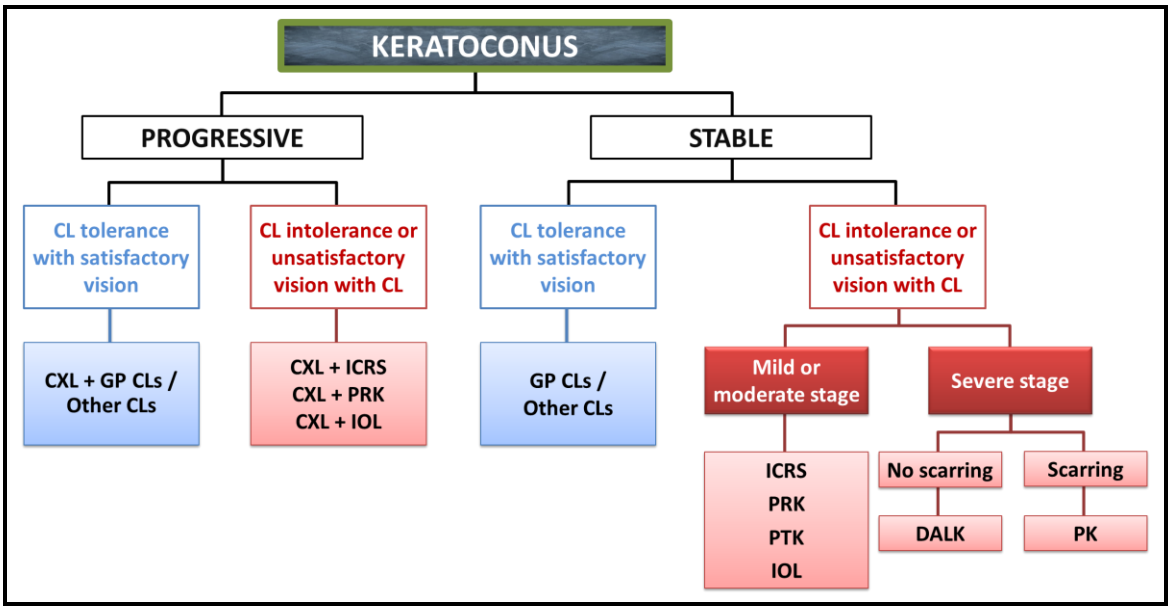

Figure 4. Management of keratoconus based on evolution or progression of disease.[1, 8]

Corneal collagen cross-linking (CXL) is a surgical technique which combines riboflavin and ultraviolet-A light to slow or halt the progression of the disease.[1, 79] CXL forms chemical bonds within the corneal stroma resulting in corneal strengthening and it is indicated when clinical progression in keratoconic corneas exists.[1, 79] This

technique allows the increasing of corneal rigidity and biomechanical stability.[80] CXL is not indicated in corneas with corneal thickness less than 400 µm,[79, 81] being uncommon in patients older than 40 years.[1]

Intracorneal ring segment (ICRS) implantation is controversial[1] being indicated when keratoconic patient presents CL intolerance or unsatisfactory vision with any type of CL. This technique consists in the implantation of one or two synthetic segments in the corneal stroma to reshape its abnormal shape.[1, 82-84] The types of ICRS more used in the clinical practice are Keraring (Mediphacos) and Intacs (Addition technologies).[82-84] The aim of this technique is to regularize the corneal geometry in an attempt to improve visual acuity and CL tolerance and decrease the irregular astigmatism.[82, 83] ICRS are recommended to treat mild and moderate cases of keratoconus, inasmuch as a minimum corneal thickness of 450 µm in the incision area and absence of corneal scarring are required.[3, 83, 85]

However, there is limited evidence for these techniques because of the lack of properly conducted randomized control trials with longer follow-up to provide higher levels of evidence on their effectiveness.[8] In addition, following these procedures, in most cases the fitting of GP CL is still necessary to achieve a good vision in keratoconic patients.[8]

Others surgical procedures have been described in keratoconic patients with intolerance or unsatisfactory vision with CLs involving ablative procedures (LASIK[86] or photorefractive keratectomy (PRK) in combination with CXL,[87, 88] phototherapeutic keratectomy (PTK) used to regularize the corneal shape and eliminate corneal opacities[89, 90]) or additive techniques such as posterior or anterior chamber phakic

intraocular lenses.[91, 92] Nevertheless, these surgical options are uncommonly used.[1, 8]

Finally, the corneal graft is indicated in advanced stage of the disease which cannot be successfully managed with CL.[1, 93] Deep anterior lamellar keratoplasty (DALK) is indicated in keratoconic patients who have transparent corneal as the superficial corneal layers are removed remaining Descement's layer and endothelium intact. DALK would be more preferred in patients with keratoconus because of the absence of risk of rejection.[1, 93, 94] Last, penetrating keratoplasty (PK; entire thickness of the cornea is removed and replaced by transparent corneal tissue) is considered where endothelial dysfunction, deep corneal scarring or corneal hydrops is present.[1, 93, 94] It is estimated that 12% of keratoconic patients required PK.[95]

2.1.6. GP contact lenses in keratoconus

GP CLs are the first option in keratoconus patient management to rehabilitate vision and improve patients' quality of life.[1, 8, 18, 62, 65-69] The fitting process of GP CLs aims to improve visual acuity, with the maximum possible comfort and respect of the ocular physiology,[62, 64] would permit surgical procedures to be postponed or avoided entirely.[8, 63] Fitting GP lenses in keratoconus patients and achieving an acceptable fit is considered a challenging for eye care practitioners, requiring more trial lenses than standard GP fitting, due to central and paracentral corneal steepening, corneal thinning, irregular corneal topography and irregular astigmatism.[17, 18, 20, 21, 62, 65, 67]

Classically, three GP fitting philosophies for keratoconus have been described:[96] *apical touch*, *three-point-touch* and *apical clearance*. *Three-point-touch* (or divided support) philosophy is the most widely-accepted and safest modality of GP CL fitting in keratoconus.[68, 96, 97] (Table 7; Figure 4).

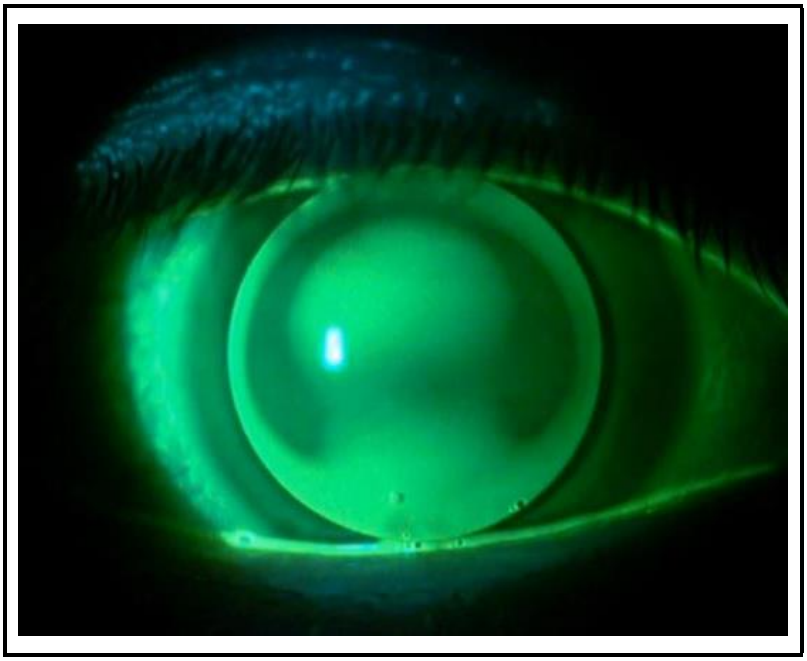

Figure 4. Fluorescein pattern of three-point-touch philosophy.

GP CLs manufacturers generally provide lenses specifically designed to keratoconus corneal shape, either with corneal, semi-scleral, or scleral designs.[1, 8, 18, 20, 62, 65-67] Corneal GP lenses are the first option to fit in these cases, using the other designs for the cases in which corneal design fails. Corneal GP designs usually incorporate a greater number of peripheral curves, different optical zone diameter or aspherical peripheral bands, with the intention of seeking a match with the keratoconic cornea.[98]

Manufacturers of GP CLs generally provide guidelines for selecting the parameters of the lens in keratoconus eyes [generally the back optic zone radius (BOZR)] based on the anterior corneal curvature (provided by manual keratometry or corneal topography). So, this procedure often

requires a long practitioner and patient chair time in order to achieve optimal fit, inasmuch as changes in the parameters of the lens are still needed, which increases the number of diagnostic and ordered CLs required for these patients[17, 18, 65, 68, 69, 99] compared with GP fitting in healthy eyes. For this reason, the fitting GP CL in keratoconic patients is considered a challenge by eye care practitioners.[17, 18, 20, 21, 62, 65, 67]

	Apical clearance	Apical touch	Three-point-touch
ADVANTAGES	Minimise apical scarring Minimal corneal oedema (swelling) Minimal corneal punctate staining	Easiest to achieve Better visual acuity	The weight of the lens is distributed over a larger area of the cornea Easier to achieve than apical clearance Minimise corneal scarring compared to apical bearing lenses
DISADVANTAGES	Poor tears exchange Dimple veiling Paracentral corneal molding Reduced VA and flare	Corneal molding Corneal abrasions Apical scarring	Timing for follow-up is critical to monitor the area of central touch

Table 7. Advantages and disadvantages of three GP fitting philosophies in keratoconus.

2.2. Motivation

In conclusion, it is widely described in the literature that corneal GP CL is the first choice in keratoconus management.[1, 8, 18, 62, 65-69] Although these lenses not slow or halt the progression of the disease,[8] it is demonstrated that its use helps to delay the need for surgery[8, 63] in these patients improving their quality of life.[100, 101]

However, GP CLs fitting is challenging because an increased number of diagnostic and ordered lenses and longer practitioner and patient chair time are required to achieve a final acceptable GP CL fit.[17, 18, 20, 21, 62, 65, 67-69, 99] Several authors have proposed the use of specific software based on the analysis of corneal topography to calculate the parameters of the GP CL in keratoconus eyes.[17, 18] Nevertheless, these software have not demonstrated a relevant reduction in the number of diagnostic lenses used[17] and represent a technological dependence on a specific model or device, which may limit its widespread use by eye care professionals.

Finally, classic studies[102] propose that almost 70% of patients with keratoconus who attend a specialized consultation to perform a corneal transplant can be correctly managed with GP CLs. This clearly indicates that it is necessary to simplify and improve the GP CLs fitting process to provide the best management to patients with keratoconus, in order to

reduce the number of patients who need an invasive surgical option,[8, 103] which may be associated with greater number of complications and financial cost for patients and health systems.[104]

Therefore, this doctoral thesis aims to develop an evidence based clinical practice guidelines that allows:

- To standardize the corneal GP CL fitting process in patients with keratoconus identifying the visits necessary to achieve optimal fit and the criteria to select and modify the parameters of the lens that can be applied by any professional.
- To simplify the corneal GP CL fitting process in patients with keratoconus by providing a method to calculate the parameters of the first diagnostic lens which reduces the difference between the parameters of the first diagnostic lens proposed with the final lens prescribed.
- To reduce the time needed to complete the corneal GP CL fitting for the professional and the patient, reducing the number of diagnostic and ordered lens, to achieve the appropriate GP CL in each case.
- To provide the best visual rehabilitation in keratoconic patients, in a safe and effective way, minimizing the impact of the disease on their quality of life.

2.3. Hypothesis

It is possible to standardize the corneal GP CL fitting in patients with keratoconus developing an evidence-based clinical practice guideline whilst reducing the patient and practitioner chair time ensuring a safe fitting procedure that provides better visual rehabilitation of these patients.

2.4. Objectives

General objective:

To develop an evidence-based clinical practice guideline to standardize and simplify corneal GP CLs fitting in keratoconic patients in a safe and effective way.

Specific objectives:

1. To quantify the impact of refractive correction (spectacles or corneal GP CLs) on the vision-related quality of life obtained with the standardized questionnaire NEI-VFQ-25 in keratoconic patients in order to identify the best visual rehabilitation in these cases. ***Chapter 3***

2. To standardize the corneal GP CL fitting process, identifying the visits required to achieve optimal fit and determining the percentage of successful GP CL fitting in healthy subjects and keratoconic patients. ***Chapter 4.1***

3. To determine the possible differences between the BOZR of GP CL following the manufacturer's recommendations with the BOZR of GP CL finally prescribed. ***Chapters 4.2 and 6.3***

4. To analyse the current optometric practices and attitudes in the management of keratoconus patients in the UK and Spain. ***Chapter 4.3***

5. To determine the reliability and usefulness of corneal topography in the GP CL fitting process in keratoconic eyes by quantifying the repeatability (Placido-based topography) of topographic values and the measurement of the corneal aberrations of the anterior corneal surface and the agreement between different topographic technologies (Placido-based versus Scheimpflug-Placido devices). ***Chapter 5***

6. To propose new cut-off values of corneal aberrations to improve the criteria used in the detection and classification of keratoconic eyes. ***Chapter 6.1***

7. To develop and validate a clinical practice guideline for corneal GP CLs fitting under the standards of the AGREE-II consortium in order to reduce the time needed to complete the fitting process and the number of diagnostic and ordered lenses necessaries to achieve the optimal GP CL in keratoconic eyes. ***Chapter 7***

2.5. Methods

The methods used in this doctoral thesis are overview described in this section. A detailed description of the methods used in each study, are provided in **Chapters 3, 4, 5, 6 and 7** of this thesis.

2.5.1. Subjects and patients

This research project was approved by the Human Sciences Ethics Committee of the University of Valladolid. Informed consent was obtained from each subject, and all subjects were treated in accordance with the Declaration of Helsinki.

In general terms, this research project has involved 74 patients with keratoconus, 115 healthy subjects, 464 eye-care practitioners (optometrists / CL opticians) and 9 experts in CL fitting in keratoconus corneas. In addition, a retrospective analysis of more than 500 CLs fitting performed by the Optometry Group of the IOBA Eye Institute (University of Valladolid, Spain) was conducted.

The diagnoses of keratoconus were confirmed after a completed eye examination, which included Scheimpflug topographical analysis and biomicroscopy examination by independent corneal specialists from IOBA

Eye Institute and the Department of Ophthalmology of the Valladolid University Hospital. Patients with any active ocular-surface disease, use of medication that could affect ocular physiology, and a history of any type of ocular surgery were excluded. Moreover, in the studies described in **Chapters 3, 4.1, 4.2 and 6.2**, keratoconic patients should also be corneal GP wearers and should not present any contraindications to wearing CL.

Control group was formed by healthy subjects without active ocular surface disease, corneal opacities, glaucoma, use of medication that could affect ocular physiology, or a history of any type of ocular surgery. Specifically, healthy subjects in **Chapter 3** should be CL wearers (soft or GP CLs); in **Chapter 4.1** healthy subjects should be CL wearers (soft or GP CLs) or should be started the fitting process with GP diagnostic lenses and finally, in **Chapters 4.2 and 6.1** healthy subjects should be corneal GP CL wearers.

Chapter 4.1 contains a retrospective analysis that included 232 CL fittings (soft or GP) started and completed by the IOBA Optometry Unit (from 2010 to 2014).

In **Chapter 4.3**, a total of 464 eye-care practitioners who completed the questionnaire designed for this study were included (126 optometrists and CL opticians in the UK and 338 optometrists in Spain).

Finally, the **Chapter 7** includes the development and evaluation process of the clinical practice guideline for the corneal GP CL fitting in which a team of nine experts belonging to different national (Universidad Complutense de Madrid, Universidad Europea de Madrid, and Universidad de Alicante) and internationals universities [Plymouth University (United Kingdom), University of New South Wales, Sydney (Australia), University of Minho

(Portugal), and Universitá del Salento (Italy)] as well as non-university professional clinics [Hospital Oftalmar (Spain), Novolent-Novovisión (Spain), Visser Contactlenzenpraktijk (The Netherlands), and Orriss & Low Optometrists (United Kingdom)] have been participated. The recommendations of the AGREE-II consortium have been used for the development and assessment of the clinical practice guideline proposed in this thesis.[105]

Table 8 summarizes the number of subjects and patients included in the different studies that compose this research project.

Chapter	Healthy	Keratoconus
3	25 subjects	25 patients
4.2	40 eyes (40 subjects)	40 eyes (22 patients)
5.1	25 eyes (25 subjects)	25 eyes (25 patients)
5.2	36 eyes (36 subjects)	36 eyes (36 patients)
5.3	56 eyes (56 subjects)	56 eyes (33 patients)
5.4	70 eyes (70 subjects)	77 eyes (45 patients)
6.1	50 eyes (50 subjects)	85 eyes (49 patients)
6.2	-	81 eyes (46 patients)

Table 8. Number of eyes, subjects and/or patients included in each chapter.

2.5.2. Contact Lenses

In this research project, several designs of GP CLs have been used depending on the nature of each study that can be summarized in:

- **KAKC GP** [Conóptica (Spain) / Hecht Contaclinsen (Germany)]: corneal GP CL with specific design for keratoconus (spherical pentacurve) (Table 9). Toric design or individual periphery design were excluded. This GP CL design has been used in **Chapters 3, 4.1, 4.2, 6.1 and 6.2.**

- **BIAS-S GP** [Conóptica (Spain) / Hecht Contaclinsen (Germany)]: Corneal GP CL with rotationally symmetric bi-aspheric design (Table 9) used in healthy subjects in the studies described in **Chapters 4.1, 4.2 and 6.1.**

	KAKC	BIAS- S
Manufacturer	Conóptica-Hecht Contactlinsen	
Design	Spherical pentacurve	Rotationally symmetric bi-aspheric
Power (D)	±30.00 D (0.25 steps)	±30.00 D (0.25 steps)
BOZR (mm)	4.80 to 8.90 (0.05 steps)	6.50 to 10.00 (0.05 steps)
Total diameter (mm)	8.40 to 12.20 (0.10 steps)	7.00 to 12.20 (0.10 steps)
Standard total diameter (mm)	9.20	9.60
Material	Boston ES/EQ/EO/XO/XO2	

Table 9. CL design description (KAKC design used in keratoconic eyes and BIAS-S design used in healthy eyes).

2.5.3. Instrumentation

The following instrumentation was used in this project:

- **Allegro-Topolyzer** (WaveLight Technologie AG, Alcon Laboratories, Erlangen, Germany) / marketed by Oculus under the name **Oculus Keratograph** (Oculus Optikgeräte GmbH, Wetzlar, Germany) [Examination Software version 1.76r45 FW1.19]. Corneal topographer based on the Placido disk system supported by 22 rings and generates high-resolution data of the anterior corneal surface with 22,000 data points. This device has been used in **Chapters 4.2, 5.1, 5.2, 5.3, 5.4, 6.1 and 6.2.**

- **APEX® CL fitting software** (version 1.1.0.6). This software has been developed by Hecht Contactlinsen in association with Oculus and it proposes a first trial GP lens according to the values of topographical

simulated keratometry readings and corneal eccentricity of Oculus Keratograph, and it displays a simulated fluorescein pattern of the specified GP design to aid the fitting procedure. This software has been used in **Chapters 4.2, 6.1 and 6.2**.

- **Galilei G4** (Ziemer, Port, Switzerland) (Software version V6.0.3). Corneal topographer/tomographer that has a rotating dual-Scheimpflug camera integrated (located 180 degrees apart to compensate for error associated with scans at an oblique angle) with a Placido disk (20 monochrome rings, 200 mm diameter). It analyzes more than 122,000 data points per each complete scan to measure the anterior and posterior corneal surfaces. This device has been used in **Chapters 5.3 and 6.1**.

- **Orbscan II** (Bausch & Lomb, Rochester, New York, USA). Corneal topographer based on slit-scanning system for 3-dimensional reconstruction of corneal shape using the analysis of the anterior and posterior corneal surfaces. This device has been used in **Chapter 6.1**.

- **Helmholtz keratometer** (OM-4, Topcon, Japan). This device allows measuring simultaneously the radii of curvature of the main corneal meridians of the anterior corneal surface (in millimeters and diopters). This keratometer has been used in the **Chapters 4.1, 6.1 and 6.2**.

2.5.4. Questionnaires

Three questionnaires have been used in this research project to carry out different studies:

- **The National Eye Institute-Vision Function Questionnaire (NEI-VFQ-25).**[106] This questionnaire is a specifically developed to measure the vision-related quality of life (VR-QoL). NEI-VFQ-25 consists of 25 questions that are easy to understand and answer, which are oriented to evaluate 11 vision-dependent domains and one general health domain, including the following: ocular pain, near vision, distance vision, vision-specific social function, vision-specific mental health, general vision, vision-specific role difficulties, vision-specific dependency, driving, color vision and peripheral vision. This questionnaire has been used in **Chapter 3** to evaluate the VR-QoL of keratoconic patients with GP CLs and spectacles.

- **Questionnaire of optometric practice and attitudes in the management of patients with keratoconus**. A questionnaire was specifically designed for **Chapter 4.3** to investigate the practice and attitudes of eye-care practitioners in relation to keratoconic patients management in UK and Spain. A link to the online survey (in English and Spanish languages) was distributed by various professional organizations: General Optical Council, Association of Optometrists (including in the online version of the journal Optometry Today) and British Contact Lens Association (via social media) in the UK and different Spanish Colleges of Optometrists in Spain.

- **The Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument.**[105] This instrument and its specific questionnaire has been used in **Chapter 7** to develop and assess the evidence-based clinical practice guidelines to fit corneal GP CL in keratoconus. It is an appraisal tool and validated instrument to provide a framework for assessing quality of clinical practice guideline. Consisting of 6 domains covering

23 key items which are scored on a scale of 1–7, with 1 being strongly disagree and 7 being strongly agree. A quality score is calculated for each of the six domains included in AGREE II, obtaining an overall score with the experts' responses that offers the value of the methodological quality of the proposed guide.

2.5.5. Statistical Analysis

The statistical analysis of this research project was performed using SPSS for Windows software (version 15.0; SPSS, Inc., Chicago, IL). Additionally, a Rasch analysis of NEI-VFQ-25 with the algorithm proposed by Massof was used in **Chapter 3.**[107]

A normal distribution of variables was assessed using the Kolmogorov-Smirnov test in all studies of this research project (P values greater than 0.05 indicated the data were normally distributed).

Each chapter of this thesis describes in detail the statistical analysis used, identifying the tests used for descriptive analysis (mean, standard deviation, 95% confidence interval, maximum and minimum range, median, mode, interquartile range, etc.) as inferential (identifying the test used and its statistical significance to determine correlations, differences, establish models, etc.) as well as other mathematical methods used such as Bland-Altman analysis, coefficient of variation, repeatability, precision or intraclass correlation coefficient.

CHAPTER	NUMBER	CL	INSTRUMENTATION	QUESTIONNAIRE
3. Influence of the refractive correction on the quality of life in keratoconus	25 healthy subjects 25 keratoconic patients	KAKC in keratoconus Anyone in healthy	----	NEI-VFQ-25
4.1. Success of GP CLs	232 fittings	Anyone	Keratometer	----
4.2. GP CL fitting using new software in keratoconic eyes	40 healthy eyes 40 keratoconic eyes	KAKC BIAS-S	Oculus Keratograph / Allegro Topolyzer APEX Software	----
4.3. Optometric keratoconus management in Spain and UK	126 UK 338 Spain	----	----	Specific designed for this study
5.1. Repeatability of Placido-based corneal topography in keratoconus	25 healthy eyes 25 keratoconic eyes	----	Oculus Keratograph / Allegro Topolyzer	----
5.2. Repeatability of wavefront aberration with a Placido-Based	36 healthy eyes 36 keratoconic eyes	----	Oculus Keratograph / Allegro Topolyzer	----
5.3. Agreement between dual rotation Scheimpflug-Placido system and Placido-based topography	56 healthy eyes 56 keratoconic eyes	----	Oculus Keratograph / Allegro Topolyzer Galilei G4	----
5.4. Anterior coma aberration in keratoconus severity classification	70 healthy eyes 77 keratoconic eyes	----	Oculus Keratograph / Allegro Topolyzer	----
6.1. New algorithm to simplify the GP CL fitting in keratoconus.	50 healthy eyes 85 keratoconic eyes	KAKC BIAS-S	Oculus Keratograph / Allegro Topolyzer Orbscan II; Galilei G4; Keratometer	----
6.2. GP CL fitting in keratoconus: comparison of different guidelines	81 keratoconic eyes	KAKC	Oculus Keratograph / Allegro Topolyzer Keratometer	----
7. Clinical practice guideline for GP CL fitting in keratoconus	----	----	----	AGREE II

Table 10. Scheme of methods used in this research project.

2.6. Results

This section summarizes the main results found in the studies that compose this doctoral thesis. A detailed description of the results is provided in each chapter.

Chapter 3. The influence of the refractive correction on the vision-related quality of life in keratoconus patients

Keratoconus patients showed a lower VR-QoL impairment ($p<0.01$) than healthy subjects in the total and all subscale score of NEI-VFQ-25 related to wearing spectacles. With CL correction, keratoconus patients showed a VR-QoL improvement with statistically significant differences ($p<0.04$) in only four subscales including distance activities, mental health, color vision and peripheral vision, compared with healthy subjects.

In the keratoconus group, compared to spectacle use, GP CL wear improved the VR-QoL global score ($p=0.01$) and in all subscales except for ocular pain ($p<0.01$) and mental health ($p=0.25$). The spectacles score was significantly worse for a high keratoconus severity stage ($p<0.01$ Kruskal–Wallis ANOVA). However, the GP CL score showed non-significantly different ($p=0.06$ Kruskal–Wallis ANOVA) between different keratoconus severity stage.

Chapter 4. Currently GP CL fitting process in keratoconus

4.1. Success of rigid GP CL fitting

This retrospective study included 232 subjects (61.2% women and 38.8% men) who started a fitting procedure for any type of CL performed by the Optometry research group. Of these fittings, 71.6% were refractive prescriptions (myopia, hyperopia, or regular astigmatism correction) and 28.4% were therapeutic prescriptions (ocular pathologic condition, irregular cornea, paediatric subjects, cosmetic, or prosthetic fitting and orthokeratology).

Refractive Prescriptions (Healthy Subjects)

A total of 166 subjects (68.7% women and 31.3% men) required a type of CL for refractive reasons. Of these refractive fittings, 88 subjects (53%) were initially fitted with GP CLs and 61 (69.3%) completed a successful GP fitting wearing their GP CL 7.61 ± 1.54 hours per day. Within this group, a different percentage of successful fits were found for neophyte (72%), previous soft lens wearers (62%), and previous GP wearers (92.3%).

Therapeutic Prescriptions

A total of 66 subjects (42.4% women and 57.6% men) were fitted with any type of CL for therapeutic reasons (63.6% for irregular cornea, 56.1% for keratoconus, 4.5% after refractive surgery or keratoplasty, and 3% for other conditions, such as eye trauma, and 28.8% for orthokeratology, 4.6% for paediatric cases, and 3% for cosmetics-prosthetic reasons). Of these therapeutic fittings, 61 subjects were initially fitted with GP CLs and 59 (96.7%) completed a successful GP fitting.

4.2. Rigid GP CL fitting using new software in keratoconic eyes

BOZR proposed by APEX® software showed good repeatability in healthy (CV=0.32%) and keratoconus eyes (CV=0.51%). APEX® proposed flatter BOZR than the diagnostic method in healthy (7.91±0.24 and 7.84±0.26 mm, $p<0.01$) and keratoconus eyes (7.34±0.38 and 7.23±0.37 mm, $p<0.01$). A strong linear correlation in healthy [BOZR_Diagnostic_Method = (BOZR_APEX® x 1.06) – 0.53; $p<0.01$ $R^2=0.969$] and keratoconus eyes [BOZR_Diagnostic_Method = (BOZR_APEX® x 0.88) + 0.77; $p<0.01$ $R^2=0.825$] was found.

A detailed analysis showed a similar trend in different keratoconus stages (Amsler-Krumeich classification); stage#1: 7.42±0.30 and 7.40±0.25 mm, BOZR_Diagnostic_Method = (BOZR_APEX® x 0.81) + 1.38; $R^2=0.973$, stage#2: 7.30±0.44 and 7.23±0.38 mm, BOZR_Diagnostic_Method = (BOZR_APEX® x 0.84) + 1.07; $R^2=0.929$ and stage#3: 7.33±0.39 and 7.11±0.40 mm, BOZR_Diagnostic_Method = (BOZR_APEX® x 0.93) + 0.28; $R^2=0.831$).

Applying these regression formulas, the BOZR difference could be reduced in healthy (-0.01±0.05 mm) and keratoconus eyes (-0.01±0.14 mm) for each keratoconus stage (+0.01±0.04; +0.03±0.10 and +0.02±0.16 mm in stages #1, #2 and #3, respectively).

4.3. Current optometric practices and attitudes in keratoconus patient management

464 eye-care practitioners (126 in the UK and 338 in Spain) who prescribed GP CLs more than once per month (54.8% of UK practitioners and 28.1% of practitioners in Spain; $p<0.01$) responded to the questionnaire. A

combination of multiple factors is considered necessary in the keratoconus detection (79.4% in the UK, 75% in Spain; p=0.68), and the use of classification criteria is considered relevant (67.5% in the UK, 70.7% in Spain; p=0.49).

There is a high consensus on the consideration that GP CL fitting is more difficult in keratoconus (79.4% in the UK, 80.5% in Spain; p=0.79) requiring more diagnostic lenses (3.2±1.4 and 3.4±1.2 in the UK and Spain, respectively; p=0.72) than are necessary for GP CL fitting in healthy eyes.

Using corneal topography is uncommon in both countries (38.1% in the UK, 59.8% in Spain; p<0.01), with a similar ophthalmologist referral pattern (at initial diagnosis, 50% in both the UK and Spain; p=1.00). Finally, few cases of co-management with ophthalmologists were noted (no co-management reported by 60.3% in the UK and 72.8% in Spain, p=0.01).

Chapter 5. Usefulness of corneal topography in GP CL fitting in keratoconic eyes

5.1. Repeatability of Placido-based corneal topography in keratoconus

Healthy eyes showed lower topographic values (p<0.05) than keratoconus eyes, except with regard to the RMin index value. Corneal diameter (p=0.45) was similar in both groups. All variables showed good coefficients of variation (CV) in healthy and keratoconus eyes [corneal dioptric power in the steepest meridian (0.21% and 0.47%, respectively), corneal dioptric power in the flattest meridian (0.19% and 0.36%), maximum corneal power point (0.22% and 0.77%), corneal diameter (0.27% and 0.33%), ISV (4.82% and 3.10%), IVA (7.05% and 3.80%), KI (0.29% and 0.72%), Rmin (0.53% and

0.78%), and aberration coefficient (0% and 4.00%)] except for the eccentricity (CV=5.79% and CV=14.53%, respectively). Statistically significant difference ($p<0.05$) between healthy and keratoconus groups were found for all variables in CV, except with respect to the maximum corneal power point, eccentricity, corneal diameter, KI and Rmin ($p>0.07$).

5.2. Repeatability of wavefront aberration measurements with a Placido-Based topographer in normal and keratoconic eyes

The repeatability of corneal wavefront aberration provided by the Allegro Topolyzer was better in keratoconus than in healthy eyes. Zernike coefficients were significantly different between the healthy and keratoconus group ($p\leq0.03$) except in Z^{+1}_3, Z^{+3}_3, Z^{-4}_4 and Z^{+4}_4.

In the healthy group, Sw was 0.031 µm or less, CV ranged from 6.49% (spherical aberration) to 37.18% (secondary astigmatism), and ICCs values ranged from 0.227 to 0.982. In the keratoconus group, Sw was 0.059 µm or less, CV ranged from 2.06% (HOAs Total RMS) to 25.82% (tetrafoil), and ICCs values ranged from 0.839 to 0.996.

Regarding to the keratoconus stages (Amsler-Krumeich classification), the repeatability of Zernike coefficients tended to improve with increasing keratoconus stage in coma, trefoil, coma-like and 3rd, 4th, HOA and Total RMS-value.

5.3. Agreement of corneal measurements between dual rotation Scheimpflug-Placido system and Placido-based topography device in normal and keratoconus eyes

The Allegro-Topolyzer underestimated all topographic values (except J_{45} and corneal diameter in healthy eyes; and J_0, maximum corneal power

point and corneal diameter in keratoconus eyes) compared to the Galilei-G4 tomographer. Astigmatism (in healthy group), FlatK (in keratoconus group), axis (in keratoconus group), J_0, J_{45} and corneal diameter showed statistical significant differences ($p<0.05$).

Healthy eyes showed better agreement (95% limits of agreement: average central corneal dioptric power -0.13 to 0.40 D; corneal dioptric power in the steepest meridian -0.30 to 0.59 D; corneal dioptric power in the flattest meridian -0.29 to 0.51D; astigmatism -0.60 to 0.64 D; axis -17.81º to 26.56º; J_0 -1.15 to 1.13 D; J_{45} -1.10 to 1.20 D; maximum corneal dioptric power point -0.70 to 1.17 D and corneal diameter -0.96 to 0.76 mm) than keratoconic eyes (average central corneal dioptric power -2.84 to 4.55D; corneal dioptric power in the steepest meridian -2.80 to 5.21 D, corneal dioptric power in the flattest meridian -3.68 to 4.70 D; astigmatism -1.90 to 2.95 D; axis -28.22º to 27.89º; J_0 -2.85 to 3.20 D; J_{45} -3.21 to 3.05 D; maximum corneal dioptric power point -7.00 to 4.51 D and corneal diameter -1.00 to 0.88mm) for all topographic values.

5.4. The usefulness of the anterior coma aberration in keratoconus severity classification

Keratoconus eyes showed (2.294 ± 0.137 µm, CI 95% 2.020-2.567) higher coma value ($P<0.01$) than normal group (0.173 ± 0.009 µm, CI 95% 0.154-0.193). A cut-off value of 0.377 µm shows 100% sensitivity and 100% specificity to discriminate between keratoconus or normal eyes.

Moreover, coma value increases with keratoconus severity; stage 1 (0.948 ± 0.069 µm, CI 95% 0.803-1.093), stage 2 (2.062 ± 0.103 µm, CI 95% 1.853-2.279) and stage 3 (3.646 ± 0.135 µm, CI 95% 3.368-3.925) ($P<0.01$ post hoc comparison) with cut-off values of 1.466 µm to discriminate between stage

1 or 2 (90% sensitivity and 100% specificity) and 2.790 µm between stage 2 or 3 (92% sensitivity and 83.3% specificity).

Chapter 6. Development of a new algorithm to simplify the GP CL fitting in keratoconus

6.1. New web-based algorithm to improve rigid GP CL fitting in keratoconus

Thirty-five keratoconus eyes were included in the retrospective phase to calculate the new algorithm to select the parameters of diagnostic lens in keratoconus eyes. A new predicting algorithm was defined (R^2=0.825, p<0.01) using a multiple regression analysis (stepwise regression). The new algorithm highly correlated with the final BOZR fitted (R^2=0.825, p<0.001 multiple regression analysis) and it was included in an open access website (www.calculens.com).

Fifty new keratoconus eyes were enrolled in the clinical validation of the new algorithm (prospective study). BOZR of the first diagnostic lens calculated with the new algorithm demonstrated lower difference with the final BOZR prescribed (-0.01±0.12 mm, p=0.65; difference between BOZR calculated and prescribed was ≤0.05 mm in 58% of the fittings) than BOZR calculated with the manufacturer guidelines (+0.12±0.22 mm, p<0.001; 26% difference≤0.05mm) and proposed by APEX® software (-0.14±0.16 mm, p=0.001; 34% difference≤0.05mm). Using Calculens.com close numbers of diagnostic lens (1.6±0.8, 1.3±0.5; p=0.02), ordered lens (1.4±0.6, 1.1±0.3; P<0.001), and visits (3.4±0.7, 3.2±0.4; p=0.08) were required to fit keratoconus and healthy eyes, respectively.

6.2. GP CL fitting in keratoconus: comparison of different guidelines to BOZR calculation

BOZR fitted in 81 keratoconic eyes were recorded and compared with the BOZR calculated following ten different guidelines identified after a literature review to fit GP CL in keratoconus.

BOZR proposed by all guidelines correlated with the final BOZR fitted (R^2>0.71; p<0.01). Statistically significant difference was found between the BOZR suggested by all guidelines with the BOZR prescribed (p<0.05), except using Calculens.com, guidelines following Centre of Contact Lens Research (University of Waterloo, Canada)[98] and K mean calculation (P≥0.11). Calculens.com showed the best agreement (mean difference of 0.00 ± 0.12 mm) and 50.6% of cases showed differences ≤0.05 mm with BOZR prescribed. One of the recommendations[67] showed a difference of -0.38 ± 0.22 mm with the BOZR prescribed and only 3.8% of the cases presented differences ≤0.05 mm with final BOZR.

Chapter 7. Clinical practice guideline to fit GP CLs in keratoconus

This chapter presents the evidence-based clinical practice guideline that has been developed in this doctoral thesis to fit corneal GP CLs in keratoconus following the recommendations proposed by the Agree Consortium (Agree II Instrument).[105] This clinical practice guideline has been evaluated by 9 independent, national and international experts with extensive experience in CLs fitting.

The proposed guideline has achieved satisfactory results in all domains evaluated with the Agree II Instrument (scope and purpose 89%,

stakeholder involvement 74%, rigor of development 84%, clarity of presentation 89%, applicability 72% and editorial independence 88%) and overall guideline assessment (85%). These results allow that developed guideline could be strongly recommended for the management of patients with keratoconus with corneal GP CLs.

2.7. Discussion

This section presents a brief discussion of the main findings of this doctoral thesis in a global way. A detailed discussion is included in each chapter that are included in this research project.

It is widely described in the literature that the GP CLs represent the first option in the keratoconus management.[1, 8, 18, 62, 65-69] The **Chapter 3** has demonstrated that the quality of life of these patients with GP CLs wear is better than spectacles, being similar compared with healthy subjects without any pathology. These results underscore the importance of adopting a comprehensive approach to the examination and care of patients with keratoconus, highlighting the need for GP CL fitting in the management of these patients. Moreover, this study emphasizes the need to consideration the optical correction (spectacles or CL wear), so a clear definition of the refractive correction should be included in the subject description[100, 101, 108-113] in studies which evaluates the effectiveness of any technique based on the visual acuity in order to collect more reliable, comparable and objective information.

On the other hand, the GP CLs fitting process in these patients is considered a challenging for eye care practitioners (**Chapter 4.4**).[17, 18, 20, 21, 62, 65, 67-69, 99] This premise is in line with the results found in **Chapter 4.3**, in

which British and Spanish professionals consider the GP CLs fitting process in keratoconus more complicated than in healthy subjects. This study shows reasonably similar attitudes regarding keratoconus diagnosis, management and GP CL practice in the two countries, despite the differences in the professional model established in each country.

Manufacturers of corneal GP CLs with specific design for keratoconus usually provide several guidelines for selecting the parameters of the first diagnostic lens in these cases. Even the manufacturers market different computerized software, which employ corneal topography to determine the optimal GP lens parameters. However, the parameters of the GP CL calculated following these indications is often far away from the parameters finally fitted[17, 18] (**Chapter 4.2**). This means that instead of simplify the GP fitting process, it can sometimes produce the opposite effect, and more diagnostic or orders lens are required, resulting in more visits and more time consuming.

Another issue raised is the importance of the use of corneal topography for GP CL fitting process. Corneal topography is especially useful in the early detection of keratoconus and follow-up.[10, 16] Placido-based topography is one of the most common tools used in clinical practice, especially in primary care (**Chapter 5.5**).[49, 114, 115] The **Chapters 5.1 and 5.2** have shown that Placido-based corneal topography provides repeatable measurements of the corneal topographic variables as well as corneal aberrations, especially useful in the detection and classification of keratoconus severity[37, 38] (**Chapter 5.4**). These results suggest that Placido-based corneal topography is very useful in the management of these patients in primary eye-care.

However, when comparing two different topography techniques (Placido versus Placido-Scheimpflug) the measures provided suggesting that these two technologies are not interchangeable in the management of keratoconic patients (**Chapter 5.3**). Therefore, although to have a corneal topographer is very useful in the management of keratoconic patients, the GP CL fitting process cannot be topographical-dependent in these cases, due to the lack of agreement that exists between different technologies. Therefore, it seems necessary to develop a clinical practice guideline of GP CL fitting in keratoconus that are independent of the equipment available for the professional.

To conduct this aim, a structured GP CL fitting process was defined with three types of visits (diagnostic, dispensing and prescribing) with relatively high percentage of successful GP fits achieved for healthy subjects (7/10 subjects) and patients with corneal irregularity (9/10 patients) (**Chapter 4.1**). Moreover, we have calculated and validated a new web-based algorithm for selecting the parameters of the initial GP diagnostic lens in keratoconus eyes (**Chapter 6.1**) which provides better start point to GP CL fitting in these patients than other methods or guidelines assessed (**Chapter 6.2**). Moreover, this new algorithm including in Calculens.com may reduce practitioner and patient chair time required to achieve a final acceptable CL fitting in keratoconus eyes

Finally, an evidence-based clinical practice guideline has been developed to fit GP CL in keratoconic patients (**Chapter 7**) that brings together the knowledge generated in this doctoral thesis. In addition, the clinical practice guideline has been developed and evaluated under the standards of the AGREE II instrument (translated into numerous languages and used in more than 400 publications) with the assessment of external experts.

This instrument aims to evaluate the quality of the proposed clinical practice guidelines, providing methodological strategies for its development and establishing the information that should be included in the guidelines and how it should be presented. The results obtained after the appraisal of eight experts suggested that developed CPG could be strongly recommended for the management of patients with keratoconus with corneal GP CLs.

2.8. Conclusions

Based on the results obtained in our studies and summarized in this doctoral thesis, these specific conclusions are proposed:

1. The quality of life of keratoconic patients measured by the standardized questionnaire NEI-VFQ-25 is higher wearing corneal GP CL than spectacles.

2. The corneal GP CL fitting following an evidence-based process, composed by a minimum of three defined visits, shows a high success rate in healthy and keratoconic patients.

3. The current recommendations offered by the manufacturers and some authors to fit GP CL in keratoconus present clinically relevant differences between the BOZR proposed and the BOZR prescribed that require a high number of changes in the parameters of the GP lens to achieve optimal fit.

4. Optometric practices and attitudes in the management of keratoconus patients are similar in the UK and Spain, being GP CLs fitting process more difficult in these patients than in healthy eyes.

5. Placido-based corneal topography provides repeatable measurements in keratoconic eyes, but there is a lack of agreement between Placido and Placido-Scheimpflug topography/tomography suggesting that these two technologies are not interchangeable in the management of keratoconus.

6. Corneal aberrations, particularly coma, applying new cut-off value of 0.377 µm may be useful in the detection and classification of keratoconic eyes.

7. The new algorithm developed for the selection of corneal GP CL parameters in keratoconic eyes (Calculens.com) allows to simplify the fitting process, reducing the difference between the parameters of the first diagnostic and prescribed GP lens.

8. The evidence-based clinical practice guidelines for corneal GP CL fitting in keratoconic eyes, developed under the AGREE-II consortium standards, allows to simplify the fitting process, reducing the number of diagnostic and ordered lens necessaries to achieve optimal GP CL fitting.

Capítulo 3

Impacto de la corrección con LC RPG en la calidad de vida de los pacientes con queratocono

CHAPTER 3: The influence of the refractive correction on the quality of life in keratoconus patients

3. Impacto de la corrección con LC RPG en la calidad de vida de los pacientes con queratocono

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The influence of the refractive correction on the vision-related quality of life in keratoconus patients

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Abstract

Purpose The aim of this study was to assess the impact of refractive correction [spectacles vs rigid gas-permeable contact lenses (RGP CLs)] on the vision-related quality of life (VR-QoL) obtained with the standardized questionnaire, NEI-VFQ-25, in keratoconus patients compared with healthy myopic subjects.

Methods The Spanish version of NEI-VFQ-25 was administered two consecutive times to 25 keratoconus patients (RGP CL wearers) and 25 healthy myopic subjects (RGP and soft CL wearers). The first time was to assess the VR-QoL for spectacle wearing, such as those for refractive correction, and the second time was for CL wearing.

Results Keratoconus patients showed a lower VR-QoL impairment ($P < 0.01$) than healthy subjects in the total and all subscale score of NEI-VFQ-25 related to wearing spectacles. With CL correction, keratoconus patients showed a VR-QoL improvement with statistically significant differences ($P < 0.04$) in only four subscales, including distance activities, mental health, color vision and peripheral vision, compared with healthy subjects. In the keratoconus group, compared to spectacle use, CL wear improved the VR-QoL score ($P = 0.01$) and all subscales except for ocular pain ($P < 0.01$) and mental health ($P = 0.25$).

Conclusions The use of the NEI-VFQ-25 to explore the difference in the VR-QoL between healthy subjects and patients with keratoconus provides further evidence of improved VR-QoL with RGP CL wear compared with spectacles in keratoconus patients. RGP CL management in keratoconus patients could minimize the impact of the disease on the patient's well-being.

Keywords Keratoconus · Quality of Life · Refractive correction · Rigid gas-permeable contact lens management

Introduction

Keratoconus is a bilateral, asymmetric and progressive corneal disorder, resulting in myopia, irregular astigmatism and reduced vision related to central and paracentral corneal thinning, steepening and scarring [1–3]. This ectatic condition affects between 50 and 230 individuals per 100,000 people [3] and commonly appears during the second decade of life and puberty, progressing until the fourth decade of life, when it usually stabilizes [1–3]. In the early stages, keratoconus can be managed with spectacles or soft contact lenses, but as keratoconus progresses, the irregular astigmatism often requires rigid gas-permeable (RGP) contact lenses (CL) that can improve the best-corrected visual acuity (BCVA) [3].

The National Eye Institute-Vision Function Questionnaire (NEI-VFQ-25) developed by the National Eye

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Institute is a specifically developed questionnaire to measure the vision-related quality of life (VR-QoL) [4]. This questionnaire is one of the most accepted and used methods for assessing the impact of different eye conditions, such as cataracts [5], age-related macular degeneration (AMD) [6], uveitis [7], post-retinal detachment surgery [8], dry eyes [9] and others in patients' VR-QoL.

Using the NEI-VFQ-25, patients with keratoconus show a significantly disproportional impaired VR-QoL [4, 10, 11] that worsens with time [12]. Moreover, these patients show similar results in the NEI-VFQ-25 to those reported for patients with advanced (categories 3 and 4) age-related macular degeneration [13].

The strongest associations with a lower VR-QoL with low visual acuity (worse than 20/40) and steeper corneal curvature (>52 D) have been described to greatly influence the patient's attitude toward his/her disease and perception of its impact on visual function when there is an increase in the 3 D corneal curvature or a visual acuity decrease of higher than ten letters occur over time [12].

However, all studies on the VR-QoL in keratoconus patients consider the BCVA obtained indiscriminately with spectacles or CL [10, 11, 14–18]. To the best of our knowledge, no studies have previously examined the effect of keratoconus correction (spectacles or RGP CL) over the VR-QoL score.

As keratoconus patients show different visual acuity corrected with spectacles or with RGP CL wear, the aim of this study was to assess the impact of refractive correction (spectacles vs RGP CL) on the VR-QoL obtained with the standardized questionnaire, NEI-VFQ-25, in keratoconus patients. As a second objective, we compared the VR-QoL score obtained with spectacles and CL in healthy myopic (non-keratoconus) subjects to assess whether refractive correction shows different impact in keratoconus patients. These data would be crucial in clinical trials that evaluate the impact of new treatment modalities for keratoconus, such as cross-linking, intracorneal rings and corneal grafts, on the VR-QoL or in future design and validation of patient-reported outcomes (PROs) to assess the VR-QoL in keratoconus patients.

Methods

This is an observational and non-randomized study. Informed consent was obtained from each subject after approval for the study was granted by the Human Sciences Ethics Committee of the University of Valladolid. All subjects were treated in accordance with the Declaration of Helsinki.

Fifty patients were classified into two study groups [healthy ($n = 25$ myopic subjects) and keratoconus ($n = 25$)] and were enrolled in the study; the study participation was proposed in a scheduled after-care eye examination. The keratoconus patients were attended at the IOBA Eye Institute (University of Valladolid, Spain), a tertiary referral clinic that addresses patients with irregular corneas and other eye disorders.

The keratoconus group included patients who were successfully fitted with RGP CLs (KAKC RGP design, Conoptica-Hecht Contactlinsen GmbH, Baden-Württembert, Germany) in at least 1 year of comfortable use. The healthy group was recruited in 1 week and included non-symptomatic myopic contact lens wearers (RGP or soft lenses) with BCVA $\geq$ 20/20 (Snellen chart) with myopia and astigmatism lower than 3.00 D. All subjects in both groups were aged 18 years or older, free of cognitive impairment, living independently and Spanish speaking.

Patients with any active ocular surface disease (e.g., significant dry eye symptoms or keratitis), corneal opacities, pellucid marginal corneal degeneration, glaucoma, use of medication that could affect ocular physiology or a history of any type of ocular surgery were excluded.

Independent corneal specialists confirmed the diagnoses of keratoconus after a completed eye examination, which included Scheimpflug topographical analysis (Galilei, Ziemer, Port, Switzerland) and biomicroscopy examination (with a demonstration of at least one biomicroscopic sign, including Vogt́s striae, Fleischeŕs ring, corneal thinning or scarring). The keratoconus stage has been identified using the Amsler-Krumeich classification [19]. The keratoconus eyes were designated as better and worse eyes based on the BCVA, simulated keratometry and stage of Amsler-Krumeich classification.

Each patient responded to the Spanish version of the NEI-VFQ-25. The questionnaire consists of 25 questions that are easy to understand and answer, which are oriented to evaluate 11 vision-dependent domains and one general health domain, including the following: ocular pain, near vision, distance vision, vision-specific social function, vision-specific mental health, general vision, vision-specific role difficulties, vision-specific dependency, driving, color vision and peripheral vision. Patients answered the questionnaire two consecutive times: the first time was to assess the VR-QoL for spectacle wearing, such as those for refractive correction, and the second time was for CL wearing. The general health domain was answered once because this subscale is the same with spectacles and CL.

Data analysis

Statistical analysis was performed using the SPSS 15.0 (SPSS, Chicago, Illinois, USA) statistical package for Windows. A nonparametric distribution of variables was

verified with the Kolmogorov–Smirnov test ($P < 0.05$ indicated that the data were nonparametric-distributed).

The total and subsection scores, ranging from 0 (worst) to 100 (best), were calculated for the questionnaire VFQ-25 as directed by the National Health Institute (following the standard method recommended by the developers) [20] for determining the mean score (±standard deviation) for healthy and keratoconus patients wearing spectacles or CL. Additionally, a Rasch analysis with the algorithm proposed by Massof [20] to be used with small sample sizes that would not be able to obtain reliable estimates with standard Rasch analysis software [21] was conducted. The correlation between the standard method recommended by the developers of the NEI-VFQ-25 [22] and the Massof's algorithm [20] for approximating Rasch analysis was calculated with Spearman coefficient. The total standard and the Massof's algorithm score obtained with spectacles and CL in each study group was compared with the Wilcoxon test ($P < 0.05$ considered statistically significant) and between healthy and keratoconus groups with the Mann–Whitney U test ($P < 0.05$ considered statistically significant). Finally, the difference between CL and spectacle wear total score was calculated with the standard method and with Massof's algorithm for each study group and compared with Wilcoxon test ($P < 0.05$ considered statistically significant).

The visual acuity and the subsection standard scores obtained with spectacles and CL in each study group were compared with the Wilcoxon test ($P < 0.05$ considered statistically significant). Visual acuity between healthy and keratoconus groups was also compared with the Mann–Whitney U test ($P < 0.05$ considered statistically significant). Subsection standard scores in healthy and keratoconus groups were compared with the Mann–Whitney U test ($P < 0.05$ considered statistically significant). Finally, differences between the degree of keratoconus (total standard score) was assessed with a nonparametric Kruskal–Wallis ANOVA ($P < 0.05$ considered statistically significant).

Results

Subjects

Fifty patients (23 women and 27 men) were included in the study. The mean age of the total sample was 33.7 ± 11.2 years (range 18–58 years).

Twenty-five subjects (17 women and 8 men) comprised the healthy group with a mean age of 30.3 ± 11.3 years (range 18–55 years) and a mean spherical equivalent refractive error of −3.63 ± 1.69 D (range from −1.50 D to −8.00 D). The mean of simulated keratometry reading was 7.83 ± 0.40 mm. The BCVA with spectacles was 1.00 ± 0.00, and CL was 1.05 ± 0.08 (Snellen chart) ($P = 0.01$). Healthy group showed better BCVA with spectacles and contact lenses than obtained by the keratoconus patients ($P < 0.01$). Twenty-four subjects were soft CL wearers, and one subject was an RGP CL wearer. The mean number of daily hours of CL use was 8.72 ± 2.93 (range 3–15 h) and 5.44 ± 2.16 days per week (range 1–7 days).

Twenty-five subjects (six women and 19 men) comprised the keratoconus group with a mean age of 37.1 ± 10.1 years (range 22–58 years) and a mean spherical equivalent refractive error of −4.56 ± 3.68 D (range from −0.25 to −11.50 D), and the BCVAs with spectacles and RGP CLs were 0.60 ± 0.30 and 0.93 ± 0.17 (Snellen chart), respectively ($P < 0.01$). According to the Amsler-Krumeich classification, there were 13 eyes in the stage 1; 17 eyes in the stage 2; 15 eyes stage 3; and only four eyes in the stage 4.

All subjects were RGP CL wearers. In the better eye, the mean of the simulated keratometry reading was 7.35 ± 0.49 mm and the BCVAs with spectacles and RGP CLs were 0.74 ± 0.26 and 0.96 ± 0.18 ($P < 0.01$) (Snellen visual chart), respectively. In the worse eye, the mean of the simulated keratometry reading was 6.99 ± 0.52 mm and the BCVAs with spectacles and RGP CLs were 0.45 ± 0.26 and 0.90 ± 0.16 ($P < 0.01$) (Snellen visual chart), respectively. The mean number of daily hours of CL wear was 9.36 ± 4.73 (range 1–17 h) 6.08 ± 1.53 days per week (range 2–7 days).

VR-QoL: keratoconus versus healthy subjects

Total score of NEI-VFQ-25 and all subscales scores were lower in the keratoconus group than in the healthy group with both refractive corrections (spectacles and CLs) (Table 1), except the general vision subscale with CLs when keratoconus patients showed a slightly better score than healthy subjects (nonsignificant, $P = 0.38$ Table 1).

Healthy subjects showed a high score ($P < 0.01$) in the VR-QoL than in keratoconus patients in the total and all subscales for spectacle wear. Nevertheless, these differences reduced with the use of CL, and there were statistically significant differences ($P < 0.04$) in the VR-QoL in only the following four subscales: distance activities, mental health, color vision and peripheral vision.

VR-QoL: spectacles versus CL wear

In the keratoconus group, the total and all subscales scores for CLs were higher than for spectacles, except in ocular pain and mental health (Table 1). The ocular pain subscale with spectacles showed a better score than with CLs ($P < 0.01$) in both study groups, but the peripheral vision

Table 1 NEI-VFQ-25 total and subscale scores in healthy and keratoconus group with both refractive method corrections (spectacles vs CL)

	Healthy ($n = 25$)		Keratoconus ($n = 25$)		P**
	Mean ± SD	Min–max	Mean ± SD	Min–max	
General health	70.00 ± 20.41	25–100	65.00 ± 27.01	25–100	0.53
General vision					
Spectacles	76.00 ± 20.00	40–100	42.50 ± 21.52	20–100	<0.01
CL	68.00 ± 16.33	40–100	72.00 ± 22.36	20–100	0.38
P*	0.02		<0.01		
Ocular pain					
Spectacles	92.50 ± 11.97	50–100	75.00 ± 21.80	37.50–100	<0.01
CL	71.00 ± 18.65	37.50–100	63.50 ± 27.46	12.50–100	0.46
P*	<0.01		<0.01		
Near activities					
Spectacles	94.00 ± 14.13	41.67–100	57.67 ± 27.94	0–100	<0.01
CL	91.00 ± 11.51	58.33–100	81.33 ± 20.73	33.33–100	0.13
P*	0.34		<0.01		
Distance activities					
Spectacles	93.33 ± 9.32	66.77–100	51.66 ± 30.90	0–100	<0.01
CL	91.67 ± 8.33	75–100	80.00 ± 18.79	41.67–100	0.04
P*	0.57		<0.01		
Social functioning					
Spectacles	96.50 ± 7.67	75–100	71.88 ± 29.32	0–100	<0.01
CL	96.50 ± 7.67	75–100	89.00 ± 17.79	37.50–100	0.13
P*	1.00		<0.01		
Mental health					
Spectacles	73.90 ± 16.85	25–90	54.33 ± 25.91	7.5–87.50	<0.01
CL	73.35 ± 14.46	25–87.50	50.80 ± 19.40	10–75	<0.01
P*	0.53		0.25		
Role difficulties					
Spectacles	89.50 ± 12.85	62.50–100	53.00 ± 38.74	0–100	<0.01
CL	90.00 ± 13.50	50–100	75.00 ± 29.97	0–100	0.12
P*	0.65		<0.01		
Dependency					
Spectacles	96.87 ± 7.27	75–100	68.40 ± 39.70	0–100	<0.01
CL	98.00 ± 5.52	75–100	87.00 ± 25.00	0–100	0.07
P*	0.32		<0.01		
Driving					
Spectacles	85.78 ± 23.71	0–100	48.75 ± 31.68	0–100	<0.01
CL	82.58 ± 20.77	75–100	79.76 ± 20.34	33.33–100	0.71
P*	0.16		<0.01		
Color vision					
Spectacles	98.00 ± 10.00	50–100	83.33 ± 26.24	0–100	<0.01
CL	100 ± 0.00	100–100	95.00 ± 10.21	75–100	0.02
P*	0.32		0.01		
Peripheral vision					
Spectacles	84.00 ± 18.93	62.73–98.86	47.00 ± 31.27	0–100	<0.01
CL	95.00 ± 10.20	75–100	82.00 ± 22.27	25–100	0.02
P*	<0.01		<0.01		
Total score					
Spectacles	88.88 ± 7.64	62.73–98.86	58.31 ± 25.65	6.14–98.18	<0.01
CL	87.38 ± 6.62	69.63–96.48	77.64 ± 16.51	40.83–96.36	0.07

Table 1 continued

	Healthy ($n = 25$)		Keratoconus ($n = 25$)		P**
	Mean ± SD	Min–max	Mean ± SD	Min–max	
P*	0.41		<0.01		

P * Wilcoxon test ($P < 0.05$ considered statistically significant). P ** Mann–Whitney U test ($P < 0.05$ considered statistically significant)

score was better with CLs ($P < 0.01$) than with spectacles in healthy and keratoconus subjects. The mental health subscale showed non-statistically significant differences ($P = 0.25$) between spectacles and CLs in both groups.

An additional analysis in each keratoconus group showed a lower score in the spectacles VR-QoL than that obtained with CLs (Fig. 1). The spectacles score was significantly worse for a high keratoconus degree ($P < 0.01$ Kruskal–Wallis ANOVA). However, the CL score was nonsignificantly different ($P = 0.06$ Kruskal–Wallis ANOVA) between the keratoconus groups.

Standard and Massof's algorithm (Rasch analysis) scoring comparison

High correlation between the Massof's algorithm and the NEI-VFQ-25 standard score in contact lens (0.93 Spearman correlation coefficient) and spectacle wear (0.97 Spearman correlation coefficient) was found. The differences between CL and spectacles wear in healthy and keratoconus patients show the same trend with the standard method ($P = 0.41$ in healthy and $P < 0.01$ in keratoconus group) or with the Massof's algorithm ($P = 0.17$ in healthy and $P < 0.01$ in keratoconus group). Both study groups showed statistically significant differences (standard method $P < 0.01$ and Massof's algorithm $P < 0.01$) in spectacles wear score; however, CL wear score showed non-statistically significant differences (standard method $P = 0.07$ and Massof algorithm $P = 0.14$).

Finally, the difference between CL and spectacle wear total score showed statistically significant differences between healthy and keratoconus patients with the standard method ($P < 0.01$) and with Massof's algorithm ($P < 0.01$).

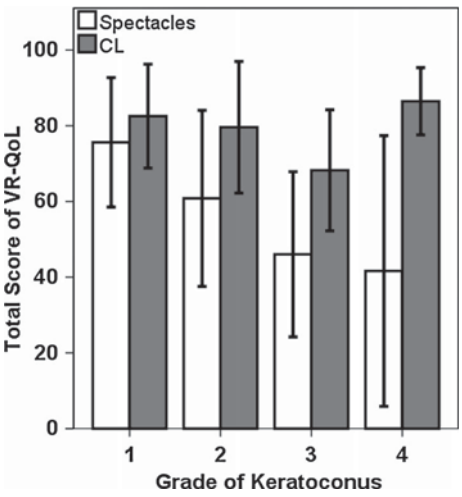

Fig. 1 NEI-VFQ-25 total score in the different grades of keratoconus with spectacles and CL correction. The CL score was not significantly different ($P = 0.06$ Kruskal–Wallis ANOVA) for different keratoconus degrees; however, the spectacles score decreased significantly ($P < .01$ Kruskal–Wallis ANOVA) with the stage of keratoconus

Discussion

In the early stages of keratoconus, the refractive error can be corrected with spectacles, but, as it progresses, corneal irregularities induce higher-order aberrations that cannot be corrected with traditional ophthalmic lenses. To compensate for these corneal irregularities, it is necessary to prescribe RGP CLs, which reduces visual distortion due to the tear that remains between the CL and the anterior surface of the cornea, correcting most of the corneal higher-order aberration-induced keratoconus and providing a generally higher BCVA than that obtained with spectacles [2, 3]. Therefore, it is reasonable to think that the VR-QoL of these patients may be affected by the method of refractive error correction using (spectacles or CL), but to the best of our knowledge, there are no previous reports of the effect of refractive correction in VR-QoL in keratoconus patients.

For this reason, our aim in this study was to explore the influence of the refractive correction (spectacles or CL) on the VR-QoL in keratoconus patients assessed with the NEI-VFQ-25. We compared the VR-QoL in healthy myopic subjects to evaluate the effect of refractive correction in non-keratoconus patients. In taking this approach, we may have detected a significantly understated VR-QoL with the use of spectacles in the keratoconus group.

There are several reports regarding the impact of keratoconus in VR-QoL using NEI-VFQ-25 [10–12, 15, 16, 18]. The National Eye Institute developed the NEI-VFQ to assess health-related quality of life of patients with visual impairments [23] showing off a high correlation between

the standard scoring method, Massof approximation and Rasch analysis in low-vision patients [21] agreeing with our results. Because the original published scoring has been criticized [24] (it does not produce interval-scaled estimates of visual ability [25]) and Rasch analysis could be preferable [26–28], a Rasch analysis using the Massof approximation [20] was conducted because the small sample size would not be able to obtain reliable estimates with standard Rasch analysis software [21]. We found a great correlation between the standard method recommended by the developers of the NEI-VFQ-25 [22] and the Massof's algorithm [20, 21, 28] but the small sample size included in our study requires that these results could be interpreted with caution and further studies with high sample sizes could be necessary.

The use of the NEI-VFQ-25 has some limitations. This questionnaire has a dysfunctional rating scale to the response options, using too many categories, long descriptors for categories, using neutral and conceptually overlapping categories and a branch questions design in some items, avoiding the evidence-based guidelines for rating scales design [29]. Some reports, in AMD patients, found a weak validation that is not included modern psychometric methods such as item response theory models or Rasch analysis [30]. Others in patients undergoing cataract surgery [29] suggest that the NEI-VFQ-25 is more complicated than others (such as VF-14 or CatScale). However, there are not previous reports that compare the responsiveness of the questionnaire in terms of effect size or difficulty with other questionnaires in keratoconus patients as have been described in cataract surgery patients [31]. These limitations could influence in the item calibration and provoke some loss of measurement quality, affecting to the quality of clinical studies and their results. But because it is difficult to directly compare research findings using different PROs [32], we used the NEI-VFQ-25 to assess VR-QoL in keratoconus patients, and our results agree with previous reports and the NEI-VFQ-25 could be useful to assess VR-QoL in keratoconus patients.

Aydin Kurna et al. [10] studied the VR-QoL in 30 patients with keratoconus (total score 75.2 ± 17.2) and 30 healthy subjects (total score 93.2 ± 5.6) and reported findings that are in agreement with the present study [CL score of 77.64 ± 16.51 and 87.38 ± 6.62, respectively, (Table 1)]. However, Aydin Kurna et al. included 20 RGP CL wearers and 10 spectacles wearers in the keratoconus group, and the different visual acuity obtained by these two options may influence the results. Additionally, in this study, the authors found nonsignificant differences between the VR-QoL of a group of RGP wearers and another group of keratoconus patients whose vision was corrected with spectacles, which may be because of the similar visual acuity for both methods, contributing to spectacle correction being indicated in early stage keratoconus. Additionally, the impact of well-being in the early stages of keratoconus has been previously reported [11]. Aydin Kurna et al. did not compare the VR-QoL with both refractive corrections in the same patient group. Tatematsu-Ogawa et al. [16] evaluated the VR-QoL in 45 keratoconus patients divided into three study groups according to the BCVA and observed a similar impact of the keratoconus on the VR-QoL that we found. Nevertheless, they included patients with RGP, soft CLs and spectacles in the same group, which can affect the BCVA obtained with each refractive correction method. Moreover, Kymes et al. [11] studied the VR-QoL with NEI-VFQ-25 in a large sample of keratoconus patients, including 75 % who wear CLs in both eyes, 6 % who wear a CL in one eye only and 19 % who wear spectacles. Jones-Jordan et al. [15] examined the relationship of keratoconus asymmetry between both eyes over time on the VR-QoL, including 85 % CL wearers, but this author also does not take into account the method of refractive correction in their results. In summary, there are not previous reports of the impact of refractive method (spectacles vs RGP contact lenses) in VR-QoL of keratoconus patients.

Other questionnaires were used in the literature to evaluate the VR-QoL in keratoconus patients. Recently, Sahebjada et al. [14] used a six-item multi-attribute utility instrument (MAUI) to assess the impact of keratoconus disease in the better and worse eyes on the VR-QoL without any indication of the type of refractive correction that the included subjects used. A similar example is the study by Gothwal et al. [17], which assessed VR-QoL with an Impact of Vision Impairment (IVI) questionnaire in keratoconus patients, including 21 % spectacle wearers, in the analysis of the results. McAlinden et al. [33] concluded that National Eye Institute Refractive Error Quality of Life (NEI-RQL-42) presents relevant deficiencies in keratoconus patients, with only one valid subscale (near vision) of the 12 assessed subscales and recommend that this tool should not be used in keratoconus studies. Moreover, McAlinden et al. [33, 34] highlighted that the NEI-RQL-42 in keratoconus patients had disordered thresholds in three subscales (symptoms, dependence on correction and suboptimal correction), six subscales had misfit items and not measure what they purport to measure, 11 subscales presented an inadequate person separation value, and these subscales could not adequately discriminate between the individuals in the sample population, and a poor targeting was found in these patients.

Future studies of VR-QoL in keratoconus patients could be conducted with other quality-of-life tools. For example, the Quality of Vision questionnaire (QoV) that analyzes the quality of life in different refractive correction situations such as spectacles or contact lenses, requires a Rasch

analysis validation in these group of patients [35, 36]. Other questionnaires, such as the Quality of Life Impact of Refractive Correction (QIRC) or The Contact Lens Impact on Quality of Life (CLIQ) could be proposed [37]. But it would be necessary a validation and reliability testing with a large collection of calibrated items that measure a defined latent trait (specific item bank) in keratoconus patients to develop better and higher-quality studies of VR-QoL in these patients, as occur in other eye diseases such as glaucoma [38].

Our study suggests that the BCVA obtained with spectacles is an important factor contributing to keratoconus patient's VR-QoL impairment. This is not surprising, as keratoconus patients prefer RGP CLs due to the better vision provided. However, the impact of CL use has a pronounced effect on their overall well-being. All the previous reports of VR-QoL in keratoconus patients use the questionnaires without consideration of the spectacles or contact lens wear, and our results suggest that this could be an important flaw in quality-of-life studies in these patients. The optical correction—spectacles or contact lenses—shows a relevant impact in keratoconus patient's answer in the NEI-VFQ-25, so this variable may be included in the methodology and statistical analysis of future studies of VR-QoL in keratoconus patients. These findings could have considerable implications for treatment decisions, as clinicians may need to consider referring patients to a CL practitioner [14]. In the management of keratoconus, it is essential to avoid significant vision loss, which substantially impacts the VR-QoL [14]. Our data suggest that RGP CLs fitting reduces the impact of the disease on the patients' VR-QoL. Moreover, there were nonsignificant differences in the total VR-QoL score (related to contact lenses wear) between keratoconus and healthy subjects, but this result will be confirmed in future studies.

The current data are also now extremely relevant to the field of research on keratoconus management, where new treatments are available. de Paranhos et al. [39] evaluated the impact of intracorneal ring segment (ICRS) implantation on the VR-QoL in 42 keratoconus patients with CL intolerance, using the NEI-RQL instrument. They found an improvement of the VR-QoL postoperatively but did not describe whether any of the patients were fit with CLs after the surgery because CLs or spectacles are needed after ICRS surgery to improve the patient's visual acuity [40, 41]. Future studies of the efficacy of these therapies will need to include the same refractive correction before and after the treatment to avoid the negative bias of the effect in the VR-QoL of spectacles correction.

The main strength of the present study is its use of a control group comprising non-keratoconus healthy subjects in which the VR-QoL is therefore unaffected by refractive correction (spectacles or CL) to compare with the keratoconus patients. So, this approach has permitted to compare the effect of refractive correction in healthy and keratoconus subjects; to the best of our knowledge, these results have not been previously described. Moreover, we found significant differences between spectacle and CL use in the healthy myopic group for general vision, ocular pain and peripheral vision, which is quite comprehensive, as wearing CLs provides more discomfort than wearing spectacles [42] and CLs are known to improve the field of view [43] compared to spectacles [44]. Differences in general vision between spectacles and CL wear in the healthy group could be the subject of further research. Potential limitations include the small sample size of the study groups; however, the results maintained significant differences between the healthy and keratoconus groups (previously described) [12, 14, 16, 18]. Other study approach with a cross-sectional design involving two keratoconus groups (one spectacle wearers and other RGP wearers) could be of interest to clarify the role of the refraction correction in VR-QoL in these patients. However, both groups may be similar in terms of vision, corneal curvature, age, socioeconomic status and gender, and these requirements could be very difficult or impossible to find because the primary indication for spectacle wearing in moderate and advance keratoconus stage patients is the intolerance to CL wear. For this reason, our study design permits a comparison between both refractive correction options in the same subjects, avoiding intrapersonal differences. This is a novel use of the NEI-VFQ-25, so these results could be interpreted with caution, and developing and validating (with adequate Rasch analysis) new PROs that follow the recommendations to be a psychometrically robust tool to assess VR-QoL in keratoconus patients [29–32] could be necessary. Future studies with larger cohorts of keratoconus patients and longitudinal examinations of the changes in the VR-QoL are needed to confirm the effect of the method for correcting the refraction on the quality of life in keratoconus and healthy subjects.

Conclusions

The results of this study could support the use of the NEI-VFQ-25 to explore the difference in the VR-QoL between healthy subjects and patients with keratoconus as well as provide further evidence that a higher VR-QoL is obtained with RGP CLs than with spectacles in these patients.

The results underscore the importance of adopting a comprehensive approach to the examination and care of patients with keratoconus, highlighting the need for RGP CL fitting in the management of keratoconus. Nevertheless, this study emphasizes the need to consider the optical

correction—spectacles or contact lenses wear—so a clear definition of the refractive correction of the patients enrolled in VR-QoL studies should be included in the subject description and the results assessment. This information must be considered in studies regarding VR-QoL that aims to collect more reliable, comparable and objective information about keratoconus patients.

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Compliance with ethical standards

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Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Rabinowitz, Y. S. (1998). Keratoconus. *Survey of Ophthalmology, 42*(4), 297–319.
2. Romero-Jiménez, M., Santodomingo-Rubido, J., & Wolffsohn, J. S. (2010). Keratoconus: A review. *Contact Lens and Anterior Eye, 33*(4), 157–166.
3. Barnett, M., & Mannis, M. J. (2011). Contact lenses in the management of keratoconus. *Cornea, 30*(12), 1510–1516.
4. Mangione, C. M., Lee, P. P., Gutierrez, P. R., Spritzer, K., Berry, S., Hays, R. D., & National Eye Institute Visual Function Questionnaire Field Test Investigators. (2001). Development of the 25-item National Eye Institute Visual Function Questionnaire. *Archives of Ophthalmology, 119*(7), 1050–1058.
5. Chatziralli, I. P., Sergentanis, T. N., Peponis, V. G., Papazisis, L. E., & Moschos, M. M. (2013). Risk factors for poor vision-related quality of life among cataract patients. Evaluation of baseline data. *Graefes Archive for Clinical and Experimental Ophthalmology, 251*(3), 783–789.
6. Orr, P., Rentz, A. M., Margolis, M. K., Revicki, D. A., Dolan, C. M., Colman, S., et al. (2011). Validation of the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) in age-related macular degeneration. *Investigative Ophthalmology & Vision Science, 52*(6), 3354–3359.
7. Lightman, S., Belfort, R, Jr, Naik, R. K., Lowder, C., Foster, C. S., Rentz, A. M., et al. (2013). Vision-related functioning outcomes of dexamethasone intravitreal implant in noninfectious intermediate or posterior uveitis. *Investigative Ophthalmology & Vision Science, 54*(7), 4864–4870.
8. Okamoto, F., Okamoto, Y., Hiraoka, T., & Oshika, T. (2008). Vision-related quality of life and visual function after retinal detachment surgery. *American Journal of Ophthalmology, 146*(1), 85–90.
9. Paulsen, A. J., Cruickshanks, K. J., Fischer, M. E., Huang, G. H., Klein, B. E., Klein, R., et al. (2014). Dry eye in the beaver dam offspring study: prevalence, risk factors, and health-related quality of life. *American Journal of Ophthalmology, 157*(4), 799–806.
10. Aydin Kurna, S., Altun, A., Gencaga, T., Akkaya, S., & Sengor, T. (2014). Vision related quality of life in patients with keratoconus. *Journal of Ophthalmology, 2014*, 694542. doi:10.1155/2014/694542.
11. Kymes, S. M., Walline, J. J., Zadnik, K., Gordon, M. O., & Collaborative Longitudinal Evaluation of Keratoconus study group. (2004). Quality of life in keratoconus. *American Journal of Ophthalmology, 138*(4), 527–535.
12. Kymes, S. M., Walline, J. J., Zadnik, K., Sterling, J., & Gordon, M. O. (2008). Changes in the quality-of-life of people with keratoconus. *American Journal of Ophthalmology, 145*(4), 611–617.
13. Age-Related Eye Disease Study Research Group. (1999). The Age-Related Eye Disease Study (AREDS): Design implications. AREDS Report No. 1. *Controlled Clinical Trials, 20*(6), 573–600.
14. Sahebjada, S., Fenwick, E. K., Xie, J., Snibson, G. R., Daniell, M. D., & Baird, P. N. (2014). Impact of keratoconus in the better eye and the worse eye on vision-related quality of life. *Investigative Ophthalmology & Vision Science, 55*(1), 412–416.
15. Jones-Jordan, L. A., Walline, J. J., Sinnott, L. T., Kymes, S. M., & Zadnik, K. (2013). Asymmetry in keratoconus and vision-related quality of life. *Cornea, 32*(3), 267–272.
16. Tatematsu-Ogawa, Y., Yamada, M., Kawashima, M., Yamazaki, Y., Bryce, T., & Tsubota, K. (2008). The disease burden of keratoconus in patients' lives: Comparisons to a Japanese normative sample. *Eye & Contact Lens, 34*(1), 13–16.
17. Gothwal, V. K., Reddy, S. P., Fathima, A., Bharani, S., Sumalini, R., Bagga, D. K., et al. (2013). Assessment of the impact of keratoconus on vision-related quality of life. *Investigative Ophthalmology & Vision Science, 54*(4), 2902–2910.
18. Labiris, G., Giarmoukakis, A., Sideroudi, H., Gkika, M., Fanariotis, M., & Kozobolis, V. (2012). Impact of keratoconus, cross-linking and cross-linking combined with photorefractive keratectomy on self-reported quality of life. *Cornea, 31*(9), 734–739.
19. Choi, J. A., & Kim, M. S. (2012). Progression of keratoconus by longitudinal assessment with corneal topography. *Investigative Ophthalmology & Vision Science, 53*(2), 927–935.
20. Massof, R. W. (2007). An interval-scaled scoring algorithm for visual function questionnaires. *Optometry and Vision Science, 84*(8), 689–704.
21. Dougherty, B. E., & Bullimore, M. A. (2010). Comparison of scoring approaches for the NEI VFQ-25 in low vision. *Optometry and Vision Science, 87*(8), 543–548.
22. National Eye Institute. (2000). NEI VFQ-25 Scoring Algorithm. http://www.nei.nih.gov/resources/visionfunction/manual_cm2000.pdf. Accessed June 4, 2014.
23. Massof, R. W., & Fletcher, D. C. (2001). Evaluation of the NEI visual functioning questionnaire as an interval measure of visual ability in low vision. *Vision Research, 41*(3), 397–413.
24. Marella, M., Pesudovs, K., Keeffe, J., O'Connor, P. M., Rees, G., & Lamoureux, E. L. (2010). The psychometric validity of the NEI VFQ-25 for use in a low vision population. *Investigative Ophthalmology & Vision Science, 51*(6), 2878–2884.

25. Massof, R. W., & Rubin, G. S. (2001). Visual function assessment questionnaires. *Survey of Ophthalmology, 45*(6), 531–548.
26. Pesudovs, K. (2010). Item banking: A generational change in patient-reported outcome measurement. *Optometry and Vision Science, 87*(4), 285–293.
27. Massof, R. W. (2005). Application of stochastic measurement models to visual function rating scale questionnaires. *Ophthalmic Epidemiology, 12*(2), 103–124.
28. de Boer, M. R., Moll, A. C., de Vet, H. C., Terwee, C. B., Völker-Dieben, H. J., & van Rens, G. H. (2004). Psychometric properties of vision-related quality of life questionnaires: A systematic review. *Ophthalmic and Physiological Optics, 24*(4), 257–273.
29. Khadka, J., Gothwal, V. K., McAlinden, C., Lamoureux, E. L., & Pesudovs, K. (2012). The importance of rating scales in measuring patient-reported outcomes. *Health and Quality of Life Outcomes, 10*, 80.
30. Khadka, J., McAlinden, C., & Pesudovs, K. (2012). Validation of the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) in age-related macular degeneration. *Investigative Ophthalmology & Vision Science, 53*(3), 1276.
31. McAlinden, C., Gothwal, V. K., Khadka, J., Wright, T. A., Lamoureux, E. L., & Pesudovs, K. (2011). A head-to-head comparison of 16 cataract surgery outcome questionnaires. *Ophthalmology, 118*(12), 2374–2381.
32. Khadka, J., McAlinden, C., Gothwal, V. K., Lamoureux, E. L., & Pesudovs, K. (2012). The importance of rating scale design in the measurement of patient-reported outcomes using questionnaires or item banks. *Investigative Ophthalmology & Vision Science, 53*(7), 4042–4054.
33. McAlinden, C., Khadka, J., de Paranhos, J. F. S., Schor, P., & Pesudovs, K. (2012). Psychometric Properties of the NEI-RQL-42 Questionnaire in Keratoconus. *Investigative Ophthalmology & Vision Science, 53*(11), 7370–7374.
34. McAlinden, C., Skiadaresi, E., Moore, J., & Pesudovs, K. (2011). Subscale assessment of the NEI-RQL-42 questionnaire with Rasch analysis. *Investigative Ophthalmology & Vision Science, 52*(8), 5685–5694.
35. McAlinden, C., Pesudovs, K., & Moore, J. E. (2010). The development of an instrument to measure quality of vision: the Quality of Vision (QoV) questionnaire. *Investigative Ophthalmology & Vision Science, 51*(11), 5537–5545.
36. McAlinden, C., Skiadaresi, E., Gatinel, D., Cabot, F., Huang, J., & Pesudovs, K. (2013). The Quality of Vision questionnaire: Subscale interchangeability. *Optometry and Vision Science, 90*(8), 760–764.
37. Khadka, J., McAlinden, C., & Pesudovs, K. (2013). Quality assessment of ophthalmic questionnaires: Review and recommendations. *Optometry and Vision Science, 90*(8), 720–744.
38. Khadka, J., McAlinden, C., Craig, J. E., Fenwick, E. K., Lamoureux, E. L., & Pesudovs, K. (2015). Identifying content for the glaucoma-specific item bank to measure quality-of-life parameters. *Journal of Glaucoma, 24*(1), 12–19.
39. de Paranhos, J., Avila, M. P., Paranhos, A, Jr, & Schor, P. (2010). Evaluation of the impact of intracorneal ring segments implantation on the quality of life of patients with keratoconus using the NEI-RQL (National Eye Institute Refractive Error Quality of life) instrument. *British Journal of Ophthalmology, 94*(1), 101–105.
40. Gore, D. M., Shortt, A. J., & Allan, B. D. (2013). New clinical pathways for keratoconus. *Eye, 27*(3), 329–339.
41. Moreira, L. B., Bardal, R. A., & Crisigiovanni, L. R. (2013). Contact lenses fitting after intracorneal ring segments implantation in keratoconus. *Arquivos Brasileiros de Oftalmologia, 76*(4), 215–217.
42. Martin, R., Sanchez, I., de la Rosa, C., de Juan, V., Rodriguez, G., de Paz, I., et al. (2010). Differences in the daily symptoms associated with the silicone hydrogel contact lens wear. *Eye & Contact Lens, 36*(1), 49–53.
43. Benjamin, W. J. (2005). Visual optics of contact lens wear. In E. S. Bennett & B. A. Weissman (Eds.), *Clinical contact lens practice* (pp. 1–42). USA: Philadelphia JB Lippincott.
44. Koller, G., Haas, A., Zulauf, M., Koerner, F., & Mojon, D. (2001). Influence of refractive correction on peripheral visual field in static perimetry. *Graefes Archive for Clinical and Experimental Ophthalmology, 239*(10), 759–762.

Capítulo 4

Estado actual del proceso de adaptación de LC RPG en pacientes con queratocono

CHAPTER 4: Current status of GP CL fitting process in keratoconus

4.1. Éxito de adaptación a LC RPG

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Success of Rigid Gas Permeable Contact Lens Fitting

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Objectives: To assess the percentage of successful rigid gas permeable (GP) contact lenses (CLs) fit for both refractive and therapeutic reasons.

Methods: New CLs (soft or GP) fittings were retrospectively analyzed and divided into refractive and therapeutic prescriptions. A standardized fitting protocol that included complete CLs information after a first eye examination, a diagnostic fitting visit, a dispensing visit, and a prescribing visit was used in all fittings. A GP fitting was defined as successful if full-time wear and optimal ocular surface physiology were both achieved at the review assessment 2 to 3 weeks after lens dispensing.

Results: Of 232 new CLs fittings analyzed, 166 were refractive fittings (71.6%) and 66 were therapeutic (28.4%). Of the refractive fittings, 88 subjects (53%) were initially fitted with GP CLs and 61 (69.3%) of these met the criteria for successful GP fitting. Within this group, a different percentage of successful fits were found for neophyte (72%), previous soft lens wearers (62%), and previous GP wearers (92.3%). Of the therapeutic fittings, 61 subjects (92.4%) were initially fitted with GP CLs and 59 (96.7%) of these met the criteria for successful GP fitting.

Conclusions: Following a standardized CLs fitting protocol, a relatively high percentage of successful GP fits was achieved for refractive (7/10 subjects) and therapeutic (9/10 subjects) prescriptions. These results will improve the information available to patients and aid in their CL choices by providing them with a realistic attitude. It will also help eye care practitioners in their clinical activities by providing evidence-based information.

Key Words: Gas permeable—Contact lenses—Success—Fitting.

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Rigid contact lenses (CLs) have been used to correct refractive errors since 1888. The lenses were initially designed as large diameter scleral lenses that used oxygen-impermeable materials (glass and later, polymethylmethacrylate). Close to a century later, in the 1970s, small diameter corneal lenses with gas permeable (GP) materials[1] were introduced. These provided rigid GP lenses that improved patient tolerance and reduced CL-related complications.[2] Later advances in manufacturing technology permitted the development of high oxygen permeability materials that were approved for continuous GP wear.

At present, more than 125 million people are estimated to wear CLs worldwide.[1] The GP fitting rate around the world has been reported to be less than 11% over the past decade.[1,3] Nevertheless, GP lenses present major advantages over soft lenses, such as greater tolerance in patients with dry eye or giant papillary conjunctivitis, in addition to more tear turnover, which provides a better physiological interaction between the lens and the ocular surface, and high oxygen transmissibility.[4–6] The lenses generally provide patients with excellent vision and more effectively correct high astigmatism.[4,5]

Gas permeable lens wearers experience a lower number of CL-related complications than soft CLs wearers, and they have a lower incidence of serious complications such as microbial keratitis.[7] The proportion of GP CLs fittings is clearly low compared with soft lens prescriptions. The low prescription rate for GP lenses suggests that these lenses are not the first choice option when fitting CLs for refractive reasons in healthy eyes (e.g., for myopia, hyperopia, and regular astigmatism correction).[3] It has been suggested that a clinician's goal should be "to prescribe a CL from a physiologically adequate material that will have minimal mechanical impact on the corneal surface while providing the required optical correction."[8] If practitioners followed this recommendation, a large number of GP lens prescriptions would be expected, but GP lenses represent less than 11% of the patients who wear this type of lens, demonstrating a poor acceptance by practitioners and a substantial failure of patients to accept this type of lenses, which may be related to initial discomfort or other problems adapting to the lens.[4,9,10] Several factors can influence a GP CLs fitting, including initial discomfort with the lenses and the additional time required to successfully fit and manage a patient, particularly for novice practitioners. Additionally, large investments on promoting and developing new soft lens designs and materials[9,10] likely affect practitioner's recommendations toward soft lenses.

However, many eye care practitioners propose GP CLs in specialty cases and for challenging patients, such as those with keratoconus or pellucid marginal degeneration, for corneal distortion or irregularity after refractive surgery, or in orthokeratology treatments,[1,3,11] especially for the control of myopia.[12]

The aim of this study was, therefore, to assess the percentage of successful GP CLs fits in healthy subjects (refractive prescriptions fitted for only refractive reasons) and in special subjects (fitted with a therapeutic objective) to provide evidence for the current percentage of successful GP lens fits, to aid eye care practitioners

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in their CL clinical activities, and to improve the information available to patients to help them to select the most adequate lens for their case.

MATERIALS AND METHODS

A retrospective analysis was conducted that included new subjects who were evaluated for the first time and fitted with any type of CL at the Optometry Group of the IOBA Eye Institute (University of Valladolid, Spain), which is a tertiary referral clinic that treats patients with irregular corneas and other eye disorders, during the period from January 2010 through December 2014. The study was approved by the Human Sciences Ethics Committee of the University of Valladolid. Informed consent was obtained from each subject, and all subjects were treated in accordance with the Declaration of Helsinki.

Subjects who received CLs fittings were divided into two major study groups: those with a refractive factors, including healthy subjects fitted just to correct their ametropia (myopia, hyperopia, or regular astigmatism correction), and those where CLs fitting involve therapeutic factors, including subjects who presented some type of ocular pathologic condition (e.g., keratoconus, pellucid marginal degeneration, trauma, or aphakia), secondary irregular cornea (e.g., after refractive surgery or eye trauma), pediatric subjects, cosmetic, or prosthetic fitting and subjects who received treatment to manage myopia (orthokeratology treatment).

The following data were collected for all subjects included in the study: age, gender, medical history, previous CLs experience, refraction, best-corrected visual acuity (BCVA) with spectacles and CLs, manual keratometry readings (OM-4 keratometer; Topcon Corp., Tokyo, Japan), type of the first diagnostic lens fitted (GP, hydrogel, or silicone hydrogel), type of the final lens fitted (GP, hydrogel, or silicone hydrogel), and maximum number of hours of wearing time for the GP fitting.

The success of the GP fittings was defined as adaptation to regular, full-time GP wear (at least 6–8 hours of comfortable wearing time) and an optimal physiology of the ocular surface without CL-related complications (grade >2; Efron Grading Scale[6]). Meanwhile, failed GP fittings were determined as unsuccessful wearers who were unable to reach either a regular daily wear schedule or who presented subjective discomfort and/or any CL-related complication.

GP Fitting Procedure

All the GP CLs fit at this clinic were produced in Spain by one of the three companies: Conoptica-Hecht Contactlinsen, Lenticon, and Menicon. All lenses fit were an aspheric design and made of a medium to high Dk material. The fitting procedure for the GP lenses involved a standardized protocol to achieve a determination of successful lens parameters and having the subject wear the lenses (Fig. 1). At the initial visit, demographic information and the subject history were collected, and a complete eye examination was conducted to determine whether the subject was a good candidate for CL wear by assessing ocular and systemic considerations and the risk of noncompliance by the subject. The subjects who successfully passed the initial examination and accepted the use of CLs after receiving complete information regarding the different types of CLs and their wearing schedules and replacement frequencies started the diagnostic CL fitting procedure, in which the

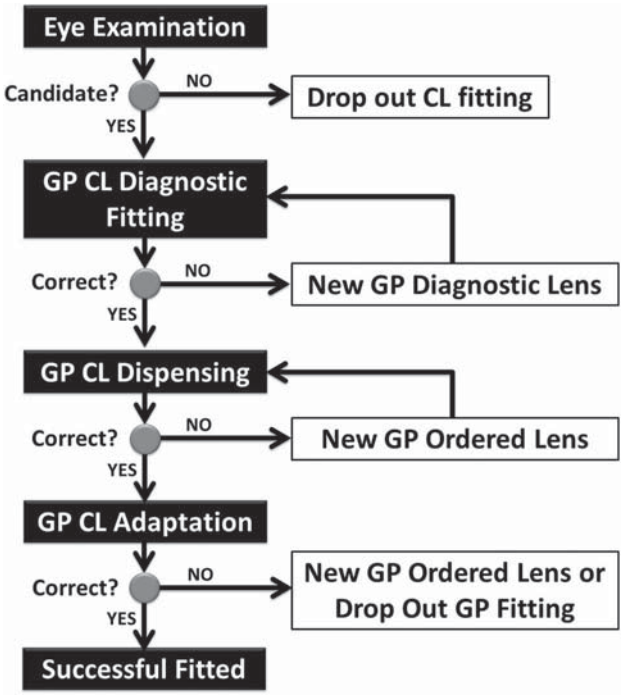

FIG. 1. Flow diagram of GP CLs standardized fitting protocol from the initial eye examination to the successful fitting of the lenses.

practitioner proposed the most adequate lens design and/or material to meet the needs of the subject. When GP lenses were chosen, the parameters of the first diagnostic lenses were selected from a trial set. The first GP diagnostic lens that was calculated was inserted into the subject's eye. After an adaptation period of approximately 30 min, the GP lens fitting assessment was evaluated (static and dynamic fit), and sodium fluorescein was instilled. An acceptable fit was achieved when a well-centered lens allowed adequate blinking and when a correct fluorescein pattern was obtained, according to the ISO 11980.2 (Ophthalmic optics, CLs and CL care products, Guidance for clinical investigation).[13] If any parameter of the diagnostic lens evaluation was inadequate, the GP was changed, and a second diagnostic lens was selected. The fitting assessment was repeated until a correct lens placement was achieved. Once the parameters for the lens were determined (back optic zone radius [BOZR] and total diameter), overrefraction was performed to determine the power of the GP lens and the BCVA, and the GP lens was ordered from the manufacturer.

The GP lens that was ordered was provided at the second visit (dispensing visit). The lens fitting, visual acuity, subject comfort, and the ocular surface were evaluated. If the GP fit was optimal, the subject was instructed in the management and care of the CLs and scheduled for a follow-up visit after 2 or 3 weeks of lens wear. However, if the GP fit was not adequate, the CL specifications (BOZR, diameter or power) were modified, and a new GP lens was reordered.

After 2 or 3 weeks of CL wear, a follow-up visit (prescribing visit) was conducted to assess whether the GP provided at least 6 hr of regular comfortable wearing time and whether an optimal ocular surface physiology was maintained without CL-related complications (grade <2, Efron Grading Scale). If all these conditions were

met, the fit was considered acceptable, the fitting procedure was concluded and an aftercare plan was scheduled for each subject. If the GP fit was inadequate or if the subject presented with subjective discomfort, a new GP was reordered, or the GP fitting was discontinued and another CL material and/or design (soft CL, etc.), depending on the subject's requirements, was proposed.

Statistical Analysis

Statistical analysis was performed using the SPSS 15.0 (SPSS, Chicago, IL) statistical package for Windows. A descriptive data presentation with mean±SD and/or percentages for each studied variable is provided for both study groups (refractive and therapeutic prescriptions). 95% confidence interval (CI) of percentage of successful fits was calculated.

Differences from a normal distribution of the variables were assessed using the Kolmogorov-Smirnov test ($P>0.05$ indicated that the data were normally distributed). The effect of a subject's previous CL history on GP fitting success was assessed using a contingency table to compare the type of the first diagnostic lens with the type of the final prescribed lens. A chi-square test was used to contrast the frequency of each CL type (GP, silicone hydrogels, or conventional soft CLs) to determine diagnostic and final prescribing lens trends ($P<0.05$ were considered significant).

Differences in age, refraction (sphere, cylinder, spherical equivalent), and keratometric readings between successfully and failed GP subjects with refractive prescriptions were assessed using nonparametric Mann-Whitney *U* tests ($P<0.05$ were considered significant). The effect of previous CL experience (neophyte CLs wearers, previous soft, or previous GP CLs wearers) was also assessed. Percentage of successful and failed GP lens fits between men and women were compared using a chi-square test ($P<0.05$ were considered significant).

RESULTS

This retrospective survey included 232 subjects (61.2% women and 38.8% men) who started a fitting procedure for any type of CL. Of these fittings, 71.6% were for refractive prescriptions, and 28.4% were for therapeutic prescriptions. The mean age was 33.2±12.9 years (range, 1–66 years). Of the included subjects, 34.4% had never worn any type of CL, and 65.6% were previous CLs wearers (84.1% soft lenses and 15.9% GP lenses).

Refractive Prescriptions (Healthy Subjects)

A total of 166 subjects (68.7% women and 31.3% men) required a type of CL for refractive reasons. Subjects had a mean age of 32.8±12.3 years (range, 11–64 years). The mean spherical equivalent refractive error was −3.25±5.29 D (range, +10.00 to −23.25 D), the mean flat meridian was 8.75±0.29 mm (range, 7.10–8.75 mm), and mean steep meridian was 7.60±0.29 mm (range, 6.70–8.40 mm). In all, 31.9% of the subjects had never previously worn any type of CL, and 68.1% were previous CLs wearers (87.6% had used soft lenses and 12.4% had used GP lenses). Contact lenses were successfully fitted for 94.6% (n=157) of the subjects (mean BOZR 7.77±0.27 mm [range, 7.35–8.45 mm] and mean lens diameter of 9.55±0.14 mm [range, 9.20–10.00]), and only nine subjects could not be fitted with any type of CL. Figure 2 summarizes the fitting trend revealed by these refractive prescriptions and illustrates the differences regarding previous subject experience in wearing CLs.

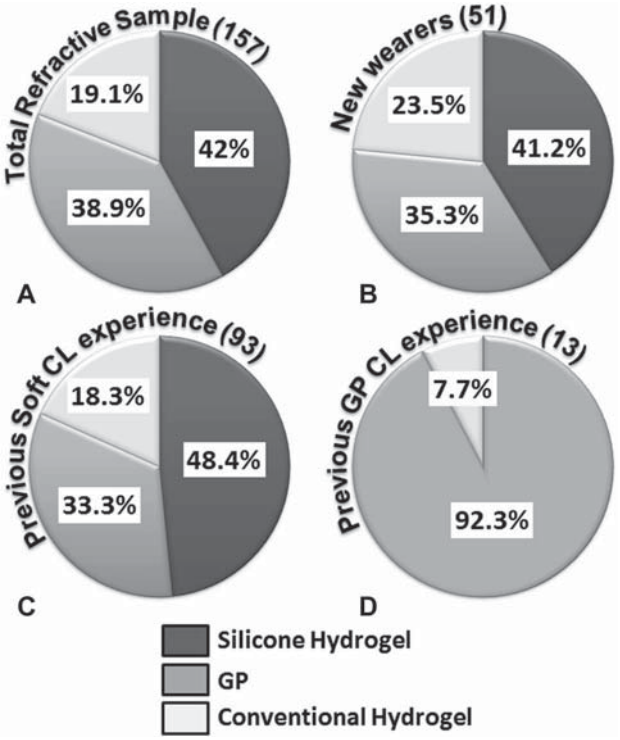

FIG. 2. Summary of the final prescribed lens type (silicone hydrogel, conventional hydrogel, or GP lenses) for those fittings that met the successful criteria in the refractive group. Differences depending on previous CL wear experience between new CLs wearers, previous soft CLs wearers, or previous GP CLs wearers are shown. ($P<0.01$, χ^2 test). The prescribing trend for (A) all refractive fits; (B) new wearers; (C) previous soft CLs wearers; and (D) previous GP CLs wearers.

This survey revealed prescribing trends for GP lenses in healthy subjects, which corresponded to 38.9% of the total fittings conducted during the study period.

Of the 166 subjects analyzed, GP was the first trial lens chosen option for 88 subjects (53%), followed by silicone hydrogels for 53 subjects (31.9%), and conventional hydrogels for 25 subjects (15.1%) ($P<0.01$; chi-square test). Of the 88 subjects who were initially fitted with GP lenses, 25 subjects (28.4%) had never worn any type of CL, 50 subjects (56.8%) were previous soft CLs wearers, and 13 subjects (14.8%) were previous GP CLs wearers.

Sixty-one subjects (69.3% successful, 95% CI, 61.6%–75.5%) of the 88 subjects who were fitted with GP diagnostic lenses were successful in that they comfortably wore the GP (an average of 7.61±1.54 hr per day) and showed an optimal ocular surface physiology. Of the remaining 27 subjects, 4 (4.6% of the refractive group) were finally fit with silicone hydrogels, 14 (15.9%) with hydrogels, and 9 (10.2% of refractive group) were unsuccessful in all CL types. Most of these (six subjects) were previous soft CLs wearers. When this refractive group was separated according to previous CL experience, a different percentage in successful fits were found between neophyte CL wearers (72% successful, 95% CI, 58.4%–83.8%), previous soft CLs wearers (62% successful, 95% CI, 52.3%–71.7%), and previous GP wearers (92.3% successful, 95% CI, 78.9%–100%) (Table 1).

Sex, age, refraction (sphere, cylinder, and spherical equivalent), keratometry readings, and BCVA spectacles were compared

TABLE 1. *Contingency Table Describing the Initial Proposal and the Final CL Fitted*

	Final Lens Prescribed			
	Conventional Hydrogel, % (n)	Silicone Hydrogel, % (n)	GP Lens, % (n)	No CL, % (n)
Refractive prescription (healthy eyes) (n=166)				
Type of initial diagnostic lens				
Conventional hydrogel (n=25)	100 (25)	0	0	0
Silicone hydrogel (n=53)	1.9 (1)	98.1 (52)	0	0
GP lens (n=88)	4.6 (4)	15.9 (14)	69.3 (61)	10.2 (9)
No previous CL wear (53)				
Type of initial diagnostic lens				
Conventional hydrogel (n=12)	100 (12)	0	0	0
Silicone hydrogel (n=16)	0	100 (16)	0	0
GP lens (n=25)	0	20 (5)	72 (18)	8 (2)
Previous soft CL wear (99)				
Type of initial diagnostic lens				
Conventional hydrogel (n=12)	100 (12)	0	0	0
Silicone hydrogel (n=37)	2.7 (1)	97.3 (36)	0	0
GP lens (n=50)	8 (4)	18 (9)	62 (31)	12 (6)
Previous GP CL wear (14)				
Type of initial diagnostic lens				
Conventional hydrogel (n=1)	100 (1)	0	0	0
Silicone hydrogel (0)	0	0	0	0
GP lens (13)	0	0	92.3 (12)	7.7 (1)

Data are presented for the refractive group as a whole and are then divided into subgroups according to previous CL experience (neophyte CL wearers, n=53; previous soft CL wearers, n=99; and previous GP CL wear, n=14).

CL, contact lens; GP, gas permeable.

between successful and failed GP fittings (Table 2). The subgroup with previous soft CLs experience showed statistically significant differences ($P<0.05$) between successful and failed fitting for age, sphere, and BCVA. However, no statistically significant differences were found in subjects who had never worn any type of CL.

Therapeutic Prescriptions

A total of 66 subjects (42.4% women and 57.6% men) were fitted with any type of CL for therapeutic reasons (63.6% for irregular cornea, 56.1% for keratoconus, 4.5% after refractive surgery or keratoplasty, and 3% for other conditions, such as eye trauma, and 28.8% for orthokeratology, 4.6% for pediatric cases, and 3% for cosmetics-prosthetic reasons), with a mean age of 34.1±14.4 years (range, 1–66 years). The mean spherical equivalent refractive error was −3.28±3.93 D (range, +3.75 to −17.50 D), the mean flat meridian was 7.55±0.65 (range, 5.50–9.10 mm), and the mean steep meridian was 7.13±0.65 (range, 5.50–9.10 mm). Of these subjects, 41% had never previously worn any type of CL, and 59% were previous CLs wearers (73% had worn soft lenses, and 27% had worn GP lenses). Only five subjects (7.6%) were fitted with therapeutic soft CLs (for pediatric and cosmetics-prosthetic indications).

Gas permeable lens was the first trial lens option that was chosen in 61 cases (92.4%, 95% CI, 93.4%–99.9%); 42 of these had an irregular cornea and 19 were fit for orthokeratology. Fifty-nine subjects (96.7%) obtained a successful fitting with comfortable GP wear and optimal ocular surface physiology. Only two subjects (3%) who displayed irregular cornea (advanced keratoconus stage) reported significant subjective discomfort with GP lenses and rejected their wear.

DISCUSSION

Contact lens prescribing trends are associated with practitioner misgivings about GP lenses and hence the number of GP fits have decreased over time, despite the advantages of this type of lens.[7,10] They represent approximately 11% of all CLs that have been fitted[3,4,9,10] over the world in past 10 years. There is considerable variance across nations, ranging from 0.2% in Lithuania to 37% in Malaysia.[3] In the United States, only 9.4% of total fittings are performed with GP lenses,[14] and in Europe, the countries with the highest number of GP fittings are Germany and the Netherlands (approximately 30%), whereas Spain and the United Kingdom present trends for GP fittings similar to those seen worldwide (approximately 10%).[3] Taking into account only refractive prescriptions, the trend for GP fittings that was found in our study (38.9%) is considerably greater than the current trend in Spain and in the rest of the world when therapeutic prescriptions are included in the results. This trend could be related to the academic status of the IOBA Eye Institute (a university center focused in vision sciences teaching and research).

In many practices, GP lenses have a limited role in refractive fittings, and this type of lens is not considered the first choice option[3,10,14] in healthy patients for correcting refractive errors. In 2010, Cardiff University[10] analyzed the effect of practitioner attitudes on GP lens prescribing in the United Kingdom and found that the practitioners know the benefits provided by GP lenses pertaining to ocular health and refractive correction. However, this report concluded that initial patient discomfort negatively influenced practitioner attitudes because the patients prefer the initial comfort benefit provided by soft lenses. This consequently results in reduced GP prescribing.[10] Nevertheless, there is no previous evidence regarding the percentage of successful GP CLs fits to support this professional practitioner behavior. For this reason, we studied the percentage of successful GP CLs fits in refractive (healthy subjects) and therapeutic prescriptions, because to our knowledge, no studies have analyzed this issue to improve the objective information that is provided to patients regarding the GP fitting process and to assist eye care practitioners in their CL clinical activities.

Previous studies have attempted to analyze the factors that can influence the success of GP fittings.[4,5,15,16] Regarding the time

TABLE 2. *Comparison Between Successful and Failed GP Fittings in the Refractive Group*

	Total GP Trial Lens Fit	Successful GP Wear	Failed GP Wear	*P*
Sex, n (men/women)				
All wearers	88 (27%/73%)	61 (28%/72%)	27 (26%/74%)	<0.01[a]
New wearers	25 (32%/68%)	18 (33%/67%)	7 (29%/71%)	0.20[a]
Previous soft CL wearers	50 (26%/74%)	31 (26%/74%)	19 (26%/74%)	<0.01[a]
Previous GP CL wearers	13 (23%/77%)	12 (25%/75%)	1 (0%/100%)	—
Age, mean ± SD (range), years				
All wearers	33.20±12.51 (11 to 64)	31.91±13.15 (11 to 64)	36.02±10.60 (14 to 60)	0.07
New wearers	23.18±11.14 (11 to 46)	21.89±11.29 (11 to 46)	26.20±10.53 (14 to 41)	0.24
Previous soft CL wearers	35.57±10.38 (14 to 60)	33.27±11.00 (14 to 50)	39.32±8.08 (23 to 60)	0.02
Previous GP CL wearers	43.48±9.86 (29 to 64)	43.14±10.27 (29 to 64)	47.00±0.00 (47)	0.51
Sphere, mean ± SD (range), D				
All wearers	−4.37±6.43 (−23.25 to +10.00)	−4.92±7.14 (−23.25 to +10.00)	−3.19±4.32 (−19.00 to +0.50)	0.04
New wearers	−2.06±4.92 (−17.25 to +7.75)	−2.21±5.56 (−17.25 to +7.75)	−1.73±3.20 (−7.00 to +4.25)	0.75
Previous soft CL wearers	−5.11±6.44 (−23.25 to +10.00)	−6.17±7.24 (−23.25 to +10.00)	−3.36±4.40 (−19.00 to +5.50)	<0.01
Previous GP CL wearers	−6.91±7.54 (−22.00 to +7.00)	−6.54±7.80 (−22.00 to +7.00)	−10.87±0.17 (−10.75 to −11.0)	0.20
Cylinder, mean ± SD (range), D				
All wearers	−1.52±1.04 (−0.25 to −5.00)	−1.55±1.04 (−0.50 to −4.25)	−1.45±1.07 (−0.25 to −5.00)	0.60
New wearers	−1.39±1.04 (−0.50 to −4.25)	−1.33±0.99 (−0.50 to −4.25)	−1.56±1.14 (−0.75 to −3.75)	0.58
Previous soft CL wearers	−1.63±1.11 (−0.25 to −5.00)	−1.77±1.12 (−0.50 to −4.00)	−1.39±1.09 (−0.25 to −5.00)	0.15
Previous GP CL wearers	−1.45±0.82 (−0.50 to −4.25)	−1.42±0.84 (−0.50 to −3.00)	−1.75±0.00 (−1.75)	0.72
Spherical equivalent, mean ± SD (range), D				
All wearers	−3.85±5.55 (−23.50 to +7.25)	−3.35±5.55 (−23.50 to +7.25)	−4.92±5.46 (−20.75 to +4.00)	0.05
New wearers	−2.54±4.93 (−17.75 to +7.25)	−2.71±6.40 (−17.75 to +7.25)	−4.93±4.75 (−7.25 to +2.25)	0.24
Previous soft CL wearers	−3.80±5.03 (−20.75 to +5.50)	−3.30±4.51 (−15.75 to +5.50)	−4.60±5.73 (−20.75 to +4.00)	0.19
Previous GP CL wearers	−5.11±6.86 (−23.50 to +5.25)	−4.58±6.94 (−23.50 to +5.25)	−10.75±1.76 (−9.50 to −12.00)	0.07
Keratometry, steep meridian, mean ± SD (range), mm				
All wearers	7.55±0.27 (7.10 to 8.20)	7.53±0.25 (7.10 to 8.20)	7.58±0.32 (7.20 to 8.05)	0.12
New wearers	7.61±0.29 (7.10 to 8.15)	7.58±0.31 (7.10 to 8.15)	7.66±0.22 (7.15 to 7.97)	0.38
Previous soft CL wearers	7.51±0.28 (7.10 to 8.20)	7.50±0.23 (7.10 to 8.20)	7.54±0.34 (7.20 to 8.05)	0.36
Previous GP CL wearers	7.56±0.19 (7.11 to 7.97)	7.51±0.15 (7.11 to 7.70)	7.95±0.04 (7.92 to 7.97)	0.01
Keratometry, flat meridian, mean±SD (range), mm				
All wearers	7.75±0.27 (7.10 to 8.50)	7.73±0.26 (7.20 to 8.50)	7.80±0.29 (7.10 to 8.35)	0.09
New wearers	7.83±0.28 (7.25 to 8.40)	7.78±0.30 (7.25 to 8.40)	7.95±0.19 (7.75 to 8.35)	0.05
Previous soft CL wearers	7.70±0.27 (7.10 to 8.50)	7.68±0.24 (7.20 to 8.50)	7.73±0.31 (7.10 to 8.23)	0.53
Previous GP CL wearers	7.77±0.22 (7.30 to 8.10)	7.78±0.30 (7.25 to 8.40)	8.04±0.02 (8.03 to 8.06)	0.04
BCVA with spectacles				
All wearers	0.93±0.30 (0.05 to 1.50)	0.85±0.32 (0.05 to 1.50)	1.06±0.21 (0.50 to 1.50)	<0.01
New wearers	1.00±0.22 (0.10 to 1.50)	0.99±0.27 (0.10 to 1.50)	1.04±0.08 (1.00 to 1.20)	0.83
Previous soft CL wearers	0.93±0.31 (0.10 to 1.50)	0.84±0.31 (0.10 to 1.50)	1.07±0.24 (0.50 to 1.50)	<0.01
Previous GP CL wearers	0.75±0.36 (0.05 to 1.20)	0.73±0.40 (0.05 to 1.20)	0.90±0.00 (0.90)	0.95

Factors included are the following: sex distribution, age, refraction (sphere, cylinder, and spherical equivalent), keratometry (steep and flat meridian) and BCVA obtained with spectacles. Details of the comparisons for the previous CL experienced groups are also summarized.

[a]Chi-square test (gender distribution difference).

BCVA, best-corrected visual acuity; CL, contact lens; GP, gas permeable.

required for successful wearers to adapt to GP lenses, Fujita el al.[16] established an average time of 23.0±22.1 days. Carracedo et al.[4] reported that unsuccessful GP wearers presented an overall trend for having more unstable levels of tear film and an increasing intensity of symptoms during the first 7 days, including dryness, discomfort, foreign body sensation, sand sensation, and irritation. However, successful GP wearers showed a steep trend toward increasing comfort and wearing time during the first 7 to 15 days. Our fitting protocol required a minimum of 2 or 3 weeks of GP CLs wear to evaluate a patient's comfort to be considered successful, in accordance with these previous reports.

Polse et al.[5] prospectively analyzed 411 GP fittings and concluded that younger patients, inexperienced patients with a steeper corneal curvature and a lower rate of predicted residual astigmatism had a higher probability of achieving successful GP wear. However, our results disagree with the conclusions of Polse et al because we did not find statistical differences in new CLs wearers in any of the clinical data proposed by Polse to calculate the probability of successful of GP wear (Table 2), suggesting that is not possible to make an accurate prediction of successful GP wear in neophytes. However, taking into account the previous CL experience of the subject, slight differences in the successful GP wear between neophyte (72%), previous soft (62%), and previous GP (92.3%) CLs wearers were found (Table 1). This could mean that previous soft CLs wear is an important factor that contributes to unsuccessful GP wear because these wearers could be accustomed to the initial comfort provided by soft lenses, and the initial discomfort produced by GP lens could be greater and unacceptable in these subjects. Moreover, in previous soft CLs wearers, statistical differences ($P<0.05$) in age, sphere, and BCVA with spectacles were found between subjects that achieved successful or unsuccessful GP lens wear (Table 2). These results suggest that younger people with a higher refractive error and a lower BCVA with spectacles are more likely to be successful when refit with GP lenses.

Moreover, Polse et al.[5] found a 69.6% percentage of successful GP fits when prescribing a spherical lens design in 1999. Nearly two decades later, even with advances in manufacturing technology that have permitted the development of new GP lenses with aspherical

designs and high oxygen permeability materials, the percentage of successful GP CLs fits remains similar (69.3% in our study). This result suggests that successful GP wear may highly depend on a patient's attitude and depend less on the relative impact of lens design, material, and so on, in agreement with the recommendations of Bennett et al.,[15] which highlighted that an important factor that contributes to achieving a successful GP fit is the method by which GP lenses are presented and the information is provided to a patient.

Bennett et al.[15] concluded in their study that information for all types of CLs should be provided to a patient, including the positive and negative factors related to each option, and that in the case of GP lenses, if the practitioners present these lenses with a positive but realistic attitude, explaining the benefits and the initial awareness that are produced, then subjects are more likely to succeed in GP wear during the initial critical period. Our study results provide evidence-based results that can improve the information provided to subjects and assist them when they choose a type of CL in clinical practice because almost 7 of 10 subjects (69.3%) who start a GP lens fitting process to correct a refractive error (refractive prescription) achieve regular and comfortable GP lens wear times (Table 1).

However, for therapeutic prescriptions for subjects with keratoconus, pellucid marginal degeneration, corneal distortion or irregularity, or have undergone refractive surgery or orthokeratology treatment, the percentage of successful GP fits (96.7%) is considerably greater than in subjects with healthy eyes (69.3%). This difference in percentage of successful fits between refractive prescriptions and therapeutic prescriptions could be related to the great improvement obtained in BCVA when GP lenses are used in patients with irregular cornea,[17] which can have a great impact on a patient's quality of life.[18] Orthokeratology subjects exhibit a great attitude when choosing this type of lens and when wearing them that may help them to accept the initial discomfort of GP lenses, which could be limited, especially in overnight wear.

This study is not free of limitations. It is a single-center retrospective study, and a multicenter, prospective, randomized clinical trial could be necessary to clarify the percentage of successful GP fits. This could include an assessment of the way the information is presented to subjects for different types of available lenses, a description of their advantages and disadvantages, and the risks of CLs wear-related complications associated with each CL type, and so on. Moreover, such a study could assess the possible factors that can influence the success of GP lens wear, including patient preferences and needs. Moreover, it would be of great interest to monitor these subjects to know whether they wear GP lenses over time.

CONCLUSIONS

Our study has revealed that following standardized CLs fitting protocol, including clear and complete information regarding the advantages and disadvantages of the different CLs types, a relatively high percentage of successful GP fits could be achieved in refractive prescriptions. In therapeutic prescriptions, the percentage of successful GP fits was higher. These results improve the information that can be provided to subjects at the beginning of the CL fitting process, which can help subjects to choose a lens type (by providing a them with positive and realistic attitude) and help eye care practitioners in their CL clinical activities (by providing evidence-based information).

REFERENCES

1. Key JE. Development of contact lenses and their worldwide use. *Eye Contact Lens* 2007;33:343–345.
2. Stapleton F, Keay L, Edwards K, et al. The incidence of contact lens-related microbial keratitis in Australia. *Ophthalmology* 2008;115:1655–1662.
3. Efron N, Morgan PB, Woods CA, et al. International survey of rigid contact lens fitting. *Optom Vis Sci* 2013;90:113–118.
4. Carracedo G, Martin-Gil A, Peixoto-de-Matos SC, et al. Symptoms and signs in rigid gas permeable lens wearers during adaptation period. *Eye Contact Lens* 2016;42:108–114.
5. Polse KA, Graham AD, Fusaro RE, et al. Predicting RGP daily wear success. *CLAO J* 1999;25:152–158.
6. Efron N. *Contact Lens Complications*, 3rd ed. Philadelphia, PA: Elsevier Saunders, 2012.
7. Morgan PB, Efron N, Hill EA, et al. Incidence of keratitis of varying severity among contact lens wearers. *Br J Ophthalmol* 2005;89:430–436.
8. American Optometric Association. *Optometric Clinical Practice Guideline: Care of the Contact Lens Patient*. 2006. Available at: http://www.aoa.org/documents/optometrists/CPG-19.pdf. Accessed August 8, 2015.
9. Efron N. Obituary—Rigid contact lenses. *Cont Lens Anterior Eye* 2010;33:245–252.
10. Gill FR, Murphy PJ, Purslow C. A survey of UK practitioner attitudes to the fitting of rigid gas permeable lenses. *Ophthalmic Physiol Opt* 2010;30:731–739.
11. Efron N, Morgan PB, Helland M, et al. International rigid contact lens prescribing. *Cont Lens Anterior Eye* 2010;33:141–143.
12. Sun Y, Xu F, Zhang T, et al. Orthokeratology to control myopia progression: A meta-analysis. *PLoS One* 2015;10:e0124535.
13. ISO 11980.2 Ophthalmic Optics. *Contact Lenses and Contact Lens Care Products. Guidance for Clinical Investigation*. Brussels, Belgium: European Committee for Standardization, 2006.
14. Efron N, Nichols JJ, Woods CA, et al. Trends in US contact lens prescribing 2002 to 2014. *Optom Vis Sci* 2015;92:758–767.
15. Bennett ES, Stulc S, Bassi CJ, et al. Effect of patient personality profile and verbal presentation on successful rigid contact lens adaptation, satisfaction and compliance. *Optom Vis Sci* 1998;75:500–505.
16. Fujita H, Sano K, Sasaki S, et al. Ocular discomfort at the initial wearing of rigid gas permeable contact lenses. *Jpn J Ophthalmol* 2004;48:376–379.
17. Martin R, De Juan V. Contact lens correction of regular and irregular astigmatism. In: Goggin M, eds. *Astigmatism—Optics, Physiology and Management*. Rijeka, Croatia, InTech—Open Access Publisher, 2012, pp 157–180.
18. Ortiz-Toquero S, Perez S, Rodriguez G, et al. The influence of the refractive correction on the Vision-Related Quality of Life in keratoconus patients. *Qual Life Res* [published online ahead of print September 3, 2015]. doi:10.1007/s11136-015-1117-1.

4.2. Fiabilidad de las recomendaciones actuales para adaptar LC RPG

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Rigid gas permeable contact lens fitting using new software in keratoconic eyes.

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ORIGINAL ARTICLE

Rigid Gas Permeable Contact Lens Fitting Using New Software in Keratoconic Eyes

Sara Ortiz-Toquero*, Guadalupe Rodriguez*, Victoria de Juan†, and Raul Martin†

ABSTRACT

Purpose. To determine the repeatability of the back optic zone radius (BOZR) of rigid gas permeable (GP) contact lens (CL) proposed by new software for fitting in healthy and keratoconus eyes and to compare with the diagnostic CL fitting method.

Methods. Three consecutive corneal topographies (Oculus-Keratograph) were performed and analyzed with APEX new software CL fitting (Hecht-Contactlinsen, Germany) in 40 healthy and 40 keratoconus eyes fitted with GP using conventional diagnostic method. The coefficient of variation (CV) of the BOZR suggested by APEX was calculated. The BOZR of both fitting methods (software versus diagnostic) were compared maintaining the same lens diameter.

Results. BOZR proposed by APEX showed good repeatability in healthy (CV = 0.32%) and keratoconus eyes (CV = 0.51%). APEX proposed flatter BOZR than the diagnostic method in healthy (7.91 ± 0.24 and 7.84 ± 0.26 mm, $p < 0.01$) and keratoconus eyes (7.34 ± 0.38 and 7.23 ± 0.37 mm, $p < 0.01$). A strong linear correlation in healthy (BOZR_Diagnostic_Method = (BOZR_APEX × 1.06) − 0.53; $p < 0.01$, $R^2 = 0.969$) and keratoconus eyes (BOZR_Diagnostic_Method = (BOZR_APEX × 0.88) + 0.77; $p < 0.01$, $R^2 = 0.825$) was found. A detailed analysis showed a similar trend in different keratoconus stages (Amsler-Krumeich classification); stage 1: 7.42 ± 0.30 and 7.40 ± 0.25 mm, BOZR_Diagnostic_Method = (BOZR_APEX × 0.81) + 1.38, $R^2 = 0.973$; stage 2: 7.30 ± 0.44 and 7.23 ± 0.38 mm, BOZR_Diagnostic_Method = (BOZR_APEX × 0.84) + 1.07, $R^2 = 0.929$; and stage 3: 7.33 ± 0.39 and 7.11 ± 0.40 mm, BOZR_Diagnostic_Method = (BOZR_APEX × 0.93) + 0.28, $R^2 = 0.831$. Applying these regression formulas, the BOZR difference could be reduced in healthy (−0.01 ± 0.05 mm) and keratoconus eyes (−0.01 ± 0.14 mm) for each keratoconus stage (0.01 ± 0.04, 0.03 ± 0.10, and 0.02 ± 0.16 mm in stages 1, 2, and 3, respectively).

Conclusions. APEX software provides repeatable BOZR in healthy and keratoconus eyes, but it tends to propose flatter BOZR than the diagnostic method. APEX BOZR should be improved with new equations and helping with the GP fitting procedure.

(Optom Vis Sci 2016;93:286–292)

Key Words: keratoconus, rigid gas permeable, contact lens fitting software

Rigid gas permeable (GP) contact lenses (CL) are the first option in keratoconus patient management.[1,2] Keratoconus is a progressive corneal disorder characterized by steepening and thinning of the central and paracentral cornea,[1–3] which results in irregular astigmatism and decreased spectacle visual acuity.[2]

The fitting of GP lenses in keratoconus patients can be considered challenging[4] because the altered corneal topography often requires long practitioner time and patient chair time, as well as several diagnostic lenses to achieve a final acceptable GP lens.[5–7]

Currently, several corneal topographers, such as Orbscan (Bausch&Lomb),[8,9] Oculus-Keratograph (Oculus Optikgeräte GmbH),[5] EyeSys 2000 (EyeSys Laboratories),[10] Atlas (Humphrey),[10] TMS1 (Tomey),[11] or Medmont-300 (Medmont),[12] incorporate different computerized software-based CL fitting methods, which employ corneal topography to determine the optimal GP lens parameters. The objective is to help eye care practitioners and simplify the fitting procedure, especially in patients with irregular corneas, such as keratoconus. The goal is to decrease the number of diagnostic lenses necessary to achieve an acceptable CL fit, reducing the chair time.[5,8] Computerized software displays a simulated fluorescein pattern, allowing for assessment of the quality of a CL fit and making changes in the parameters or position of the simulated lens to obtain the correct GP lens.[5–9]

However, the repeatability of the GP parameters proposed by CL fitting software in normal and keratoconus patients has not

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TABLE 1.

CL design description. BIAS-S design was fitted in healthy eyes and KAKC design was fitted in Keratoconus eyes

	BIAS-S	KAKC
Manufacturer	Conoptica-Hecht Contactlinsen	Conoptica-Hecht Contactlinsen
Design	Rotationally symmetric bi-aspheric	Spherical pentacurve
Optical zone	Spherical 14° central	Spherical 5.5 to 7.00 mm*
Peripheral zone	Two aspheric zones	Four spherical zones
Power (D)	−30.00 to 30.00 (0.25 steps)	−30.00 to 30.00 (0.25 steps)
BOZR (mm)	6.50 to 10.00 (0.05 steps)	4.80 to 8.90 (0.05 steps)
Total diameter (mm)	7.00 to 12.20 (0.10 steps)	8.40 to 12.20 (0.10 steps)
Standard total diameter	9.60	9.20
Material	Boston ES/EQ/EO/XO/XO2	Boston ES/EQ/EO/XO/XO2
Fit guidelines (BOZR)	Flat meridian + 0.05	Horizontal meridian − 0.10

*Optical zone decrease when BOZR decrease.

been previously reported; the clinical utility of these tools could be affected by the decreased corneal topography repeatability in irregular corneas.[13,14] These software programs normally use topographical keratometry and corneal eccentricity[5] to calculate a spherical or toric lens for an initial suggestion. Moreover, low to moderate agreement between software calculated CL parameters and the final fitted lens has been reported in keratoconus patients.[8,9]

APEX is a new CL fitting software developed by Hecht Contactlinsen GmbH (Baden-Württemberg, Germany), and it is available in different Oculus devices (Oculus-Easygraph, Oculus-Keratograph, and Pentacam, Wetzlar, Germany). With this software, the user can define the initial lens selection to match the corneal features as closely as possible. However, the role of APEX in GP lens fitting in healthy and keratoconus patients had not been previously reported.

The aim of this study is to analyze the repeatability of the GP proposed by APEX CL fitting software and compare this back optic zone radius (BOZR) with the BOZR fit by the conventional diagnostic methods in healthy and keratoconus eyes.

MATERIALS AND METHODS

Subjects

Eighty eyes in 62 patients successfully fitted with GP lens were retrospectively analyzed to compare the BOZR of the final fitted lenses with that proposed by the APEX software. Patients were classified into two groups, healthy eyes and keratoconus eyes. Independent corneal specialists confirmed the diagnoses of keratoconus after a complete eye examination, which included Scheimpflug topographical analysis and biomicroscopy

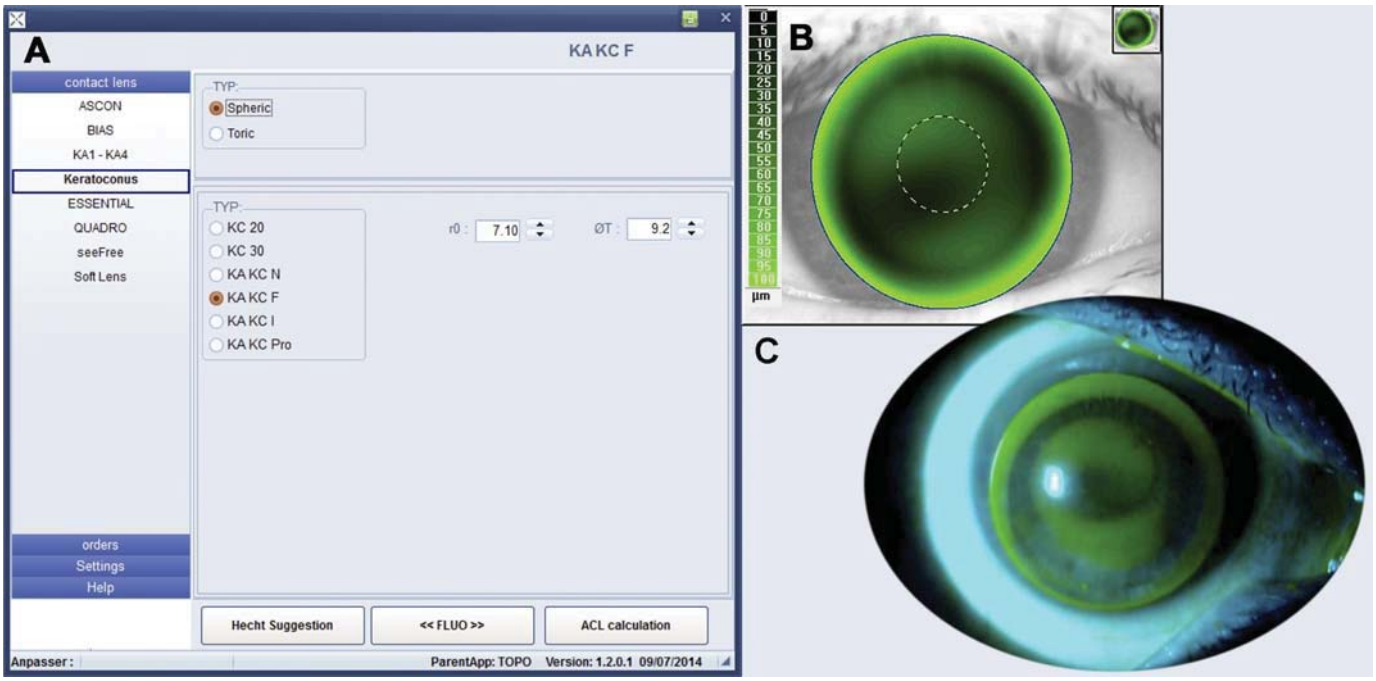

FIGURE 1.

APEX software screen showing the software menu (A), simulated fluorescein pattern (B), and clinically fluorescein pattern (C) of GP CL in the same keratoconus eye.

TABLE 2.

Summary of the mean of the age (years), spherical equivalent refractive error (D), and maximum (Sim K max) and minimum (Sim K Min) simulated keratometry (mm) in healthy and keratoconus groups

	Healthy group	Keratoconus group
Age (years)	29.6 ± 9.4 (12 to 48)	35.6 ± 10.9 (19 to 55)
Spherical equivalent refractive error (D)	−5.30 ± 5.37 (−0.25 to −23.00)	−3.53 ± 4.19 (−0.25 to −13.25)
Sim K max (mm)	7.71 ± 0.23 (7.32 to 8.12)	7.10 ± 0.41 (6.27 to 7.95)
Sim K min (mm)	7.87 ± 0.28 (7.40 to 8.32)	7.44 ± 0.42 (6.62 to 8.17)

examination. The keratoconus stage was identified using the Amsler-Krumeich classification.[14,15]

Patients with any active ocular-surface disease, corneal opacities, glaucoma, use of medication that could affect ocular physiology, and a history of any type of ocular surgery were excluded. Eyes with stage 4 keratoconus, according to the Amsler-Krumeich classification, were also excluded from the study to guarantee an optimal quality of corneal topography. Healthy group patients fitted with any type of GP toric design and those with corneal astigmatism higher than 1.50 D were also excluded.

Informed consent was obtained from each subject after the Human Sciences Ethics Committee of the University of Valladolid granted approval of the study. All subjects were treated in accordance with the Declaration of Helsinki.

Contact Lens Fitting Procedure

A rotationally symmetric bi-aspheric GP lens design (BIAS-S GP; Conoptica-Hecht Contactlinsen, Baden-Württemberg, Germany) and spherical pentacurve GP lens design (KAKC GP; Conoptica-Hecht Contactlinsen) were fitted in healthy and keratoconus eyes, respectively. Table 1 summarizes both lens designs used in this study. Four experienced practitioners, belonging to the same eye-care center (IOBA Eye Institute), performed the GP CL fitting; the practitioners work at a tertiary referral clinic that addresses patients with irregular corneas and other eye disorders.

The BOZR of the first trial lens was selected based on the keratometry value. This selected GP CL was inserted into the subject's eye to evaluate the static and dynamic fit after an adaptation period of approximately 30 minutes. Changes in the GP lens parameters were performed to find an acceptable fit of a well-centered lens with adequate movement with blinking that provided a fluorescein pattern recommended by the manufacturer (three-point touch in the keratoconus and alignment pattern in the healthy group).[1,2] Trials were repeated until an acceptable static and dynamic fit was achieved. The parameters (BOZR and lens diameter) of the prescribed GP CLs were analyzed.

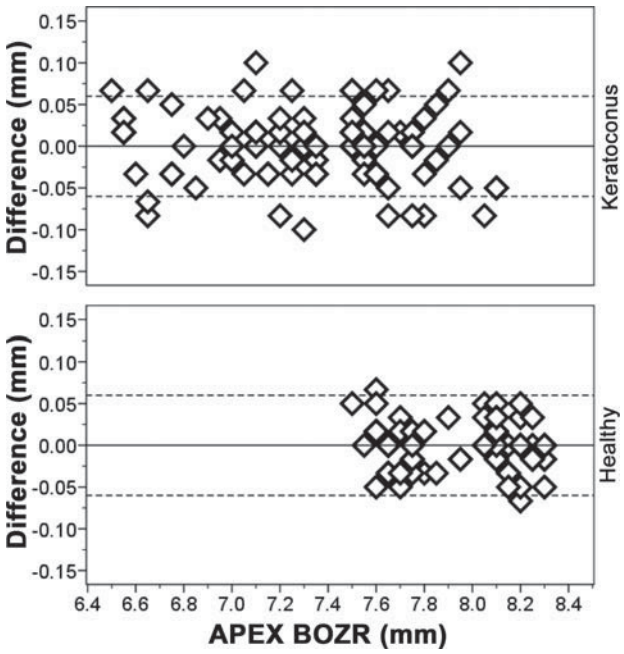

FIGURE 2.

Bland-Altman plot showing the repeatability of the BOZR suggested by APEX in keratoconus (top) and healthy (below) eyes. The mean difference (solid line) of the three repeated measurements was 0.00 ± 0.03 mm and LoA (discontinuous line) were −0.06 to 0.06 mm in both groups.

Instrumentation

APEX (version 1.1.0.6) is a new CL fitting software developed by Hecht Contactlinsen in association with Oculus. APEX proposes a first trial lens according to the values of topographical simulated keratometry readings and corneal eccentricity, and it displays a simulated fluorescein pattern of the specified design of CL to help in the GP lens fitting procedure including the specialty design for keratoconus (KAKC GP lens) and healthy eyes (BIAS S GP lens) included in this study (Fig. 1).

Three consecutive corneal topographies were performed with the Oculus-Keratograph (Patient Data Management Software version 6.02r24 and Examination Software version 1.75r11) in the baseline visit. Topographic data were exported to APEX software to determine and record the BOZR of the CL suggested by APEX (using exactly the same design that was clinically fitted; BIAS-S design in healthy eyes and KAKC design in keratoconus eyes) for each corneal topography. The Oculus-Keratograph is a Placido-based device with 22 rings that evaluate 22,000 points on the anterior corneal surface. The repeatability of Oculus-Keratograph topography in healthy and keratoconus eyes has recently been reported, providing repeatable measurements of the corneal power.[14] The same blinded and experienced operators performed all Oculus-Keratograph measurements. The corneal topographer was previously calibrated by the manufacturer. The patients were asked to perform a complete blink just before each measurement to spread an optically smooth tear film over the cornea. The patients moved their chin from the chinrest between scans to eliminate the interdependence of successive measurements.

TABLE 3.

Summary of the mean and standard deviation (SD) of the BOZR calculated by the diagnostic method and BOZR suggested by APEX

	BOZR diagnostic method (mm)	BOZR APEX (mm)	p value*	R^2	Arithmetic difference (mm)	Absolute difference (mm)
Healthy (n = 40)	7.84 ± 0.26	7.91 ± 0.24	<0.01	0.969	0.07 ± 0.05	0.07 ± 0.05
Keratoconus (n = 40)	7.23 ± 0.37	7.34 ± 0.38	<0.01	0.852	0.11 ± 0.15	0.14 ± 0.12
Stage 1 (n = 9)	7.40 ± 0.25	7.42 ± 0.30	0.25	0.973	0.03 ± 0.02	0.07 ± 0.02
Stage 2 (n = 17)	7.23 ± 0.38	7.30 ± 0.44	<0.01	0.929	0.07 ± 0.12	0.11 ± 0.09
Stage 3 (n = 14)	7.11 ± 0.40	7.33 ± 0.39	<0.01	0.831	0.21 ± 0.16	0.22 ± 0.16

The arithmetic and absolute mean and SD of the BOZR difference between both methods in healthy and keratoconus eyes are shown.
*Paired *t* test ($p < 0.05$ statistically significant).

Data Analysis

Statistical analysis was performed using the SPSS 15.0 (SPSS, Chicago, IL, USA) statistical package for Windows. We used the definition of repeatability from the British Standards Institution,[16,17] as recommended by Bland and Altman.[18] A normal distribution of variables was assessed using the Kolmogorov-Smirnov test (p values >0.05 indicated that the data were normally distributed).

The BOZR of the GP CL (BIAS-S and KAKC GP design) proposed by APEX to each corneal topography conducted in the same visit was calculated and recorded. The intraclass correlation coefficient (ICC; classified as follows: less than 0.75 = poor agreement; 0.75 to less than 0.90 = moderate agreement; 0.90 or greater = high agreement)[19] was calculated and the differences between the three BOZR were determined with a repeated measured analysis of variance (RM-ANOVA) (p values <0.05 were considered statistically significant). The coefficient of variation (CV) of repeatability was calculated by dividing the standard deviation by the mean value (normalized standard deviation) and multiplying by 100 to represent the percentage value of the variation [CV = SD/mean × 100 (%)] of the BOZR proposed by APEX software.

As suggested by Bland and Altman, graphs of the differences between pairs of BOZR obtained in the same session were plotted against the average of the means of each pair of values (three data points per subject) to ensure that there was no relationship between the differences and ranges of measurement. The limits of the agreement (LoA) were calculated (mean of the difference ± 1.96 × standard deviations).

BOZR differences between APEX and the diagnostic method were compared with a paired *t* test. A p value <0.05 was considered statistically significant. The mean value of the BOZR proposed by APEX was used as the final value for comparison with the BOZR prescribed with the diagnostic method. The same lens diameter was maintained to guarantee the comparison between the BOZR of the fitted lens (diagnostic method) and the BOZR calculated by the APEX software.

The arithmetic and absolute mean difference of the BOZR were calculated between the APEX and diagnostic fitting method. The absolute difference was calculated to avoid the effect of positive and negative differences that could affect the mean value. An absolute difference could be clearly represented if the BOZR proposed by the software is close to the final fitted BOZR.

Single linear regression (R^2 coefficient) was used to quantify the correlation between the APEX BOZR and final GP lens that was conventionally fitted and to propose an equation for improving the BOZR suggested by the software. A p value <0.05 was considered statistically significant.

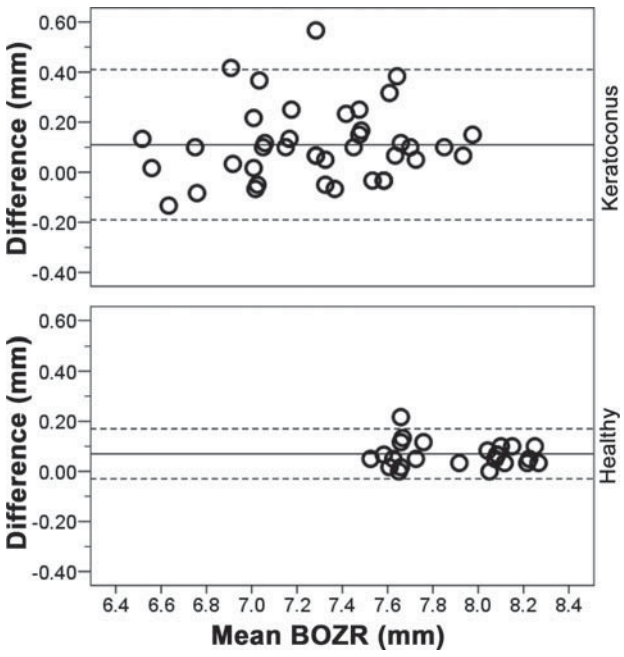

FIGURE 3.

Bland-Altman plot showing the agreement between the BOZR suggested by APEX software and the BOZR fit by the diagnostic method in keratoconus (top) and healthy (below) eyes. The mean difference between APEX and the BOZR fitted (solid line) were 0.11 ± 0.15 mm (LoA (discontinuous line) of −0.19 to 0.41) in keratoconus eyes and 0.07 ± 0.05 mm (LoA of −0.03 to 0.17) in healthy eyes.

RESULTS

Sixty-two patients (35 women, 27 men) were included in the study. The mean age of the total sample was 31.8 ± 10.3 years (range 12 to 55). Forty eyes of 40 patients (28 women, 12 men) comprised the healthy group and 40 eyes of 22 patients (7 women, 15 men) comprised the keratoconus group (Table 2).

Good repeatability was found in the BOZR proposed by APEX in both groups. The CV of the BOZR was 0.32% (95% CI: 0.24

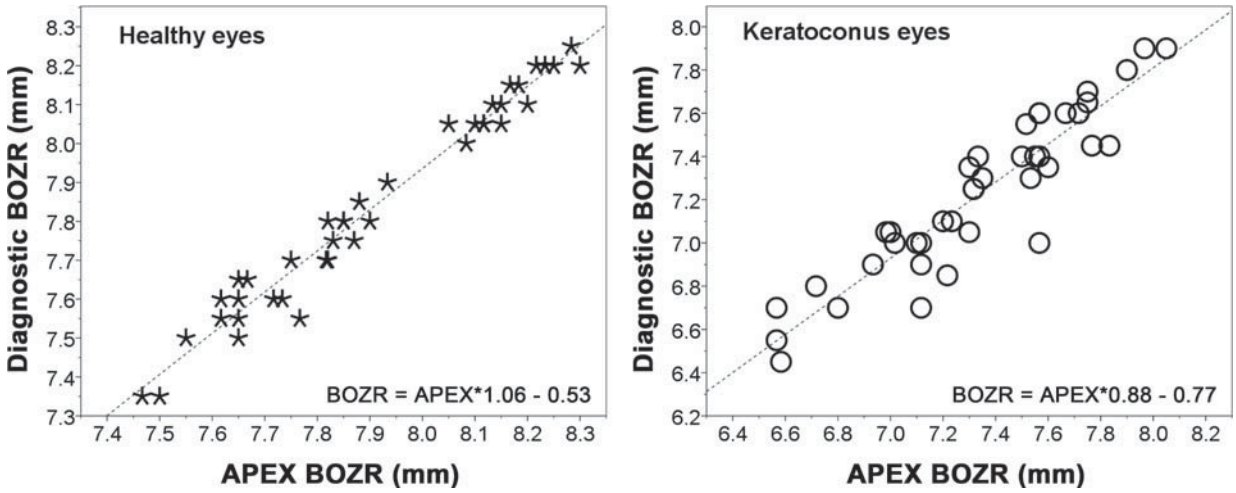

FIGURE 4.

Single linear regression analysis between the BOZR proposed by APEX and the BOZR calculated by the diagnostic method in the healthy (left) and keratoconus (right) group.

to 0.39%) in the healthy group with ICC of 0.994 (95% CI: 0.991 to 0.997, p = 0.846, RM-ANOVA) and 0.51% (95% CI: 0.38 to 0.63%) in the keratoconus group with ICC of 0.989 (95% CI: 0.982 to 0.994, p = 0.323, RM-ANOVA) (Fig. 2).

The BOZR of GP lens achieved with the diagnostic fitting method and the BOZR proposed by APEX in healthy and keratoconus eyes are summarized in Table 3. The difference between both BOZR (APEX minus diagnostic method) is plotted in Fig. 3.

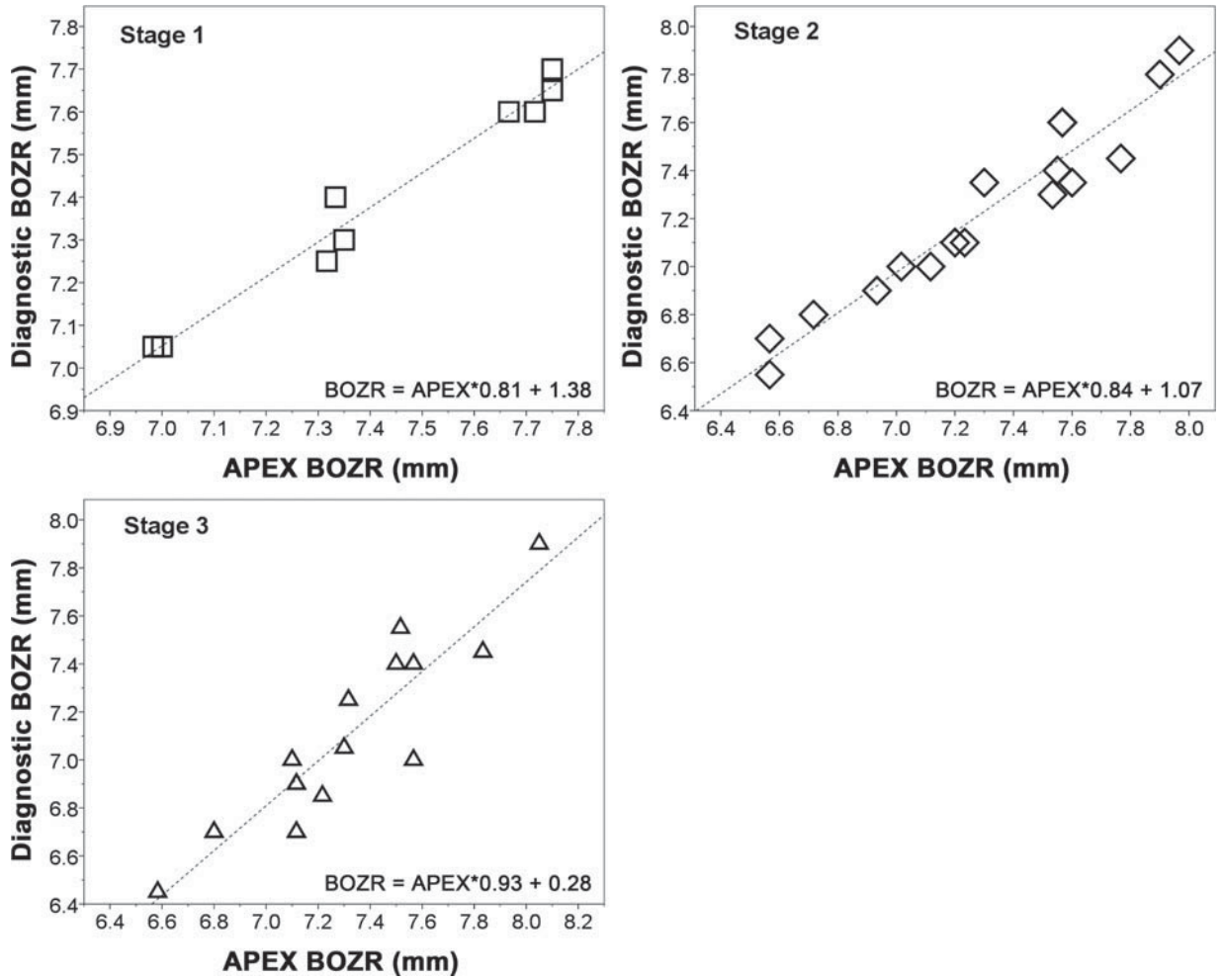

FIGURE 5.

Single linear regression analysis between the BOZR proposed by APEX and the BOZR calculated by the diagnostic method in different keratoconus severity stages (Amsler-Krumeich classification).

TABLE 4.

Summary of the mean and standard deviation (SD) of the BOZR calculated by the diagnostic method and BOZR calculated by new equations to improve the BOZR suggested by APEX software

	BOZR diagnostic method (mm)	BOZR calculated by new equations (mm)	p value*	R^2	Arithmetic difference (mm)	Absolute difference (mm)
Healthy (n = 40)	7.84 ± 0.26	7.84 ± 0.26	0.48	0.969	−0.01 ± 0.05	0.04 ± 0.03
Keratoconus (n = 40)	7.23 ± 0.37	7.23 ± 0.34	0.42	0.852	−0.01 ± 0.14	0.11 ± 0.09
Stage 1 (n = 9)	7.40 ± 0.25	7.39 ± 0.25	0.89	0.973	0.01 ± 0.04	0.03 ± 0.03
Stage 2 (n = 17)	7.23 ± 0.38	7.20 ± 0.36	0.37	0.929	0.03 ± 0.10	0.09 ± 0.06
Stage 3 (n = 14)	7.11 ± 0.40	7.10 ± 0.36	0.55	0.831	0.02 ± 0.16	0.13 ± 0.09

The arithmetic and absolute mean and SD of the BOZR difference between the diagnostic method and BOZR calculated with new equations in healthy and keratoconus eyes is shown.

*Paired *t* test ($p < 0.05$ statistically significant).

A strong linear relationship was found in the BOZR between the diagnostic fitting method and APEX in healthy ($R^2 = 0.969$, $p < 0.01$; BOZR_diagnostic_method (mm) = (BOZR_APEX (mm) × 1.06) − 0.53) and keratoconus eyes ($R^2 = 0.852$, $p < 0.01$; BOZR_diagnostic_method (mm) = (BOZR_APEX (mm) × 0.88) + 0.77) (Fig. 4).

We analyzed the sample of keratoconus eyes by the severity stage and found a similar trend with a strong linear relationship in stage 1 ($R^2 = 0.973$, $p < 0.01$; BOZR_diagnostic_method (mm) = (BOZR_APEX (mm) × 0.81) + 1.38), stage 2 ($R^2 = 0.929$, $p < 0.01$; BOZR_diagnostic_method (mm) = (BOZR_APEX (mm) × 0.84) + 1.07), and stage 3 ($R^2 = 0.831$ $p < 0.01$; BOZR_diagnostic_method (mm) = (BOZR_APEX (mm) × 0.93) + 0.28) (Fig. 5).

The BOZR of the GP lens calculated by the APEX software could be improved with these new formulas in healthy and keratoconus eyes (Table 4). The absolute differences between the BOZR calculated by APEX software and the BOZR fitted by diagnostic method could be reduced.

DISCUSSION

Keratoconus patients can be managed with glasses or soft CLs in the early stages. However, as keratoconus progresses, the irregular astigmatism often requires GP lenses that can improve the visual acuity.[1,2] Fitting GP lenses in keratoconus often requires several diagnostic lenses and can be considered more difficult than fitting GP in healthy patients.[5,8,10]

Computerized Placido disk-based videokeratography is the most extensively used technique for keratoconus detection and monitoring the progression of this condition. It is a valuable tool for various patient management approaches, including the fitting of specifically designed CLs.[5–8,20] Moreover, different software have been designed to help eye care practitioners in CL parameter selection, proposing a BOZR and lens design and showing a simulation of the fluorescein pattern.

To the best of our knowledge, this is the first report on the repeatability of GP lens selections proposed by any CL fitting software in healthy and keratoconus patients. The BOZR suggested by APEX in healthy (CV = 0.32%) and keratoconus eyes (CV = 0.51%) is repeatable. These results could be explained because Oculus-Keratograph topography provides repeatable measurements of the corneal power (simulated keratometry and maximum corneal power) in healthy (CV ≤ 0.22%) and keratoconus (CV ≤ 0.77%) corneal assessment.[14] As a result, a single Oculus-Keratograph topography could be sufficient to fit GP lenses using APEX software.

The fitting software, provided by different topographers, is helpful in fitting CLs, but the first lens proposed by the software usually requires some changes and input from an eye care practitioner before it is considered clinically acceptable, especially in irregular cornea management.[5,7–9,12] Our results are in agreement with previous reports; we found statistically significant differences between the BOZR proposed by APEX and the diagnostic method in healthy and keratoconus eyes. Using the software FITSCAN (Orbscan II topography) in a keratoconus sample, Mandathara et al.[8] found that the BOZR provided by this software was 0.22 mm flatter (mean difference) than the clinical fit curve. Bhatoa et al.[9] stressed the existence of poor to moderate agreement between the BOZR calculated by FITSCAN software and the final BOZR in keratoconus patients. However, the BOZR calculated with APEX showed a smaller difference with the final lens fit (0.14 ± 0.12 mm; absolute difference) in keratoconus eyes, advancing the findings from previous reports. The difference between the BOZR proposed by APEX and the final fit lens could be related to the effect of the eccentricity value. In a recent publication that analyzed the repeatability of the Oculus-Keratograph, the eccentricity value showed lower repeatability in healthy (CV = 5.79%) and keratoconus (CV = 14.53%) eyes,[14] and this value is included in the BOZR calculation.[5] Moreover, the difference between the simulation of the software and final CL fit may also be related to the repeatability of the other CL fitting software corneal topographers and with the effect of the eyelids in the lens movement or tear film and dynamic fit assessment.[9,12]

We calculated the difference between two fitting methods in the arithmetic and absolute value to improve the data presentation because the mean value (arithmetic difference) could compensate the positive (BOZR_APEX > BOZR_diagnostic_method) differences with negative (BOZR_APEX < BOZR_diagnostic_method) differences, and the absolute difference could show the difference between the final BOZR and APEX BOZR proposal. In healthy eyes, we found the same arithmetic and absolute difference (0.07 ± 0.05 mm) between two fitting methods; therefore, APEX tends to propose the BOZR of GP at least as flat as the BOZR for the conventional fitting method (positive difference). This bias could

be minimized using the equation calculated for healthy eyes in this study [BOZR_diagnostic_method = (BOZR_APEX × 1.06) − 0.53)].

However, in keratoconus eyes, the difference (arithmetic and absolute value) between the BOZR of both fitting methods is higher than in healthy eyes. Generally, APEX suggested flatter BOZR than the conventional fitting method; consequently, the number of trial lens required for fitting the KAKC GP lens using this software may be increased. For this reason, we proposed some equations to improve the suggested BOZR for the total keratoconus sample and for each severity stage.

With these new formulas, the difference between the BOZR that was initially proposed by APEX and the BOZR fitted by diagnostic method (Table 3) in keratoconus eyes could be reduced (Table 4), but advanced keratoconus (stage 3) showed greater differences than the lower disease stage. This could be related to the high corneal irregularity in the advanced keratoconus eyes. This may help practitioners select the BOZR of the GP lens and reduce the number of trials, improving the practitioner's chair time and reducing the patient's discomfort associated with multiple trials in the keratoconus GP lens fitting procedure.

Nevertheless, further clinical research is needed to prove the usefulness of these new equations in the correlation between the BOZR proposed by the software and the final BOZR fitted with a larger sample of keratoconus and healthy subjects. Moreover, a comparison of the number of trial lens required to achieve the final BOZR using both methods (diagnostic method versus APEX software) could be interesting in future studies.

The APEX software for fitting GP CL provides repeatable BOZR in both healthy and keratoconus eyes in combination with Oculus-Keratograph topography. This software could be useful in selecting the BOZR of GP lenses, but the software tends to propose a flatter BOZR than conventional CL fitting in healthy and keratoconus eyes. The BOZR suggested by APEX in keratoconus eyes should be improved with new equations to reduce this difference, helping the practitioner in the keratoconus GP lens fitting procedure.

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REFERENCES

1. Barnett M, Mannis MJ. Contact lenses in the management of keratoconus. Cornea 2011;30:1510–6.
2. Romero-Jiménez M, Santodomingo-Rubido J, Wolffsohn JS. Keratoconus: a review. Cont Lens Anterior Eye 2010;33:157–66.
3. Rabinowitz YS. Keratoconus. Surv Ophthalmol 1998;42:297–319.
4. Zhou AJ, Kitamura K, Weissman BA. Contact lens care in keratoconus. Cont Lens Anterior Eye 2003;26:171–4.
5. Nosch DS, Ong GL, Mavrikakis I, Morris J. The application of a computerised videokeratography (CVK) based contact lens fitting software programme on irregularly shaped corneal surfaces. Cont Lens Anterior Eye 2007;30:239–48.
6. Nejabat M, Khalili MR, Dehghani C. Cone location and correction of keratoconus with rigid gas-permeable contact lenses. Cont Lens Anterior Eye 2012;35:17–21.
7. Sorbara L, Dalton K. The use of video-keratoscopy in predicting contact lens parameters for keratoconic fitting. Cont Lens Anterior Eye 2010;33:112–8.
8. Mandathara PS, Fatima M, Taureen S, Dumpati S, Ali MH, Rathi V. RGP contact lens fitting in keratoconus using FITSCAN technology. Cont Lens Anterior Eye 2013;36:126–9.
9. Bhatoa NS, Hau S, Ehrlich DP. A comparison of a topography-based rigid gas permeable contact lens design with a conventionally fitted lens in patients with keratoconus. Cont Lens Anterior Eye 2010; 33:128–35.
10. Jani BR, Szczotka LB. Efficiency and accuracy of two computerized topography software systems for fitting rigid gas permeable contact lenses. CLAO J 2000;26:91–6.
11. Szczotka LB, Reinhart W. Computerized videokeratoscopy contact lens software for RGP fitting in a bilateral postkeratoplasty patient: a clinical case report. CLAO J 1995;21:52–6.
12. Siddireddy JS, Mahadevan R. Comparison of conventional method of contact lens fitting and software based contact lens fitting with Medmont corneal topographer in eyes with corneal scar. Cont Lens Anterior Eye 2013;36:176–81.
13. McMahon TT, Anderson RJ, Roberts C, Mahmoud AM, Szczotka-Flynn LB, Raasch TW, Friedman NE, Davis LJ, CLEK Study Group. Repeatability of corneal topography measurement in keratoconus with the TMS-1. Optom Vis Sci 2005;82:405–15.
14. Ortiz-Toquero S, Rodriguez G, de Juan V, Martin R. Repeatability of placido-based corneal topography in keratoconus. Optom Vis Sci 2014;91:1467–73.
15. Choi JA, Kim MS. Progression of keratoconus by longitudinal assessment with corneal topography. Invest Ophthalmol Vis Sci 2012;53:927–35.
16. British Standards Institution. Accuracy (trueness and precision) of measurement methods and results: general principles and definitions: BS ISO 5725:1. London: Her Majesty's Stationary Office; 1994.
17. British Standards Institution. Accuracy (trueness and precision) of measurement methods and results: basic methods for the determination of repeatability and reproducibility of a standard measurement method: BS ISO 5725:2. London: Her Majesty's Stationary Office; 1994.
18. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986; 1:307–10.
19. McGraw KO, Wong SP. Forming inferences about some intraclass correlation coefficients. Psychol Meth 1996;1:30–46.
20. Piñero DP, Nieto JC, Lopez-Miguel A. Characterization of corneal structure in keratoconus. J Cataract Refract Surg 2012;38:2167–83.

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4.3. Manejo optométrico de los pacientes con queratocono en España y Reino Unido

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Current optometric practices and attitudes in keratoconus patient management.

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Current optometric practices and attitudes in keratoconus patient management

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ABSTRACT

Purpose: To compare the current optometric practices and attitudes in the management of keratoconus patients in the UK and Spain.
Methods: An online survey (adapted to optometric practices) was distributed via a newsletter emailed by various professional organizations in the UK and Spain.
Results: Four hundred and sixty-four practitioners (126 in the UK; 338 in Spain) who prescribed gas permeable GP contact lenses (CLs) more than once per month (54.8% of UK practitioners and 28.1% of practitioners in Spain; $p < 0.01$) responded to the questionnaire. A combination of multiple factors is considered necessary in the keratoconus detection (79.4% in the UK, 75% in Spain; $p = 0.68$), and the use of classification criteria is considered relevant (67.5% in the UK, 70.7% in Spain; $p = 0.49$). There is a high consensus on the consideration that GP CL fitting is more difficult in keratoconus (79.4% in the UK, 80.5% in Spain; $p = 0.79$) requiring more diagnostic lenses (3.2 ± 1.4 and 3.4 ± 1.2 in the UK and Spain, respectively; $p = 0.72$) than are necessary for healthy eyes. Using corneal topography is uncommon from both countries (38.1% in the UK, 59.8% in Spain; $p < 0.01$), with a similar ophthalmologist referral pattern (at initial diagnosis, 50% in both the UK and Spain; $p = 1.00$). Few cases of co-management with ophthalmologists were noted (no co-management reported by 60.3% in the UK and 72.8% in Spain, $p = 0.01$).
Conclusion: This study provides initial observations and evidence regarding keratoconus management by optometrists in the UK and Spain and shows similarity in the professional practices and attitudes of practitioners in these two countries.

1. Introduction

Keratoconus is a progressive, bilateral and asymmetric corneal disorder characterized by a thinning of the corneal stroma, protrusion of the anterior corneal surface, and an irregular astigmatism [1,2]. Keratoconus commonly appears during puberty, in the second decade of life, and it progresses until the fourth decade of life, at which point it generally stabilizes [1,2]. The estimated prevalence in the general population has been 1 per 2000 [1,2], although a recent study raises this prevalence up to one case per 375 habitants [3].

There are several ocular symptoms and signs of keratoconus that are important in the diagnosis of this disease in a routine eye exam, such as significant loss of visual acuity which cannot be compensated with spectacles, increasing against-the-rule astigmatism, appearance of "scissor" shadows while performing retinoscopy, or presence of biomicroscopy findings (Fleischer's ring, Vogt's striae, corneal scarring or Munson's sign) [1,2]. In addition, corneal topography and tomography are of paramount importance in keratoconus diagnosis [2].

In the very early stages of the disease, spectacles and soft contact lenses (CL) with toric design are adequate to correct myopia and regular astigmatism [4,5]. When keratoconus progresses, rigid gas permeable (GP) CL with specific design to keratoconic eyes are used to improve visual acuity because the tear layer between the CL and the anterior surface of the cornea reduces

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visual distortion and forms a new regular optical surface [4,5], thereby improving patients' visual acuity. Moreover, in a patient with advanced keratoconus or who has failed a trial of GP lenses, other types of CL can be prescribed, as hybrid CL or scleral CL [4,5].

If the condition appears to be undergoing progression, ultraviolet crosslinking (UV-CXL) has been proposed to halt keratoconus progression [2,6]. The aim of the UV-CXL is to increase the corneal rigidity and biomechanical stability of the cornea to stop the progression of keratoconus and save patients' vision [2,6] in early and moderate keratoconus patients (with corneal thicknesses >400 μm younger than 40 years old) [2,6].

Intrastromal corneal ring segments (ICRS) can be indicated when keratoconus patients have unsatisfactory vision with spectacles and/or CL or when continued CL wear is intolerable [2,6]. Finally, corneal transplant is the last option in the management of keratoconus patients [2,6].

Optometrists are primary health care specialists trained to examine the eyes to detect defects in vision, signs of injury, ocular diseases or abnormality and problems with general health, as highlighted by the College of Optometrists in the UK [7] and the Spanish Council of Optometrists following Spanish's regulations [8]. Furthermore optometrists play a paramount role in the early diagnosis and management of keratoconus [2,9], but little is known about the reality of the optometric management of these patients in Europe. In 2015, Hodge et al. [10] analysed the patterns of practice and referral criteria of optometrists in Australia regarding patients with keratoconus. However, there is no reported evidence regarding the attitudes of optometrists involved in the management of keratoconus patients in European countries, such as the United Kingdom (UK) or Spain.

The aim of this study is to survey a large number of optometrists and CL opticians in the UK and Spain to explore their current practices and attitudes regarding the management of keratoconus patients and describe how current practices and attitudes are influenced by infrastructure such as corneal topographers and years of experience.

2. Materials and methods

2.1. Questionnaire design

A questionnaire was specifically designed and adapted to European (UK and Spain) professional practice, based on previous questionnaires used to investigate the practice and attitudes of optometrists in relation to keratoconus patients in other countries [10] to facilitate results comparison. The questionnaire was developed using Google Forms (www.google.com/forms/about/) in English and Spanish languages. Prior to its dissemination, the questionnaire was revised by five different experts (two from the UK and three from Spain) to guarantee that the questions were clear, understandable, and relevant to optometry practice in the UK and Spain. A consensus was reached between the authors and experts.

The questionnaire began with a brief explanation of the purpose of the study and invited optometrists to provide anonymous responses. The questionnaire comprised 17 questions (Appendix A in the Supplementary material): Questions 1 to 8 asked about the general CL practice of respondents. In the remaining 11 questions, practitioners were asked to consider a statement with respect to the management of keratoconus; specifically, the statements related to the detection of the disease, classification of severity, GP CL fittings, patient management and referral practice. The majority of questions were multiple choice, with several options provided for respondents. Just one item (11.c) required an open-ended response (concerning the disease classification that practitioners used in their practice). All collected responses remained anonymous, and the respondents consented to the use of the data upon completion of the survey.

2.2. Data collection

A link to the online survey was distributed via a newsletter emailed between April and August 2016 to local optometrists by various professional organizations: the General Optical Council, Association of Optometrists (including in the online version of the journal Optometry Today) and British Contact Lens Association (via social media) in the UK and The Spanish College of Optometrists in Spain.

2.3. Data analysis

Statistical analysis was performed using the SPSS 15.0 (SPSS, Chicago, IL, USA) statistical package for Windows. Deviations of the variables from a normal distribution were assessed using the Kolmogorov-Smirnov test ($p < 0.05$ indicated that the data were normally distributed). Descriptive data analysis was performed with the mean ± standard deviation (SD) in continuous variables and/or percentages reported for each question.

Response frequencies were calculated, and the association between practice variables was assessed with a chi-squared test for ordinal categorical data.

Differences in years of experience (question 2) and diagnostic lenses used in GP CL fittings (question 13) between practitioners in the two countries were analysed for statistical significance using Student's *t*-test. P values <0.05 were considered statistically significant.

3. Results

3.1. Demographic information

A total of 464 eye-care practitioners (126 practitioners [115 optometrists and 11 CL opticians] in the UK and 338 Spanish optometrists) responded to the questionnaire. UK practitioners reported a significantly higher number of years of experience (21.5 ± 13.3 years; range from 1 to 48) than did the Spanish optometrists (16.0 ± 9.0 years; range from 1 to 40) ($p < 0.01$).

Only 38.1% of UK respondents had a corneal topographer in their practice; however, the majority of Spanish respondents (59.8%) reported the use of this device in their clinical practice ($p < 0.01$). Of all respondents who reported having a corneal topographer, the most common technology was Placido-based videokeratography (86.4% for UK respondents and 73.6% for Spanish respondents), followed by the mixed (combined Placido-based with Scheimpflug) topographer (6.8% for UK respondents and 13.2% for Spanish respondents), and Scheimpflug topographer (6.8% for UK respondents and 5.1% for Spanish respondents). Finally, 8.1% of Spanish optometrists with a corneal topographer had more than one corneal topographer available.

Additional post-qualification or specific training on cornea and/or CL was by approximately half of the respondents in each country (61.1% for the UK and 50.3% for Spain; $p = 0.04$); however, British practitioners were more likely to be a member of some contact lens association (31.0%) than Spanish optometrists (7.7%) ($p < 0.01$).

3.2. GP CL clinical practice

There was a difference in the rate of prescription of GP lenses between practitioners in the two countries. UK practitioners prescribed more GP lenses (54.8% prescribed GP CL once per month or more) than were prescribed by the Spanish optometrists (28.1%) ($p < 0.01$) (Fig. 1). The main barriers to fitting GP lenses reported by

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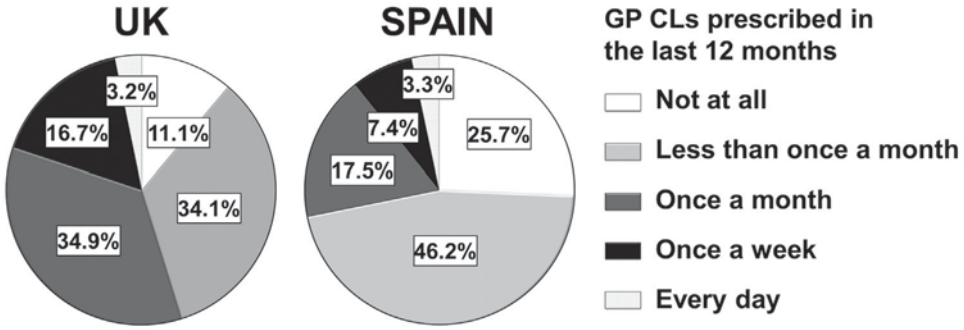

Fig. 1. Percentage of GP CLs prescribed in the two countries in the last 12 months.

practitioners of both countries were: time, cost to practice, lack of experience and low demand for this type of lenses by patients who prefer soft CL due to initial comfort.

More than a quarter of respondents (29.4% in the UK and 25.4% in Spain) reported that they would fit more GP lenses if they underwent further training in GP CL fitting. However, nearly a third of respondents in the UK (31%) and nearly half in Spain (46.4%) were unsure whether further training may help them to fit more GP CL ($p < 0.01$).

3.3. Keratoconus diagnosis and classification

Predominantly, respondents detected less than 5 new patients with keratoconus per year, and this situation was similar in both countries (65.1% in the UK and 65.7% in Spain; $p = 0.21$). Several practitioners detected between 5 and 10 new cases per year (18.3% in the UK and 14.8% in Spain), and a small percentage detected between 10 and 20 (2.4% in the UK and 6.5% in Spain) or more than 20 cases per year (8.7% in the UK and 2.1% in Spain). Finally, 5.6% of respondents in the UK and 10.9% in Spain did not diagnose any new cases of keratoconus in the last year.

In regards to investigations necessary to arrive at the diagnosis of keratoconus, a majority of practitioners (79.4% in the UK and 75% in Spain; $p = 0.68$) considered that a combination of multiple factors is necessary, including history, visual acuity, scissor shadows in retinoscopy, manual keratometry, corneal topography and slit lamp signs.

Generally, practitioners reported that the use of keratoconus severity classification is relevant in clinical practice (67.5% in the UK and 70.7% in Spain; $p = 0.50$); however, only 7.1% in the UK and 17.8% of practitioners in Spain ($p = 0.01$) use some type of keratoconus classification. The most commonly used were: Amsler-Krumeich, cone location, mild/moderate/severe or the KSS (Keratoconus Severity Score) index.

3.4. Keratoconus management with GP lenses

Practitioners tended to consider GP CL fittings more difficult in keratoconic eyes than in healthy eyes in both countries (79.4% in the UK and 80.5% in Spain; $p = 0.79$). The average number of GP diagnostic lenses used in keratoconus CL fittings was 3.2 ± 1.4 (median 3; range 1–10) among UK practitioners and 3.4 ± 1.2 (median 3; range 1–10) among Spanish optometrists ($p = 0.72$) (Fig. 2).

In regards to the method for choosing the back optic zone radius (BOZR) of the first GP diagnostic lens in keratoconic eyes, the trend is different between practitioners in the two countries. The majority of UK practitioners calculate the BOZR of GP lenses using manufacturer's guidelines (based on manual keratometry [34.9%] or based on corneal topography [23.0%]), followed by practitioners who choose BOZR based on their own experience (22.2%), practitioners who send the corneal topography to the manufacturer (16.7%) and a small number that use CL software (3.2%). Meanwhile, in Spain, the most common method of calculating the BOZR is to send the corneal topography to the manufacturer (39.9%), followed by practitioners that follow manufacturer's guidelines (based on corneal topography [32.2%] or manual keratometry [19.5%]) and a minority that select the BOZR based on their own experience (5%) or using CL software (3.3%).

3.5. Keratoconus referral practice

In regards to referral patterns for patients with keratoconus, the majority of respondents did not prefer to refer these patients to another optometrist for CL fitting prior to consulting an ophthalmologist for surgical intervention (56.3% in the UK and 50.3% in Spain; $p < 0.01$), while other practitioners were undecided (23.8% in the UK and 38.5% in Spain).

Half of the practitioners in each country suggested referring keratoconic patients to an ophthalmologist upon initial diagnosis (50% in the UK and 50% in Spain; $p = 1.00$). Other respondents would refer to ophthalmologists when signs of progression are detected (17.5% in the UK and 29.9% in Spain), if the patient shows a reduction of visual acuity (8.7% in the UK and 5.6% in Spain), or at the patient's request (1.6% in the UK and 2.1% in Spain). However, 22.2% in the UK and 12.4% in Spain responded that there was no set time for a referral to an ophthalmologist.

Finally, the majority of respondents do not participate in co-management with ophthalmologists after surgical treatment (60.3% in the UK and 72.8% in Spain; $p = 0.01$).

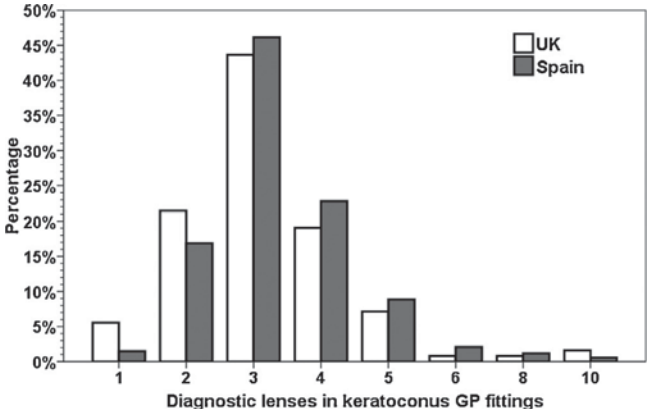

Fig. 2. Number of diagnostic lenses used to fit a keratoconic eye with a GP CL in the two countries ($p = 0.18$, Chi-Square).

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Table 1
Responses to several questions for practitioners with and without a topographer in the two countries.

		UK (126)			Spain (338)		
Question	Response	With Topographer (48)	Without Topographer (78)	P	With Topographer (202)	Without Topographer (136)	P
#4	Yes	52.1%	30.8%	0.01	58.9%	36%	<0.01
	No	47.9%	69.2%		41.1%	64%	
#5	Yes	45.8%	21.8%	0.04	11.4%	2.2%	<0.01
	No	54.2%	78.2%		88.6%	97.8%	
#6	GP not prescribed	4.2%	15.4%	0.04	13.4%	44.1%	<0.01
	GP prescribed	95.8%	84.6%		86.6%	55.9%	
#9	<5	58.3%	78.2%	0.02	62.9%	96.3%	<0.01
	>5	41.7%	21.8%		37.1%	3.7%	
#12	Yes	64.6%	88.5%	0.02	78.7%	83.1%	0.33
	No	35.4%	11.5%		21.3%	16.9%	
#15	Yes	8.3%	26.9%	0.01	6.9%	17.6%	<0.01
	No	77.1%	43.6%		57.9%	39%	
	Maybe	14.6%	29.5%		35.1%	43.4%	
#17	Yes	66.7%	23.1%	<0.01	40.6%	7.4%	<0.01
	No	33.3%	76.9%		59.4%	92.6%	

3.6. Practices and attitudes influenced by corneal topographer

Responses of practitioners based on the availability of corneal topographer are shown in Table 1. It should be noted that practitioners who have a topographer were more likely to prescribe GP CL and detect more new patients with keratoconus per year that those without topographer in both countries. Using corneal topography did not produce a clinically relevant change in the number of diagnostic lenses necessary to complete the GP fitting procedure ($p = 0.31$ for the UK and $p = 0.05$ for Spain, Mann-Whitney *U* test) (Fig. 3). Finally, practitioners who have a topographer were more likely to co-manage with ophthalmologists than respondents without a topographer in UK and Spain.

3.7. Practices and attitudes influenced by optometric experience

Table 2 exhibits the responses of practitioners according their optometric experience in both countries. There seem no clinically relevant differences in practices and attitudes in keratoconus management in UK and Spain based on years of experience. However, practitioners with <5 years of experience prescribed less GP CL in Spain who those with more years of optometric practice. Moreover, optometric experience seems not to influence the number of diagnostic lenses used to achieve optimal GP CL fitting in keratoconus in Spain; however, practitioners in the UK with less experience indicated that a higher number of diagnostic lenses are necessary (Table 3). Finally, in Spain practitioners with <5 years of experiences were more likely to refer a keratoconic patient to another optometrist for contact lens fitting.

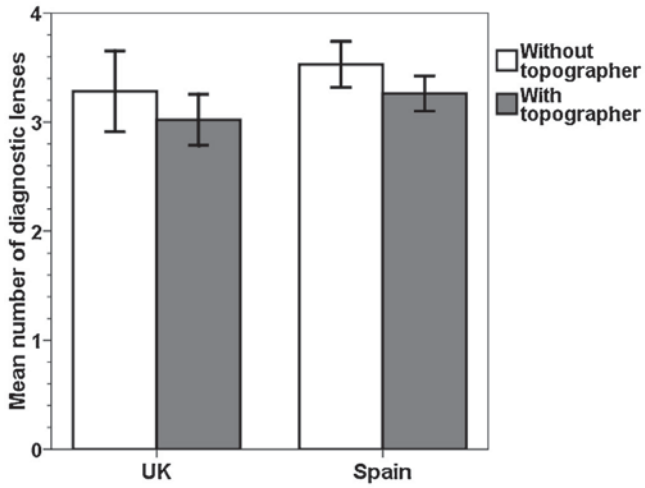

Fig. 3. Mean number of diagnostic lenses used to fit a keratoconic eye with a GP CL for practitioners with and without a topographer in the two countries.

4. Discussion

Optometrists are primary health care specialists trained to examine the eyes with the aim to detect defects in vision or ocular diseases, such as keratoconus. Currently, a total of 14,975 and 14,642 optometrists were registered in Spain [11] and the UK [12], respectively. The results of this survey shed light on the current practice and attitudes in keratoconus patient management in these countries, being the first investigation of optometric practice in relation to this type of disease in Europe. The survey had better reception in Spain, and there were more than three times as many Spanish respondents as UK respondents; however, as is usual in this type of survey [10] a low number of responses were received, and these results must be interpreted with caution. Therefore, the low level of participation in this survey provides a snapshot that suggests that optometrists may be unaware of the importance of investigations to improve their knowledge and their clinical practice.

Placido disk-based videokeratography is the most extensively used technique amongst corneal topographic assessments of the corneal curvature [13,14]. The results suggest that the use of corneal topographers is more common in Spain (59.8%) than in the UK (38.1%), with a possible increase of this technology in the last year, because in 2010, just 9.6% of UK optometrists reported having a topographer (in a survey of 451 UK optometrists) [15]. Because corneal topography assessment is highly recommended prior to keratoconus diagnosis [2], it might be reasonable to assume that UK practitioners would detect fewer new patients with keratoconus than would Spanish optometrists. However, no differences were found between UK and Spanish respondents in the number of new keratoconus cases detected. This could be due to several reasons. For example, due to the prevalence of keratoconus, practices with high patient turnover have a greater chance to detect any eye disease; alternatively, because a combination of multiple factors is necessary to detect keratoconus and not just corneal topography assessment, clinical data such as the patient's history, visual acuity, scissor shadows in retinoscopy, manual keratometry findings, or slit lamp signs are of paramount importance in optometry practice and keratoconus diagnosis [1], as the results suggest.

Currently, there are a number of classifications of keratoconus severity or staging based on morphology, ocular signs, refraction and index-based systems proposed in the literature [16,17].

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Table 2
Responses to several questions for practitioners according to their optometric experience in the two countries.

Question	Response	UK (126)					Spain (338)				
		<5 (22)	5–10 (12)	10–20 (24)	>20 (68)	P	<5 (55)	5–10 (53)	10–20 (136)	>20 (94)	P
#4	Yes	22.7%	33.3%	45.8%	42.6%	0.32	43.6%	41.5%	37.5%	75.5%	<0.01
	No	77.3%	66.7%	54.2%	57.4%		56.4%	58.5%	62.5%	24.5%	
#5	Yes	13.6%	33.3%	16.7%	41.2%	0.03	3.6%	3.8%	5.9%	14.9%	0.03
	No	86.4%	66.7%	83.3%	58.8%		96.4%	96.2%	94.1%	85.1%	
#6	GP not prescribed	9.1%	25%	4.2%	11.8%	0.34	45.5%	28.3%	25%	13.8%	<0.01
	GP prescribed	90.9%	75%	95.8%	88.2%		54.5%	71.7%	75%	86.2%	
#9	<5	59.1%	83.3%	83.3%	67.6%	0.21	81.8%	75.5%	79.4%	69.1%	0.22
	>5	40.9%	16.7%	16.7%	32.4%		18.2%	24.5%	20.6%	30.9%	
#12	Yes	59.1%	83.3%	83.3%	83.8%	0.08	85.5%	83%	75%	84%	0.22
	No	40.9%	16.7%	16.7%	16.2%		14.5%	17%	25%	16%	
#15	Yes	22.7%	8.3%	29.2%	17.6%	0.16	18.2%	13.2%	9.6%	8.5%	0.03
	No	50%	50%	37.5%	66.2%		32.7%	50.9%	48.5%	62.8%	
	Maybe	27.3%	41.7%	33.3%	16.2%		49.1%	35.8%	41.9%	28.7%	
#17	Yes	40.9%	25%	25%	47.1%	0.18	16.4%	32.1%	27.2%	30.9%	0.21
	No	59.1%	75%	75%	52.9%		83.6%	67.9%	72.8%	69.1%	

Table 3
Mean number of diagnostic lenses used by respondents in keratoconus GP CL fittings according to optometric experience.

	Spain (n)	UK (n)
<5 years	3.22 ± 1.07 (55)	3.86 ± 1.88 (22)
5–10 years	3.45 ± 1.28 (53)	2.67 ± 0.98 (12)
10–20 years	3.29 ± 0.99 (136)	3.13 ± 1.03 (24)
>20 years	3.52 ± 1.48 (94)	3.07 ± 1.33 (68)
P-Value	P = 0.37	P = 0.06

Unfortunately, there is no single clinically adequate classification for keratoconus [2]. This lack of consensus in keratoconus classification can be seen in the results of this survey. Only a small percentage of practitioners (7.1% in the UK and 17.8% in Spain) use some type of classification system in keratoconus management, whereas most practitioners think that the use of keratoconus severity classification is relevant in optometric practice. More research and consensus might be necessary to define and propose a keratoconus severity classification to be used by eye-care practitioners.

Currently, the proportion of GP CL fittings in the general population is clearly low compared with soft lens prescriptions [18–20] and this type of lens is not considered the first choice option to correct refractive errors in healthy patients [15,17]. A GP fitting rate of less than 11% around the world has been reported over the past decade, despite the theoretical advantages of this type of lens [15,21]. In this survey a similar trend was found in both countries, with a low percentage of GP lens fitting relating primarily to the cost to practice, lack of experience and initial discomfort. Hodge et al. [10] reported similar trends in an optometric survey in Australia in which only 9.2% of the 71 respondents prescribed GP lenses daily (approximately 3% in the UK and Spain), 47.7% prescribed GP lenses less than once per month (34.9% in the UK and 46.2% in Spain) and 15.4% never prescribed this type of lens (11.1% in the UK and 25.7% in Spain). It was found that respondents with a topographer were more likely to prescribe GP CL, a finding similar to previous reports [10].

In 2010, Gill et al. [15] analysed the effect of practitioner attitudes on GP lens prescribing in the UK and found that the practitioners know the benefits provided by GP lenses pertaining to ocular health and refractive correction. However, Gill et al. concluded that initial patient discomfort negatively influenced practitioner attitudes because the patients prefer the initial comfort benefit provided by soft lenses, and consequently, this translates to reduced GP prescribing. However, close to a quarter of the respondents (29.4% in the UK and 25.4% in Spain) indicated that they would fit more GP lenses if they underwent further training courses about this type of CL.

Fitting of GP lenses in keratoconus patients is the first option for visual rehabilitation of these patients [2–5] and improves their quality of life [22,23]. However, this fitting is described in the literature as challenging for eye care practitioners and patients, because the irregular cornea often requires several diagnostic lenses to achieve a final acceptable GP lens fit, which prolongs practitioner and patient chair time [1,24,25]. The respondents agreed with this fact, as a majority of practitioners (79.4% in the UK and 80.5% in Spain) consider GP CL fittings more difficult in keratoconic than in healthy eyes.

The average number of diagnostic lenses used by respondents in keratoconus GP CL fittings was similar in the two countries (in the UK 3.2 ± 1.4 lenses and in Spain 3.4 ± 1.2 lenses). These results are similar to those reported by Nosch et al. [24], who retrospectively analysed the GP lens fits in 68 eyes with irregular corneal surfaces (75% of keratoconus eyes) and reported that 3.25 ± 1.70 diagnostic lenses are necessary to complete GP CL fitting. These results highlight the need to improve the GP fitting procedure in keratoconus eyes to decrease the number of diagnostic lenses and reduce the practitioner and patient chair time that is required to achieve an acceptable GP fit.

Optometrists and other eye-care professionals have a duty of care to their patients and the results of this survey highlight that there are no specific guidelines to manage or propose referral patterns for patients with keratoconus in primary eye care [10]. Half of UK and Spanish practitioners refer the patient to an ophthalmologist upon initial diagnosis, but only a minority (7.8%) of Australian optometrists follow this practice [10]. However, approximately 30% of respondents (20% in the UK) referred patients to an ophthalmologist when signs of progression are detected, similar to Australian optometrists [10]. This behaviour could be influenced by the variety of clinical practice, because some practitioners have an emphasis on the diagnosis rather than the management of keratoconus. The American Academy of Ophthalmology suggests that a keratoconus patient must be referred to an ophthalmologist when glasses or CL cannot improve visual function [26]. Hodge et al. [10] found a relative consensus to refer a keratoconus patient when visual acuity is between 6/9 and 6/12 (an option chosen by 62.9% of surveyed optometrists), in line with American Academy of Ophthalmology recommendations. This criterion suggests that a large number of patients could receive a treatment to reduce keratoconus progression after

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impairment in their visual acuity that induces a deep impact in their quality of life [22,23]. Moreover, following this recommendation is highly dependent on the capacity to provide an adequate CL fitting in these patients [10]. So, evidence-based guidelines to improve CL fitting in keratoconus could be necessary, because a lack of consensus was found in the procedure to calculate the BOZR of the first diagnostic lens (most respondents follow the manufacturer recommendations, while a minority, less than 4%, use CL software).

Co-management with ophthalmologists is low in the UK (39.7%) and in Spain (27.2%) compared with Australian optometrists (42.9%) [10]. These results suggest that there is a need to increase co-management between optometrists and ophthalmologists, because new therapeutic options, such as collagen crosslinking [27] or the insertion of intra-stromal corneal rings [28] provide new opportunities for optometrists and ophthalmologists to work together to optimize the treatment of keratoconus and improve visual care in these patients.

Therefore, the results of this study highlight the great impact that a routine management guideline for the treatment and referral of keratoconus patients could have in primary eye care and optometry practice, as previous reports proposed [10]. Some clinical issues must be taken into consideration, because patients under 30 years old could benefit from crosslinking treatment to reduce keratoconus progression [27], and corneal topography monitoring is recommended yearly [10] 0.2 D of change in flat meridian per year has been proposed as a threshold [29] with high repeatable topographers in keratoconic cornea assessment [13,30].

A limitation of this study is the low number of responses received from practitioners with an interest in CL practice. It was not possible with the methodology used to determine an exact completion rate for the questionnaire. However, a strength of this study is that it is the first to analyse the current optometric practice in relation to keratoconus in two European countries with high standards in optometry practice, namely, the UK and Spain. Regarding keratoconus disease, there did not appear to be clinically significant differences between the two countries in the diagnostic methods and in GP CL management (which is considered more complicated than in healthy eyes), with a similar number of diagnostic lenses required to achieve the optimal lens. Respondents from both countries show a reasonable consensus regarding the lack of clinical guidelines for management and referral of these patients to ophthalmologists or other eye-care practitioners and the necessity to increase co-management with ophthalmologists to improve eye care in these patients. Finally, there is slight differences in the scope of Optometry practice in the UK and Spain that it is mainly related with the use of diagnostic drugs and collaboration with public health care system. However, CL practice it is similar in both countries, where Optometrists are the qualified professional to prescribe CL, so the scope differences could be showed low impact in the results and conclusions.

5. Conclusion

This survey provides initial observations and evidence regarding current optometric practices in keratoconus management by UK and Spanish practitioners. This study shows reasonably similar attitudes regarding keratoconus diagnosis, management and GP CL practice in the two countries, suggesting that keratoconus patient care could be improved with new evidence-based guidelines for the management and referral of these patients that would provide guidance on GP CL fitting procedure, clarify corneal topography monitoring criteria, determine referral criteria and enhance co-management between optometrists and ophthalmologists.

Additional research and consensus between ophthalmologists and optometrists are necessary to provide better eye care to keratoconus patients, minimizing disease progression and visual acuity impairment, providing the best treatment and increasing patients' quality of life.

Disclosure of conflicts of interest

None of the authors has a financial or proprietary interest in any material or method mentioned.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.clae.2017.03.005.

References

[1] M. Romero-Jiménez, J. Santodomingo-Rubido, J.S. Wolffsohn, Keratoconus: a review, Contact Lens Anterior Eye 33 (2010) 157–166.
[2] J.A. Gomes, D. Tan, C.J. Rapuano, R. Ambrósio Jr., Group of panelists for the global delphi panel of keratoconus and ectatic diseases, global consensus on keratoconus and ectatic diseases, Cornea 34 (2015) 359–369.
[3] D.A. Godefrooij, G.A. de Wit, C.S. Uiterwaal, S.M. Imhof, R.P. Wisse, Age-specific incidence and prevalence of keratoconus: a nationwide registration study, Am. J. Ophthalmol. 175 (2016) 169–172.
[4] M. Barnett, M.J. Mannis, Contact lenses in the management of keratoconus, Cornea 30 (2011) 1510–1516.
[5] L.E. Downie, R.G. Lindsay, Contact lens management of keratoconus, Clin. Exp. Optom. 98 (2015) 299–311.
[6] F. Arnalich-Montiel, J.L. Alió Del Barrio, J.L. Alió, Corneal surgery in keratoconus: which type, which technique, which outcomes? Eye Vision (Lond.) 3 (2016) 2.
[7] The College of Optometrists of UK. http://www.college-optometrists.org/en/college/about-optometry/What_is_an_optometrist.cfm. (Accessed 10 October 2016).
[8] Spanish regulation for Optometrists qualification. Spanish law number CIN/727/2009. https://www.boe.es/boe/dias/2009/03/26/pdfs/BOE-A-2009-5034.pdf. (Accessed 18 January 2017).
[9] D.P. Piñero, J.L. Alio, R.I. Barraquer, R. Michael, R. Jiménez, Corneal biomechanics, refraction, and corneal aberrometry in keratoconus: an integrated study, Invest. Ophthalmol. Vis. Sci. 51 (2010) 1948–1955.
[10] C. Hodge, C. Chan, S. Zantos, J. Kokkinakis, F. Stapleton, G. Sutton, Therapeutic treatment of keratoconus: a survey of local optometric practice criteria, Clin. Exp. Optom. 98 (2015) 312–318.
[11] Gaceta de Optometría y Óptica Oftálmica 510 (2016) 24.
[12] The College of Optometrists of UK. http://www.college-optometrists.org/en/college/about-optometry/What_is_an_optometrist.cfm. (Accessed 10 October 2016).
[13] S. Ortiz-Toquero, G. Rodriguez, V. de Juan, R. Martin, Repeatability of placido-based corneal topography in keratoconus, Optom. Vision Sci. 91 (2014) 1467–1473.
[14] D.P. Piñero, J.C. Nieto, A. Lopez-Miguel, Characterization of corneal structure in keratoconus, J. Cataract Refract. Surg. 38 (2012) 2167–2183.
[15] F.R. Gill, P.J. Murphy, C. Purslow, A survey of UK practitioner attitudes to the fitting of rigid gas permeable lenses, Ophthalmic Physiol. Opt. 30 (2010) 731–739.
[16] Y.S. Rabinowitz, K. Rasheed, KISA% index: a quantitative videokeratography algorithm embodying minimal topographic criteria for diagnosing keratoconus, J. Cataract Refract. Surg. 25 (1999) 1327–1335.
[17] J.L. Alió, M.H. Shabayek, Corneal higher order aberrations: a method to grade keratoconus, J. Refract. Surg. 22 (2006) 539–545.
[18] N. Efron, P.B. Morgan, M. Helland, M. Itoi, D. Jones, J.J. Nichols, E. Van der Worp, C.A. Woods, International rigid contact lens prescribing, Contact Lens Anterior Eye 33 (2010) 141–143.
[19] N. Efron, J.J. Nichols, C.A. Woods, P.B. Morgan, Trends in US contact lens prescribing 2002 to 2014, Optom. Vision Sci. 92 (2015) 758–767.
[20] S. Ortiz-Toquero, M. Martin, G. Rodriguez, V. de Juan, R. Martin, Success of rigid gas permeable contact lens fitting, Eye Contact Lens (2016), doi:http://dx.doi.org/10.1097/icl.0000000000000254.

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[21] N. Efron, P.B. Morgan, C.A. Woods, Consortium ICLPS, international survey of rigid contact lens fitting, Optom. Vision Sci. 90 (2013) 113–118.
[22] S. Ortiz-Toquero, S. Perez, G. Rodriguez, A. Mayo-Iscar, R. Martin, The influence of the refractive correction on the vision-related quality of life in keratoconus patients, Qual. Life Res. 25 (2016) 1043–1051.
[23] S.M. Kymes, J.J. Walline, K. Zadnik, M.O. Gordon, Collaborative longitudinal evaluation of Keratoconus study group. Quality of life in keratoconus, Am. J. Ophthalmol. 138 (2004) 527–535.
[24] D.S. Nosch, G.L. Ong, I. Mavrikakis, J. Morris, The application of a computerised videokeratography (CVK) based contact lens fitting software programme on irregularly shaped corneal surfaces, Contact Lens Anterior Eye 30 (2007) 239–248.
[25] L. Sorbara, K. Dalton, The use of video-keratoscopy in predicting contact lens parameters for keratoconic fitting, Contact Lens Anterior Eye 13 (2010) 112–118.
[26] American Academy of Ophthalmology Corneal Ectasia Summary Benchmarks for Preferred Practice Pattern Guidelines. 2013. http://one.aao.org/summary-benchmark-detail/corneal-ectasia-summary-benchmark-2013. (Accessed 4 October 2016).
[27] E. Sykakis, R. Karim, J.R. Evans, C. Bunce, K.N. Amissah-Arthur, S. Patwary, P.J. McDonnell, S. Hamada, Corneal collagen cross-linking for treating keratoconus, Cochrane Database Syst Rev. 3 (2015) CD010621.
[28] K. Zadnik, K. Lindsley, Intrastromal corneal ring segments for treating keratoconus, Cochrane Database Syst. Rev. 6 (2014) CD011150.
[29] H. Wagner, J.T. Barr, K. Zadnik, Collaborative longitudinal evaluation of keratoconus (CLEK) study: methods and findings to date, Contact Lens Anterior Eye 30 (2007) 223–232.
[30] S. Ortiz-Toquero, G. Rodriguez, V. de Juan, R. Martin, Repeatability of wavefront aberration measurements with a Placido-based topographer in normal and keratoconic eyes, J. Refract. Surg. 32 (2016) 338–344.

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APPENDIX 1

Keratoconic patient management in Optometric practice

Dear Optometrist

We are working on a research project at Plymouth University (UK) and the University of Valladolid (Spain), to establish how keratoconic patients are managed in Optometric practice. So, we would be grateful if you could spend a few minutes of your time answering this short questionnaire about your contact lens practice to help us in our research project.

Thank you very much

Dr. Martin and Ms Ortiz-Toquero

General Contact Lens Practice Questions

1. Please choose your qualification

Optometrist
Contact lens optician
Other (Choose): _____

2. How many years have you been practising for?

3.a. Does your practice own a corneal topographer?

Yes
No

3.b. If you answered "yes" to the previous question, what type of corneal topographer do you use in your practice?

Placido-based videokeratography
Scheimpflug
Mixed (combined Placido-based with Scheimpflug)
Scanning-slit topography
Other

4. Have you completed any post qualification or specific training on Cornea and/or Contact Lens?

Yes
No

5. Are you a member of any Contact Lens Association (e.g. British Contact Lens Association)?

Yes
No

6. In the past 12 months, how often have you prescribed (either fit or refit) rigid gas-permeable lenses?

Every day
Once a week
Once a month
Less than once a month
Not at all

7. What, if any, is the main barrier to fitting rigid gas-permeable lenses?

Time
Cost to practice
Experience
Not applicable
Other (please specify):

8**. Would you consider prescribing more rigid gas-permeable lenses, if you were able to undergo further training courses?**

Yes
No
Maybe
Not applicable

Keratoconus Related Questions

9. How many new patients would you detect with keratoconus per year?

None
<5
5-10
10-20
>20

10. What investigations would you consider most important in making a diagnosis of keratoconus?

History and visual acuity
Scissor shadows in retinoscopy
Manual keratometry and slit lamp signs
Corneal topography and slit lamp signs
Combination of the above

11.a. Do you think that a keratoconus severity classification seems relevant in the clinical practice?

Yes
No

11.b. Do you use any classification of the keratoconus based on the cone location?

Yes
No

11.c. If yes, please indicate the name of the classification:

12. Do you consider rigid gas-permeable lens fitting more difficult in keratoconic eyes than healthy eyes?

Yes
No

13. On average, how many diagnostic lenses do you need to use to fit a keratoconic eye with a rigid gas-permeable lens?

1-10

14. How do you choose the back optic zone radius (BOZR) of the first diagnostic lens in rigid gas-permeable lens fitting in keratoconic eyes?

I calculate the BOZR following manufacturer´s guidelines, based on corneal keratometry
I calculate the BOZR following manufacturer´s guidelines, based on corneal topography
I calculate the BOZR using my own experience
I calculate the BOZR using software for contact lenses fitting
I do not calculate the BOZR; I send the corneal topography to the manufacturer

15. Would you refer a keratoconic patient to another optometrist for contact lens fitting, prior to referring an ophthalmologist for surgical intervention?

Yes
No
Maybe

16. At what stage would you consider referring the patient to an ophthalmologist?

Upon initial diagnosis
At patient's request
With reduction of visual acuity
With progression of corneal signs
No set time

17. Do you currently co-manage patients with ophthalmologists after surgical treatment, for example: collagen cross-linking or contact lens fitting following intra-stromal corneal rings or penetrating keratoplasty?

Yes
No

Thank you for your time

4.4. Dificultad de la adaptación de LC RPG en queratocono

Ortiz-Toquero S[1,2,3], Martin R[1,2,3,4]

Fitting gas permeable contact lens in keratoconus, still a challenge?

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Editorial

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Fitting Gas Permeable Contact Lens in Keratoconus; Still a Challenge?

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Gas permeable (GP) contact lenses (CL) are of paramount importance in keratoconus patient management[1] to rehabilitate vision and improve patients' quality of life (QoL).[2] Different surgical and non-surgical options are available in keratoconus management. Early stages could be managed with conventional optical corrections (spectacles and/or soft CL), however if disease progress, and corneal irregularity affects to visual acuity GP (conventional or with keratoconus specific design) lenses should be necessaries to patients' visual rehabilitation. Other alternative CL options (piggy-back, mini-scleral, semi-scleral, scleral designs etc.) have been, also, proposed. If patients show CL intolerance or disease progresses and/or corneal integrity could be affected surgical techniques are required.

Keratoconus diagnosis and management is a challenge. The first difficulty is related with an accurate identification of keratoconus patient.[1] Clear diagnosis of early stage (in opposition to moderate or advanced disease), subclinical keratoconus, or how distinguish keratoconus from other ectatic diseases imposes greater diagnostic challenges.[1,3] A complete eye exam is necessary to confirm keratoconus diagnosis, make the differential diagnosis with subclinical keratoconus and differentiate of other ectatic diseases. Anterior eye investigation; based on slit lamp findings (stromal thinning, conical protrusion, Fleischer ring and Vogt striae); corneal tomography (Scheimpflug or optical coherence tomography) assessing anterior and posterior corneal surface; and full corneal thickness map analysis (because normal central thickness could be present in keratoconus cornea) are mandatory. Anterior topographical analysis (Placido-based topographers) still plays a relevant role in keratoconus detection, especially in primary care, because these devices are one of the most extensively used in clinical practice[4,5] and aid to differentiate between keratoconus and pellucid marginal degeneration (PMD).[1] Patients' history may identify major risk factors for keratoconus; such as: down syndrome, relatives of affected patients, ocular allergy, Asian or Arabian ethnicity, eye rubbing, floppy eyelid syndrome, atopy, connective tissue disorders (Marfan syndrome), and others.[1,6]

The second challenge is related with disease classification because there is no clinically adequate classification system for keratoconus disease.[1] Amsler-Krumeich classification[7,8] and collaborative longitudinal evaluation of keratoconus (CLEK)[9] classifications are the most commonly used to classify the keratoconus severity. Amsler-Krumeich classification proposes four different levels using refractive, topographic and biomicroscopic corneal signs. The CLEK classification[9] proposes to use the average corneal power and root mean square (RMS) error for higher-order Zernike terms (derived from the first corneal surface wavefront) combined with clinical biomicroscopic signs. However, both classifications fail to address current information and technological advances[1] and a new classification criterion is necessary. Although, there is a lack of consensus in this issue, high order corneal aberration analysis could play a relevant role in future keratoconus classification[3] because larger values of vertical coma has been founded in these patients.[4,9-11] Clinical progression requires changes in at least 2 of these 3 parameters; corneal steepening (anterior and/or posterior) and progressive corneal thinning.[1] That means that disease progression is directly dependent of the accuracy and reliability of the corneal device used in patient assessment.[5,10]

After diagnosis and gradation of the keratoconus disease, management and treatment could be the third challenge. Two major approaches; surgical and non-surgical management have been proposed, with the objective of halt progression of the disease and patients' visual rehabilitation. Non-surgical approach may be the first action in patient management (less invasive therapeutic strategies), highlighting GP CL fitting to improve patients' vision, although GP CL wear do not halt the progression of the disease.[12] Patient education avoiding eye rubbing is, also, necessary.[1,6]

Different surgical options are currently available without clear consensus regarding what could be the best surgical approach for keratoconus. Corneal cross-linking (CXL) has been proposed in patients younger than 40 years to halt disease progression with limited evidence provided by properly conducted randomized controlled trial (RCT)[13] and requires a well-documented clinical progression or risk of progression patient. It is, also, unclear it uses in subclinical keratoconus patients.[1] Light improvement of visual acuity (1 to 2 Snellen lines) could be expected after CXL.[14] Descemetic deep anterior lamellar (dDALK), in patients without Descemet membrane compromise, or penetrating keratoplasty (PK) are the "techniques of choice" when a corneal transplant was needed (in advance disease stages; severe corneal thinning; or in non-CL tolerant patients). These techniques achieved best-corrected visual acuity of 20/40 or better in 3 of 4 patients,[15] with insufficient evidence to determine which technique offer better overall outcomes.[16] Intracorneal ring segment (ICRS) increases corneal stability decreasing the astigmatism asymmetry helping in normalization of the corneal contour with slight improvement of patients' visual acuity,[12,17] without clear consensus about its indication.

Notwithstanding, if patient is satisfied with their vision (with spectacles or CL) no surgical treatment is indicated (except CXL), so visual rehabilitation of keratoconus patient is of paramount importance.[1] Although GP CL raises keratoconus patients' visual acuity (VA) near to 20/20,[18] achieve the correct lens parameters is a challenge to practitioners and patients[19] requiring several diagnostic lenses to achieve a final acceptable GP lens fit, which prolongs practitioner and patient chair time. To improve CL fitting procedure, different CL design and strategies have been proposed. For example, the use of CL fitting software linked with different corneal topographers could help in GP lens fitting[20,21] but, a lack in clinical studies that analyze the real impact of these software in clinical practice exists. Some of these software propose GP lens with systematic bias that could be improve with new equations.[22]

Recently, a new clinically validated open access web-calculator (www.calculens.com) has been developed with the aim to aid CL practitioners to calculate CL parameters of the GP lens to be fitted in keratoconus patients (European Academy of Optic and Optometry 2016 Meeting). This new tool will allow that keratoconus patients receive the most adequate lens and help CL practitioners to provide a sound fitting process, decreasing the number of diagnostic lenses, trials, and chair time to those achieved in standard GP CL fitting.[23] Therefore with this new tool, keratoconus management with GP CL will be not a challenge any more; and both, patients and practitioners, will be benefited.

In conclusion, Keratoconus is a multifactorial disease with genetic, biochemical, biomechanical, and environmental pathophysiology[1]; that requires a multiprofessional approach for early detection, correct diagnosis, follow-up, monitoring and adequate patient management that involve; primary eye care practitioners, optometrists, CL practitioners and ophthalmologists with the last aim to provide better care and improve patients' quality of life.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Gomes JA, Tan D, Rapuano CJ, et al. Global consensus on keratoconus and ectatic diseases. *Cornea*. 2015; 34: 359-369. doi: 10.1097/ICO.0000000000000408

2. Ortiz-Toquero S, Perez S, De Juan V, Rodriguez G, Agustin Mayo-Iscar A, Martin R. The influence of the refractive correction on the vision-related quality of life in keratoconus patients. *Qual Life Res*. 2015; 25(4): 1043-1051. doi: 10.1007/s11136-015-1117-1

3. Sideroudi H, Labiris G, Georgatzoglou K, Ditzel F, Siganos C, Kozobolis V. Fourier analysis of videokeratography data: Clinical usefulness in grade I and subclinical keratoconus. *J Cataract Refract Surg.* 2016; 42: 731-737. doi: 10.1016/j.jcrs.2016.01.049

4. Piñero DP, Nieto JC, Lopez-Miguel A. Characterization of corneal structure in keratoconus. *J Cataract Refract Surg*. 2012; 38: 2167-2183. doi: 10.1016/j.jcrs.2012.10.022

5. Ortiz-Toquero S, Rodriguez G, de Juan V, Martin R. Repeatability of placido-based corneal topography in keratoconus. *Optom Vis Sci*. 2014; 91(12): 1467-1473. doi: 10.1097/OPX.0000000000000421

6. Gordon-Shaag A, Millodot M, Shneor E, Liu Y. The genetic and environmental factors for keratoconus. *Biomed Res Int.* 2015; 2015: 795738. doi: 10.1155/2015/795738

7. Amsler M. Kératocõne classique et kératocône fruste; arguments unitaires [In French]. *Ophthalmologica*. 1946; 111: 96-101.

8. Krumeich JH, Daniel J, Knülle A. Live-epikeratophakia for keratoconus. *J Cataract Refract Surg.* 1998; 24: 456-463. doi: 10.1016/S0886-3350(98)80284-8

9. McMahon TT, Szczotka-Flynn L, Barr JT, et al. A new method for grading the severity of keratoconus: The Keratoconus Severity Score (KSS). *Cornea.* 2006; 25(7): 794-800. Web site. https://vrcc.wustl.edu/clekarchive/pdf/31%20McMahon%20-%20A%20New%20Method.pdf. Accessed August 14, 2016

10. Ortiz-Toquero S, Rodriguez G, de Juan V, Martin R. Repeatability of wavefront aberration measurements with a placido-based topographer in normal and keratoconic eyes. *J Refract Surg.* 2016; 32: 338-334. doi: 10.3928/1081597X-20160121-04

11. Alió JL, Shabayek MH. Corneal higher order aberrations: A method to grade keratoconus. *J Refract Surg.* 2006; 22: 539-545. doi: 10.3928/1081-597X-20060601-05

12. Mandathara PS, Stapleton FJ, Willcox MD. Outcome of keratoconus management: Review of the past 20 years' contemporary treatment modalities. *Eye Contact Lens*. 2016; 11. doi: 10.1097/ICL.0000000000000270

13. Sykakis E, Karim R, Evans JR, et al. Corneal collagen cross-linking for treating keratoconus. *Cochrane Database Syst Rev*. 2015; 24: CD010621. doi: 10.1002/14651858.CD010621.pub2

14. Meiri Z, Keren S, Rosenblatt A, Sarig T, Shenhav L, Varssano D. Efficacy of corneal collagen cross-linking for the treatment of Keratoconus: A systematic review and meta-analysis. *Cornea.* 2016; 35: 417-428. doi: 10.1097/ICO.0000000000000723

15. Arnalich-Montiel F, Alió del Barrio JL, Alió JL. Corneal surgery in keratoconus: Which type, which technique, which outcomes? *Eye Vis (Lond).* 2016; 3: 2. doi: 10.1186/s40662-016-0033-y

16. Keane M, Coster D, Ziaei M, Williams K. Deep anterior lamellar keratoplasty versus penetrating keratoplasty for treating keratoconus. *Cochrane Database Syst Rev*. 2014; 22: CD009700. doi: 10.1002/14651858.CD009700.pub2

17. Poulsen DM, Kang JJ. Recent advances in the treatment of corneal ectasia with intrastromal corneal ring segments. *Curr Opin Ophthalmol*. 2015; 26: 273-277. doi: 10.1097/ICU.0000000000000163

18. Visser ES, Wisse RP, Soeters N, Imhof SM, Van der Lelij A. Objective and subjective evaluation of the performance of medical contact lenses fitted using a contact lens selection algorithm. *Cont Lens Anterior Eye.* 2016; 39(4): 298-306. doi: 10.1016/j.clae.2016.02.006

19. Zhou AJ, Kitamura K, Weissman BA. Contact lens care in keratoconus. *Cont Lens Anterior Eye.* 2003; 26: 171-174. doi: 10.1016/S1367-0484(03)00042-0

20. Mandathara PS, Fatima M, Taureen S, et al. GP contact lens fitting in keratoconus using FITSCAN technology. *Cont Lens Anterior Eye.* 2013; 36: 126-129. doi: 10.1016/j.clae.2012.12.002

21. Nosch DS, Ong GL, Mavrikakis I, et al. The application of a computerised videokeratography (CVK) based contact lens fitting software programme on irregularly shaped corneal surfaces. *Cont Lens Anterior Eye*. 2007; 30: 239-248. doi: 10.1016/j.clae.2007.06.003

22. Ortiz-Toquero S, Rodriguez G, De Juan V, Martin R. Rigid gas permeable contact lens fitting using new software in keratoconic eyes. *Optom Vis Sci.* 2016; 93: 286-292. doi: 10.1097/OPX.0000000000000804

http://dx.doi.org/10.17140/OOJ-1-e004

23. Ortiz-Toquero S, Martin M, Rodriguez G, De Juan V, Martin R. Success of rigid gas permeable contact lens fitting. *Eye Contact Lens*. 2016; 13. doi: 10.1097/ICL.0000000000000254

Capítulo 5

Fiabilidad y utilidad de la topografía corneal en el proceso de adaptación de LC RPG en queratocono

CHAPTER 5: Usefulness of corneal topography in GP CL fitting in keratoconus eyes

5.1. Repetibilidad de la topografía de Plácido en queratocono

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ORIGINAL ARTICLE

Repeatability of Placido-Based Corneal Topography in Keratoconus

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ABSTRACT

Purpose. To determine and compare the repeatability of a Placido-based corneal topography (Oculus Keratograph) in a sample of healthy and keratoconus eyes.

Methods. The corneal topography, determined using the Oculus Keratograph, of 25 healthy and 25 keratoconus eyes was assessed three consecutive times. A single randomized eye was included per patient. Coefficient of variation (CV) of the eccentricity, corneal diameter, index of surface variance, index of vertical asymmetry, keratoconus index (KI), smallest sagittal curvature radius (Rmin), aberration coefficient, and maximum corneal power and minimum corneal power (diopters) in the 3.0-mm zone in addition to the maximum corneal power point (MCPP) (diopters) were calculated and compared between healthy and keratoconus eyes.

Results. Healthy eyes showed lower topographic values ($p < 0.05$) than keratoconus eyes, except with regard to the Rmin value. Corneal diameter ($p = 0.45$) was similar in both groups. All variables showed good CVs in healthy and keratoconus eyes (maximum corneal power [0.21 and 0.47%, respectively], minimum corneal power [0.19 and 0.36%], MCPP [0.22 and 0.77%], corneal diameter [0.27 and 0.33%], index of surface variance [4.82 and 3.10%], index of vertical asymmetry [7.05 and 3.80%], KI [0.29 and 0.72%], Rmin [0.53 and 0.78%], and aberration coefficient [0 and 4.00%]) except for the eccentricity CV (5.79 and 14.53%, respectively). Statistically significant differences ($p < 0.05$) between healthy and keratoconus groups were found for all variables, except with respect to the MCPP, eccentricity, corneal diameter, KI, and Rmin ($p > 0.07$).

Conclusions. The Oculus Keratograph provides repeatable measurements of corneal topography in healthy and keratoconus eyes. These results could improve the topographical diagnosis of keratoconus, thus aiding in patient management.
(Optom Vis Sci 2014;91:1467–1473)

Key Words: keratoconus, Placido disk–based videokeratography, repeatability, Oculus Keratograph

Keratoconus is a progressive corneal disorder characterized by the thinning and steepening of the central and paracentral cornea, leading to protrusion.[1–4] This ectatic condition is bilateral and asymmetric and appears during the second decade of life, normally during puberty, progressing until the fourth decade of life, when it usually stabilizes.[1–3] Corneal protrusion causes high myopia and irregular astigmatism, affecting between 50 and 230 subjects per 100,000 population.[3]

In the early stages, keratoconus patients can be managed with glasses or soft contact lenses, but as keratoconus progresses, the irregular astigmatism often requires rigid gas-permeable (RGP) lenses that can improve visual acuity.[3] The surgery management of keratoconus can be approached through an intrastromal corneal ring segment surgery or cross-linking. In the advanced stages, corneal transplantation may be necessary.[2]

Placido disk–based videokeratography is the most extensively used technique among corneal topographic assessments of the corneal curvature. In keratoconus, information on the corneal topography permits an early diagnosis in the absence of slit-lamp findings.[1,4] Grading the keratoconus and monitoring its progression aid in patient management through different approaches, including the fitting of specifically designed contact lenses.[5–8] Moreover, this analysis is of paramount importance in the preoperative assessment of patients undergoing corneal refractive surgery to avoid potentially undesirable side effects.[8,9]

The Oculus Keratograph (Oculus Optikgeräte GmbH, Wetzlar, Germany) is a computerized Placido-based videokeratography system that was developed especially for use by eye care practitioners in such procedures as refractive surgery and the fitting of RGP contact lenses.[10]

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TABLE 1.
Amsler-Krumeich keratoconus classification

Stage I	Eccentric steepening Myopia and/or astigmatism < 5.00 D Mean central K readings < 48.00 D Vogt striae, no corneal opacities
Stage II	Myopia and/or astigmatism from 5.00 to 8.00 D Mean central K readings < 53.00 D Absence of scarring Minimum corneal thickness ≥ 400 μm
Stage III	Myopia and/or astigmatism from 8.00 to 12.00 D Mean central K readings > 53.00 D Absence of scarring Minimum corneal thickness from 200 to 400 μm
Stage IV	Refraction not measurable Mean central K readings > 55.00 D Central corneal scarring Minimum corneal thickness < 200 μm

However, to our knowledge, the repeatability of this device has been incompletely evaluated to date, with only a few reports published on exclusively healthy eyes.[11] Moreover, its repeatability in keratoconus eyes has not been previously described. Understanding the differences in repeatability between healthy and keratoconus eyes may improve eye examinations and early diagnosis, especially during preassessments of refractive surgery patients and RGP contact lenses fitting.

Therefore, the aim of this study was to determine and compare the repeatability of the main topographical indices provided by the Oculus Keratograph in a sample of healthy and keratoconus eyes.

METHODS

This was a comparative, prospective, and single-masked study.

Subjects

Fifty eyes of 50 patients were randomized, included in the study, and classified into two groups: healthy eyes (n = 25) and keratoconus eyes (n = 25). The diagnoses of keratoconus were confirmed after a completed eye examination, which included Scheimpflug topographical analysis and biomicroscopy examination by independent corneal specialists. The keratoconus stage can be identified using the Amsler-Krumeich classification (Table 1).[12] The research team was blinded to the results of the eye examination conducted before the diagnosis of keratoconus.

Patients with any active ocular-surface disease (e.g., significant dry eye symptoms or keratitis), corneal opacities, pellucid marginal corneal degeneration, corneal astigmatism greater than 2.00 diopters (D) (except in the keratoconus group), glaucoma, use of medication that could affect ocular physiology, and a history of any type of ocular surgery were excluded. Eyes with stage IV keratoconus, according to the Amsler-Krumeich classification, were also excluded from the study.

Informed consent was obtained from each subject after approval for the study was granted by the Human Sciences Ethics Committee of the University of Valladolid. All subjects were treated in accordance with the Declaration of Helsinki.

Instrumentation

Three consecutive corneal measurements were performed with the Oculus Keratograph (Patient Data Management Software version 6.02r24 and Examination Software version 1.75r11). The Oculus Keratograph is a computerized Placido-based videokeratography device with 22 rings that evaluate 22,000 points on the anterior corneal surface with optional computerized corneal topography software system for the fitting procedure of RGP contact lenses.

The corneal indices resulting from the Oculus Keratograph assessment are summarized in Table 2. The same blinded

TABLE 2.
Corneal indices measured with the Oculus Keratograph

Corneal indices	Description
MaxP, D	Simulated keratometry in the steepening meridian in the 3.00-mm zone Calculated according to the formula $D = (1.3375 - 1)*(1000)/R$ mm
MinP, D	Simulated keratometry in the flattening meridian in the 3.00-mm zone Calculated according to the formula $D = (1.3375 - 1)*(1000)/R$ mm
MCPP, D	Maximum power point represents the maximum corneal power of the anterior surface Calculated according to the formula $D = (1.3375 - 1)*(1000)/R$ mm (in the entire measurement range, not in the 3.00-mm zone)
Eccentricity	Degree of corneal peripheral applanation, where 0 is a spherical cornea, positive is a prolate ellipse, and negative is an oblate ellipse
Corneal diameter, mm	Horizontal limbus-to-limbus distance
ISV	SD of the axial/sagittal radii of the measured eye from the mean value
IVA	Measurement of the symmetry of the corneal radii relative to the horizontal meridian as an axis of reflection
KI	Ratio of the sagittal radii mean values in the top and bottom segments
Smallest sagittal curvature—Rmin	Smallest sagittal curvature radius in the entire measurement range
Aberration coefficient, %	Value of the aberrations of the cornea calculated with Fourier and Zernike analysis of the anterior surface The aberration coefficient is zero if no (single) coefficient deviates from the respective normal value Healthy eyes have to show the value zero

and experienced operators performed all Oculus Keratograph measurements during all visits. The corneal topographer had been previously calibrated by the manufacturer to be suitable for use in this study. Patients were asked to perform a complete blink just before each measurement to spread an optically smooth tear film over the cornea. They move their chin from the chinrest between scans to eliminate interdependence of successive measurements.

Data Analysis

Statistical analysis was performed using the SPSS 14.0 (SPSS, Chicago, IL) statistical package for Windows.

We used the definition of repeatability from the British Standards Institution,[13,14] as recommended by Bland and Altman.[15] Repeatability is the condition under which independent test results are obtained by the same method on identical test items in the same laboratory by the same operator using the same equipment with the shortest time lapse possible between successive sets of readings.[13] We investigated repeatability by obtaining three Oculus Keratograph measurements in the same study visit; the differences between three measurements were determined with one-way analysis of variance (ANOVA) (p values < 0.05 were considered statistically significant). The intraclass correlation coefficient was also calculated. The coefficient of variation (CV) of repeatability was calculated by dividing the SD by the mean value

TABLE 3.

Repeatability data of the Oculus Keratograph in keratoconus (n = 25) and healthy (n = 25) eyes

Group (n = 25)	Mean ± SD	95% CI	ICC	CV, %	Mean Diff ± SD	LoA
MaxP, D						
Keratoconus	47.84 ± 2.87	47.18 to 48.50	0.99	0.47	0.00 ± 0.23	0.45 to −0.45
Healthy	43.98 ± 1.43	43.93–44.32	0.99	0.21	0.00 ± 0.10	0.20 to −0.20
p*	<0.01	—	—	<0.01	1.00	—
MinP, D						
Keratoconus	45.30 ± 2.42	44.74–45.86	0.98	0.36	0.00 ± 0.24	0.46 to −0.46
Healthy	43.21 ± 1.31	42.91–43.50	0.99	0.19	0.00 ± 0.09	0.17 to −0.17
p*	<0.01	—	—	<0.01	1.00	—
MCPP, D						
Keratoconus	56.07 ± 5.99	54.69–57.44	0.96	0.77	0.00 ± 0.60	1.17 to −1.17
Healthy	44.68 ± 1.31	44.38–44.98	0.96	0.22	0.00 ± 0.35	0.68 to −0.68
p*	<0.01	—	—	0.22	1.00	—
Eccentricity						
Keratoconus	0.57 ± 0.31	0.50–0.64	0.93	14.53	0.00 ± 0.07	0.14 to −0.14
Healthy	0.48 ± 0.12	0.45–0.51	0.96	5.79	0.00 ± 0.03	0.06 to −0.06
p*	0.02	—	—	0.16	1.00	—
Corneal diameter, mm						
Keratoconus	11.76 ± 0.48	11.65–11.87	0.99	0.33	0.00 ± 0.04	0.09 to −0.09
Healthy	11.82 ± 0.49	11.71–11.94	0.99	0.27	0.00 ± 0.04	0.07 to −0.07
p*	0.45	—	—	0.43	1.00	—
ISV						
Keratoconus	76.95 ± 26.74	70.80–83.10	0.98	3.10	0.00 ± 3.01	5.89 to −5.89
Healthy	17.17 ± 4.48	16.14–18.20	0.98	4.82	0.00 ± 0.88	1.72 to −1.72
p*	<0.01	—	—	0.03	1.00	—
IVA						
Keratoconus	0.89 ± 0.36	0.81–0.97	0.99	3.80	0.00 ± 0.03	0.07 to −0.07
Healthy	0.12 ± 0.05	0.11–0.13	0.97	7.05	0.00 ± 0.01	0.02 to −0.02
p*	<0.01	—	—	<0.01	1.00	—
KI						
Keratoconus	1.20 ± 0.10	1.17–1.22	0.99	0.72	0.00 ± 0.01	0.02 to −0.02
Healthy	1.02 ± 0.02	1.01–1.02	0.97	0.29	0.00 ± 0.00	0.01 to −0.01
p*	<0.01	—	—	0.07	1.00	—
Smallest sagittal curvature radius—Rmin, mm						
Keratoconus	6.33 ± 0.50	6.22–6.45	0.98	0.78	0.00 ± 0.06	0.13 to −0.13
Healthy	7.59 ± 0.23	7.53–7.64	0.98	0.53	0.00 ± 0.04	0.08 to −0.08
p*	<0.01	—	—	0.64	1.00	—
Aberration coefficient, %						
Keratoconus	2.25 ± 0.54	2.25–2.37	0.96	4.00	0.00 ± 0.10	0.19 to −0.19
Healthy	0.00	—	—	0.00	—	—
p*	<0.01	—	—	<0.01	—	—

*Kruskal-Wallis ANOVA.

CI, confidence interval; ICC, intraclass correlation coefficient; LoA, limits of agreement.

(normalized SD) and multiplying it by 100 to represent the percentage value of the variation [CV = SD/mean × 100 (%)].

As suggested by Bland and Altman,[15] graphs of the differences between pairs of measurements obtained in the same session divided by the average of the means of each pair of readings were plotted (three data points per subject) to ensure that there was no relationship between the differences and the ranges of measurement. The limits of agreement were calculated (mean of the difference ± 1.96*SDs).[15]

Differences between the healthy and keratoconus eyes in all the topographic outcomes (maximum corneal power [MaxP] and minimum corneal power [MinP], maximum corneal power point [MCPP], eccentricity, horizontal corneal diameter, index of surface variance [ISV], index of vertical asymmetry [IVA], keratoconus index [KI], Rmin, and aberration coefficient) and between the CVs were compared with nonparametric Kruskal-Wallis ANOVAs (p values < 0.05 were considered statistically significant). If statistical differences between healthy and keratoconus eyes were detected in topographic outcomes, a pairwise analysis was conducted to show the differences with the stages of the keratoconus eyes according to the Amsler-Krumeich classification (Games-Howell ANOVA; p values < 0.05 were considered statistically significant).

RESULTS

Fifty patients (28 women, 22 men) were included in the study. The mean (±SD) age of the total sample was 31.6 (±10.1) years (range, 19 to 55 years).

Twenty-five eyes of 25 patients (19 women, 6 men) comprised the healthy group, with a mean (±SD) age of 28.7 (±7.0) years (range, 20 to 44 years) and a mean (±SD) spherical equivalent refractive error of −1.07 (±1.50) D (range, +1.00 D to −4.50 D).

Twenty-five eyes of 25 patients (9 women, 16 men) comprised the keratoconus group (4 keratoconus eyes in stage I, 14 eyes in stage II, and 7 eyes in stage III, according to the Amsler-Krumeich classification) with a mean (±SD) age of 35.6 (±10.5) years (range,

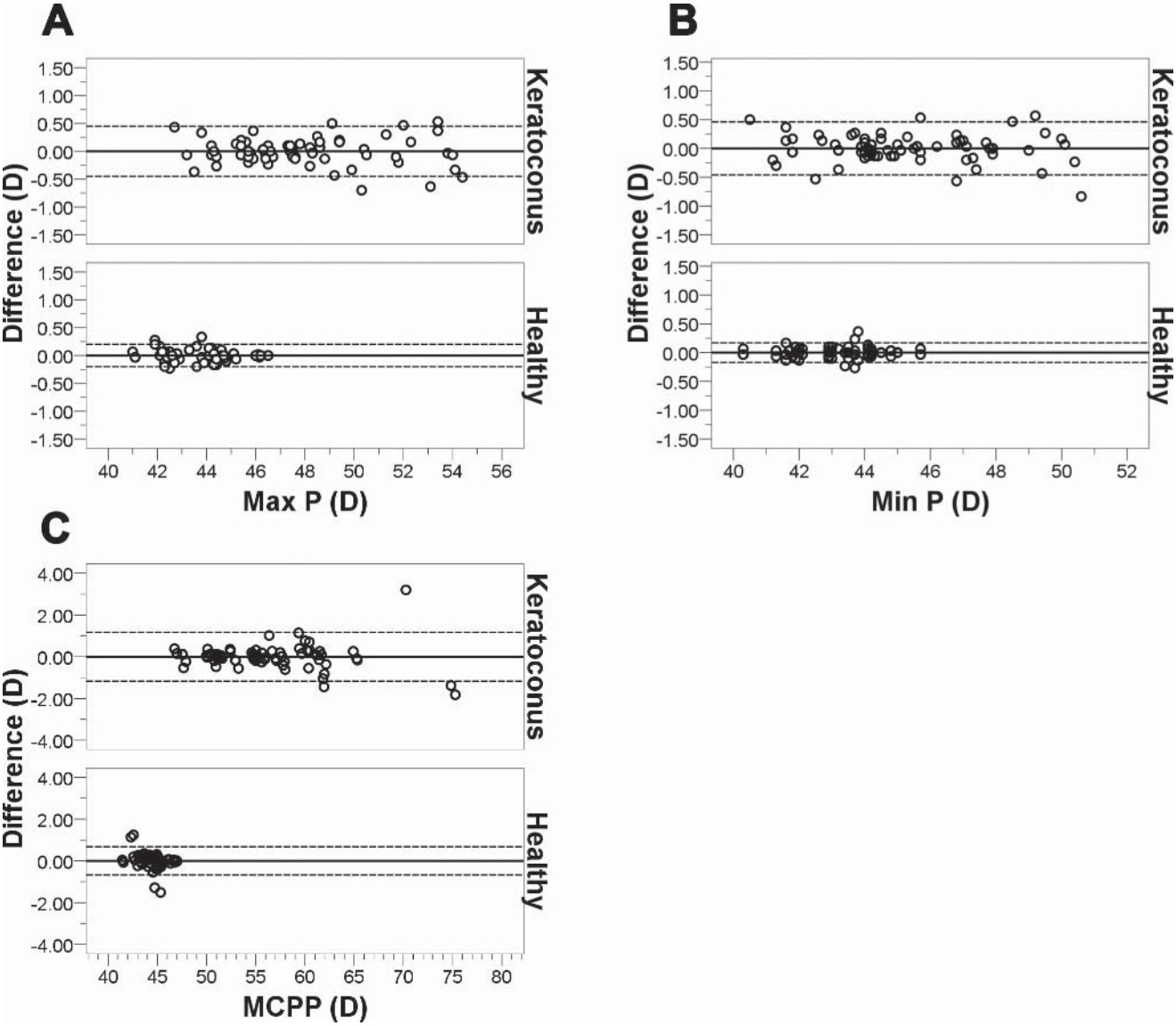

FIGURE 1.

Bland-Altman plot comparing the MaxP and MinP and MCPP repeatability between healthy and keratoconus eyes. The mean difference (solid line) and limits of agreement (discontinuous line) were represented for the MaxP (A), MinP (B), and MCPP (C).

19 to 55 years) and a mean (±SD) spherical equivalent refractive error of −4.33 (±4.23) D (range, −0.50 to −13.25 D).

Corneal Topography Outcomes

All the Oculus Keratograph indices in healthy and keratoconus eyes are summarized in Table 3. The differences between the healthy and keratoconus topographical indices were statistically significant ($p < 0.02$, Kruskal-Wallis ANOVA), except in the horizontal corneal diameter ($p = 0.45$, Kruskal-Wallis ANOVA). These differences were statistically significant between healthy eyes and stage I Amsler-Krumeich ($p < 0.03$, Games-Howell ANOVA) except in MaxP ($p = 0.15$), MinP ($p = 0.27$), eccentricity ($p = 0.17$), and Rmin ($p = 0.06$). Healthy eyes showed statistically significant differences with stage II Amsler-Krumeich eyes in all variables except in MinP ($p = 0.12$) and eccentricity ($p = 0.86$). Finally, healthy eyes showed statistically significant differences with stage III Amsler-Krumeich eyes in all topographical indices.

Corneal Topography Repeatability

Good repeatability was found in the MaxP, MinP, MCPP (Fig. 1), eccentricity, horizontal corneal diameter (Fig. 2), ISV, IVA, KI, Rmin (Fig. 3), and aberration coefficient, without statistically significant differences between the three measurements ($p > 0.94$, ANOVA) in all topographical outcomes. Keratoconus eyes showed higher CV and limits of agreement than healthy eyes (Table 3 and Figs. 1, 2, and 3) except in ISV and IVA coefficients. Eccentricity showed a CV of 5.79% in healthy eyes and a CV of 14.53% in keratoconus eyes. The aberration coefficient had a value of zero in healthy eyes and a good repeatability in keratoconus eyes.

Statistically significant differences in the CV (Table 3) between groups ($p < 0.05$, Kruskal-Wallis ANOVA) were found for all Oculus Keratograph outcomes, except for MCPP ($p = 0.22$), eccentricity ($p = 0.16$), horizontal corneal diameter ($p = 0.43$), KI ($p = 0.07$), and Rmin ($p = 0.63$).

DISCUSSION

Placido-based anterior corneal topography is an affordable and valuable tool for the screening and management of keratoconus.[1,6,7,16] To the best of our knowledge, the repeatability of the topographic corneal measurements assessed using the Oculus Keratograph in keratoconus patients has not been previously reported.

Placido-based videokeratography is a reflection-based technique that is therefore likely to suffer from a similar decrease in repeatability with increased corneal steepness, irregularity, and scarring. Our study demonstrated that the Oculus Keratograph is a repeatable device in both healthy and moderately keratoconus eyes that can be used to detect keratoconus in addition to a clinical examination and can be helpful in the management of this disease.

A corneal power higher than 45.00 D is considered a key finding in suspected ectatic conditions[9]; hence, a repeatable measurement of simulated keratometry is necessary for the assessment of these patients. Good repeatability was found for Keratograph-simulated keratometry (MaxP and MinP) in both healthy (CV < 0.22%) and keratoconus (CV < 0.47%) eyes. The repeatability of Keratograph in healthy eyes was recently tested by Mao et al.[11] who reported similar CV (0.23% in MaxP and 0.22% in MinP), according with our results.

Wang et al.[17] also found a similar CV in the simulated keratometry for MaxP (CV = 0.29%) and MinP (CV = 0.23%) using the Allegro Topolyzer (with similar capturing camera and analysis software to Keratograph) in 35 healthy eyes, in accordance with our results. Kawamorita et al.[18] found a higher CV (>0.35%) in healthy eyes with the Pentacam (Oculus Optikgeräte GmbH) and Keratron (Optikon 2000 SpA), whereas Montalban et al.,[19] using a Sirius topographic system (Costruzione Strumenti Oftalmici), found a CV of 0.36% for the MaxP and MinP of healthy eyes.

However, there is a lack of studies that directly analyze the repeatability of corneal topographic outcomes in keratoconus eyes. Szalai et al.[20] reported a coefficient of repeatability higher than 1% for simulated keratometry with the Pentacam (1.56 and 2.08%

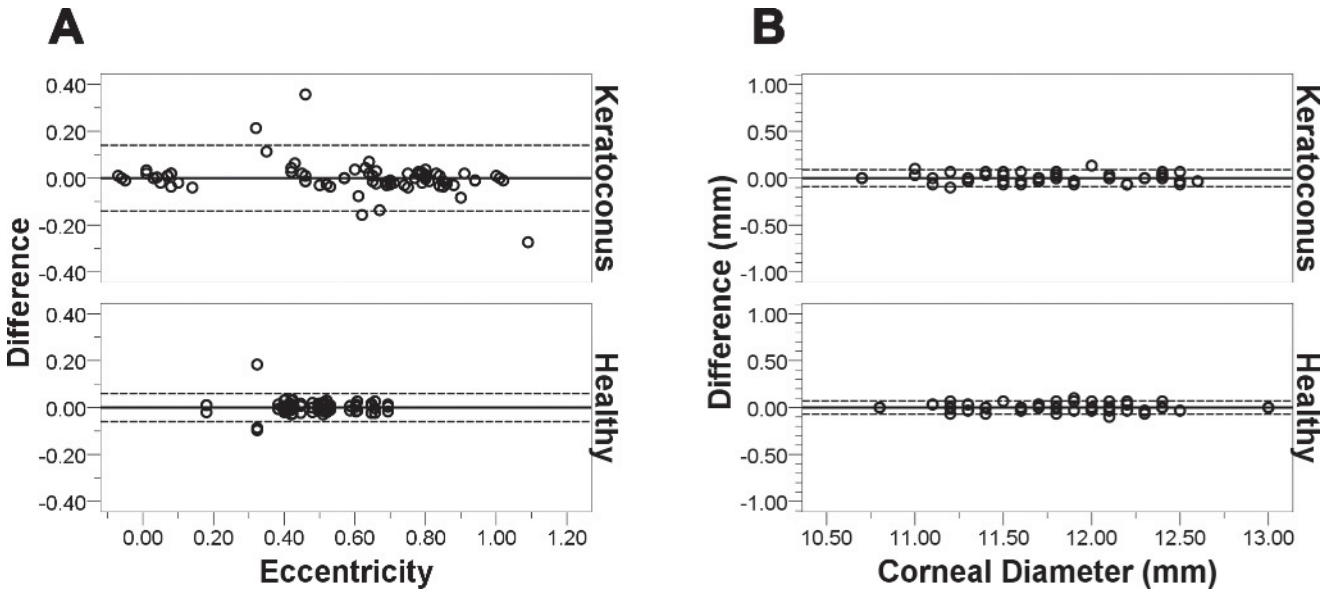

FIGURE 2.

Bland-Altman plot comparing the horizontal corneal diameter and eccentricity repeatability between healthy and keratoconus eyes. The mean difference (solid line) and limits of agreement (discontinuous line) were represented for the horizontal corneal diameter (A) and eccentricity (B).

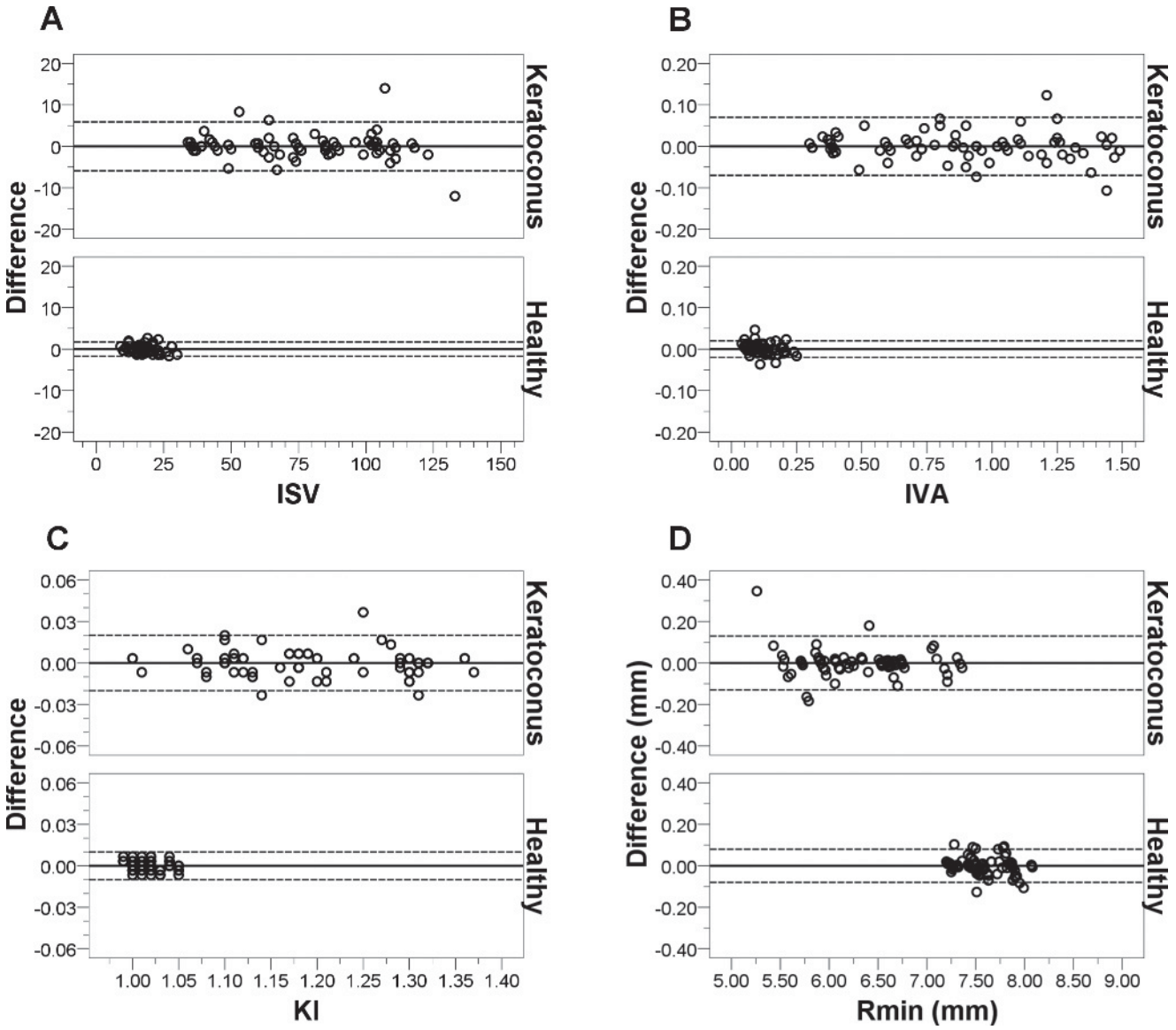

FIGURE 3.

Bland-Altman plot comparing ISV, IVA, KI, and Rmin repeatability between healthy and keratoconus eyes. The mean difference (solid line) and limits of agreement (discontinuous line) were represented for the ISV (A), IVA (B), KI (C), and Rmin (D).

for the MaxP and MinP, respectively) and the anterior-segment OCT system (1.09 and 1.27% for the MaxP and MinP, respectively) in 84 keratoconus eyes. McMahon et al.[21] reported CVs of 0.80 and 1.22% for the MaxP and MinP, respectively, using TMS-1 topography. Thus, the Oculus Keratograph has a better repeatability (0.47 and 0.36% for the MaxP and MinP, respectively) in simulated keratometry in keratoconus eyes than that found in previous reports.

The horizontal corneal diameter was not different between healthy and keratoconus eyes ($p = 0.45$), suggesting a limited utility in keratoconus detection. Horizontal corneal diameter is an important parameter in the selection of the diameter of RGP, and the Oculus Keratograph showed excellent repeatability in both study groups (CV < 0.36%).

To our knowledge, the repeatability of the eccentricity has not been reported previously with any topography device in either healthy or keratoconus eyes. Eccentricity is a relevant parameter in the selection of initial trial RGP contact lenses.[22,23] However, the high CV suggests that this value should be used with caution in RGP contact lens fitting using this device.

The Oculus Keratograph provides a variety of corneal indices developed especially for the detection of keratoconus. Different cutoff values for each index were proposed to help in the keratoconus diagnosis, including a score higher than 37 for the ISV index, a score higher than 0.28 for the IVA index, a score higher than 1.06 for the KI index, and a score lower than 6.71 mm for the Rmin.[24] Our results are in agreement with these values with statistically significant differences between healthy and keratoconus eyes for all of these outcomes. Index of surface variance showed greater differences than other Keratograph's corneal outcomes between both study groups. These topographic indices (especially KI and Rmin with a CV < 1.00%) are repeatable in both healthy and keratoconus eyes. These results suggest that these indices may aid in the detection of keratoconus with the Oculus Keratograph.

Complementary clinical information is provided by refractive wavefront maps.[25] Keratoconus induces severe corneal

irregularities and, consequently, elevated corneal aberrations.[2] The Oculus Keratograph analyzed Zernike polynomials to describe several orders of corneal wavefronts, in particular the third-order values, or coma, as these aberrations are the most affected by ectatic conditions such as keratoconus.[21] Additionally, the software calculates the so-called aberration coefficient from Fourier and Zernike coefficients. Values exceeding a score of 1.0 suggest an irregular corneal surface with a reduction of the corneal optical quality.[24] The aberration coefficient was higher in keratoconus eyes than in healthy eyes (with a value of zero). Thus, wavefront analysis can be beneficial in the early detection, diagnosis, and management of keratoconus patients.

CONCLUSIONS

The Oculus Keratograph provides repeatable measurements of the principal corneal indices (simulated keratometry, MCPP, horizontal corneal diameter, eccentricity, ISV, IVA, KI, Rmin, and aberration coefficient) in healthy and keratoconus eyes. These measurements may improve the topographical diagnosis of keratoconus when used in combination with a clinical examination and may also facilitate keratoconus patient management.

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REFERENCES

1. Rabinowitz YS. Keratoconus. Surv Ophthalmol 1998;42:297–319.
2. Romero-Jiménez M, Santodomingo-Rubido J, Wolffsohn JS. Keratoconus: a review. Cont Lens Anterior Eye 2010;33:157–66.
3. Barnett M, Mannis MJ. Contact lenses in the management of keratoconus. Cornea 2011;30:1510–6.
4. Zadnik K, Barr JT, Edrington TB, Everett DF, Jameson M, McMahon TT, Shin JA, Sterling JL, Wagner H, Gordon MO. Baseline findings in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study. Invest Ophthalmol Vis Sci 1998;39:2537–46.
5. Nejabat M, Khalili MR, Dehghani C. Cone location and correction of keratoconus with rigid gas-permeable contact lenses. Cont Lens Anterior Eye 2012;35:17–21.
6. Sorbara L, Dalton K. The use of video-keratoscopy in predicting contact lens parameters for keratoconic fitting. Cont Lens Anterior Eye 2010;33:112–8.
7. Nosch DS, Ong GL, Mavrikakis I, Morris J. The application of a computerised videokeratography (CVK) based contact lens fitting software programme on irregularly shaped corneal surfaces. Cont Lens Anterior Eye 2007;30:239–48.
8. Chastang PJ, Borderie VM, Carvajal-Gonzalez S, Rostène W, Laroche L. Automated keratoconus detection using the EyeSys videokeratoscope. J Cataract Refract Surg 2000;26:675–83.
9. Holladay JT. Keratoconus detection using corneal topography. J Refract Surg 2009;25:S958–62.
10. Best N, Drury L, Wolffsohn JS. Clinical evaluation of the Oculus Keratograph. Cont Lens Anterior Eye 2012;35:171–4.
11. Mao X, Savini G, Zhuo Z, Feng Y, Zhang J, Wang Q, Chen H, Huang J. Repeatability, reproducibility, and agreement of corneal power measurements obtained with a new corneal topographer. J Cataract Refract Surg 2013;39:1561–9.
12. Choi JA, Kim MS. Progression of keratoconus by longitudinal assessment with corneal topography. Invest Ophthalmol Vis Sci 2012;53:927–35.
13. British Standards Institution. Accuracy (Trueness and Precision) of Measurement Methods and Results: General Principles and Definitions, Part 1. London: BSI; 1995.
14. British Standards Institution. Accuracy (Trueness and Precision) of Measurement Methods and Results: Basic Methods for the Determination of Repeatability and Reproducibility of a Standard Measurement Method, Part 2. London: BSI; 1995.
15. Bland M, Altman D. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307–10.
16. Piñero DP, Nieto JC, Lopez-Miguel A. Characterization of corneal structure in keratoconus. J Cataract Refract Surg 2012;38:2167–83.
17. Wang Q, Savini G, Hoffer KJ, Xu Z, Feng Y, Wen D, Hua Y, Yang F, Pan C, Huang J. A comprehensive assessment of the precision and agreement of anterior corneal power measurements obtained using 8 different devices. PLoS One 2012;7:e45607.
18. Kawamorita T, Nakayama N, Uozato H. Repeatability and reproducibility of corneal curvature measurements using the Pentacam and Keratron topography systems. J Refract Surg 2009;25:539–44.
19. Montalban R, Pinero DP, Javaloy J, Alio JL. Intrasubject repeatability of corneal morphology measurements obtained with a new Scheimpflug photography-based system. J Cataract Refract Surg 2012;38:971–7.
20. Szalai E, Berta A, Hassan Z, Módis L, Jr. Reliability and repeatability of swept-source Fourier-domain optical coherence tomography and Scheimpflug imaging in keratoconus. J Cataract Refract Surg 2012;38:485–94.
21. McMahon TT, Anderson RJ, Roberts C, Mahmoud AM, Szczotka-Flynn LB, Raasch TW, Friedman NE, Davis LJ. Repeatability of corneal topography measurement in keratoconus with the TMS-1. CLEK Study Group. Optom Vis Sci 2005;82:405–15.
22. Chan JS, Mandell RB, Johnson L, Reed C, Fusaro R. Contact lens base curve prediction from videokeratography. Optom Vis Sci 1998;75:445–9.
23. de Brabander J, Kok JH, Nuijts RM. Evaluation of a new system of lens parameter selection and comparison of traditional vs one-step lens care systems for aspheric high-Dk RGP contact lenses. CLAO J 2000;26:193–9.
24. Murta J, Martins A. Measurement and topography guided treatment of irregular astigmatism. In: Goggin M, ed. Astigmatism—Optics, Physiology and Management. Rijeka, Croatia: InTech Open Access Publisher; 2012:247–66.
25. Ramos-López D, Martínez-Finkelshtein A, Castro-Luna GM, Burguera-Gimenez N, Vega-Estrada A, Piþero D, Aliœ JL. Screening subclinical keratoconus with placido-based corneal indices. Optom Vis Sci 2013;90:335–43.

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5.2. Repetibilidad de la medida de las aberraciones corneales en queratocono

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Repeatability of wavefront aberration measurements with a Placido-Based topographer in normal and keratoconic eyes.

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Repeatability of Wavefront Aberration Measurements With a Placido-Based Topographer in Normal and Keratoconic Eyes

Sara Ortiz-Toquero, MSc; Guadalupe Rodriguez, MSc; Victoria de Juan, PhD; Raul Martin, PhD

ABSTRACT

PURPOSE: To determine and compare the repeatability of anterior corneal higher order aberrations (HOAs) using a Placido-based topographer (Allegro Topolyzer; WaveLight Technologie AG, Alcon Laboratories, Erlangen, Germany) in a sample of normal and keratoconic eyes.

METHODS: Three repeated measurements of each cornea of normal and keratoconic eyes were taken with the Allegro Topolyzer. Repeatability of the HOAs (3rd- and 4th-order individual values and normalized polar Zernike coefficients, coma-like, root mean square (RMS) up to 8th-order values, HOA RMS, and total RMS for 6-mm pupil diameter) and central corneal power (3-mm pupil) were analyzed. Within-subject standard deviation (S_w), precision, repeatability, coefficient of variation (CV), and the intraclass correlation coefficient (ICC) were calculated.

RESULTS: Zernike coefficients were significantly different between the normal (36 eyes of 36 patients) and keratoconus (36 eyes of 36 patients) groups ($P \leq .03$) except in Z^{+1}_3, Z^{+3}_3, Z^{-4}_4, and Z^{+4}_4. In the normal group, S_w was 0.031 μm or less, CV ranged from 6.49% (spherical aberration) to 37.18% (secondary astigmatism), and ICC values ranged from 0.227 to 0.982. In the keratoconus group, S_w was 0.059 μm or less, CV ranged from 2.06% (total RMS) to 25.82% (tetrafoil), and ICC values ranged from 0.839 to 0.996. In analyzing the keratoconus stages (Amsler–Krumeich classification), the repeatability of the Zernike coefficients tended to improve with increasing keratoconus stage.

CONCLUSIONS: The repeatability of corneal wavefront aberration provided by the Allegro Topolyzer was better in keratoconic eyes (good and moderate repeatability) than in normal eyes (moderate and poor repeatability). These results are important to eye care practitioners and refractive surgeons during refractive surgery planning or keratoconus detection, classification, and management.

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Wavefront aberrations can be defined as differences from the perfect optical system, in which the rays that form the image of a point coincide in a single point.[1] In the eye, wavefront aberrations can be divided into two types: low order aberrations, which can be corrected using spectacles (sphere and cylinder), and higher order aberrations (HOAs), which cannot be corrected with standard methods.[1,2] Wavefront analysis allows a detailed assessment of the corneal surface (corneal wavefront) or the entire eye (wavefront).[1]

Currently, HOA assessment is important in corneal refractive surgery in the development of custom ablations based on corneal topography,[3] intraocular lens implantation,[4] contact lens fitting,[5] myopia control,[6] or the diagnosis and follow-up of irregular or ectatic corneal conditions (eg, keratoconus, pellucid marginal degeneration, or iatrogenic ectasia).[7] Moreover, the aberration measurements of the anterior corneal surface have been used in the identification and gradation of the severity of keratoconus disease,[8,9] particularly in early cases without slit-lamp findings.[10]

The Allegro Topolyzer (WaveLight Technologie AG, Alcon Laboratories, Erlangen, Germany) is a computerized Placido-based videokeratography system that was developed for use in refractive surgery procedures. The Allegro Topolyzer cor-

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neal topographer is exportable and can be linked with the WaveLight Excimer Laser systems, allowing customized, topography-guided surgical treatments.[3]

The success of clinical applications of wavefront analysis depends on the repeatability of the topographic corneal data measurements.[2] Moreover, knowledge of repeatability is mandatory to introduce any device into clinical practice,[11] but, to the best of our knowledge, there are no previous reports on the intrasubject repeatability of the Allegro Topolyzer for wavefront aberrations in normal and keratoconic eyes. Thus, the aim of the current study was to determine and compare the repeatability of the anterior corneal surface HOAs provided by the Allegro Topolyzer in a sample of normal and keratoconic eyes.

PATIENTS AND METHODS

This study was a prospective, clinic-based, observational and single-masked investigation.

Patients

The patients in this study were divided into the following two study groups: normal and keratoconic eyes. A randomly selected single eye of each patient was chosen for the study. Independent corneal specialists confirmed the diagnosis of keratoconus after a complete eye examination, which included Scheimpflug analysis and anterior eye biomicroscopy assessment. The keratoconus stage was identified using the Amsler–Krumeich classification.[12]

Patients with any active ocular surface disease, corneal opacities, glaucoma, use of medication that could affect ocular physiology, or a history of any type of ocular surgery, pellucid marginal corneal degeneration, or corneal astigmatism greater than 2.00 diopters (D) (except in the keratoconus group) were excluded. Eyes with stage 4 keratoconus according to the Amsler–Krumeich classification were also excluded from the study to guarantee an optimal quality of corneal topography. Normal patients showed a corrected distance visual acuity of 20/20 and refractive errors of ±5.00 diopters. Contact lens wear was discontinued for at least 2 weeks before the eye examination.

Informed consent was obtained from each patient after the Human Sciences Ethics Committee of the University of Valladolid approved the study. All patients were treated in accordance with the tenets of the Declaration of Helsinki.

Instrumentation

The Allegro Topolyzer is a diagnostic device based on the Placido disk system supported by 22 measurement rings with 22,000 elevation points. Its software module allows data transfer from the Allegro Topolyzer to the WaveLight Excimer Laser systems and enables customized topography-guided treatments. A Zernike analysis of the anterior corneal surface up to the 8th order was computed.

Measurement Procedure

Three separate measurements of each cornea were taken with the Allegro Topolyzer topographer (Examination Software Version 1.76r45 FW1.19) following the manufacturer's guidelines in a darkened room. The patients were asked to perform a complete blink just before each measurement to spread an optically smooth tear film over the cornea. The patients moved their chin from the chinrest between scans to eliminate the interdependence of successive measurements. The patients were repositioned and the device was realigned after each measurement. Poor quality topographies with an "Analyze Area" value less than 70% were deleted (these included artefacts from tear film or movement and shadows from eyelids, eyelashes, or nose). The same experienced operator performed all measurements and the device was calibrated before the study.

Measurements Obtained

The individual values of Zernike coefficients of the 3rd [Z^{-3}_{3}; Z^{-1}_{3}; Z^{+1}_{3}; Z^{+3}_{3}] and 4th [Z^{-4}_{4}; Z^{-2}_{4}; Z^{0}_{4}; Z^{+2}_{4}; Z^{+4}_{4}] orders of each corneal assessment were collected from the Allegro Topolyzer display (Option Display – Zernike Analysis of the Software Version 1.76r45 FW1.19). The normalized polar Zernike coefficients (coma [$Z^{\pm1}_{3}$]; trefoil [$Z^{\pm3}_{3}$], secondary astigmatism [$Z^{\pm2}_{4}$]; and tetrafoil [$Z^{\pm4}_{4}$]) that combine the paired terms in the same order to give a single value (ie, the 3rd-order coma [$Z^{\pm1}_{3}$] was obtained with the combination of vertical coma [Z^{-1}_{3}] and horizontal coma [Z^{+1}_{3}]) were also recorded. Root mean square (RMS) (3rd to 8th order), HOA RMS (3rd to 8th order), and total RMS (1st to 8th order) also calculated for each corneal assessment. Coma-like (3rd, 5th, and 7th order) was analyzed for its usefulness in keratoconus classification.[9] All wavefront measurements were recorded with a 6-mm optic diameter. Maximum and minimum anterior corneal powers in the 3-mm zone were also recorded in all patients. The Allegro Topolyzer provided the individual values of Zernike coefficients in Malacara notation,[13] but the results are presented in Optical Society of America standard notation to compare with previous studies.[14,15] Malacara notation was converted to Optical Society of America standard notation following the manufacturer recommendations (the orientation of the Zernike coefficients were swapped, maintaining the coefficient value in microns).

Statistical Analysis

Statistical analysis was performed using SPSS for Windows software (version 15.0; SPSS, Inc., Chicago, IL). The intraobserver repeatability of the set of three consecutive measurements of each wavefront coefficient was calculated using the following five parameters: within-subject standard deviation (S_w),[16] intrasubject precision ($1.96 \times S_w$, which shows the error range for 95% of the repeated measurements and the true value),[16] repeatability ($2.77 \times S_w$, which defines the difference between two measurements of the same patient for 95% of pairs of observation),[16] coefficient of variation (CV; percentage value of the measurement's variation and defined as the ratio of the S_w to the overall mean [$CV = S_w/\text{mean} \times 100$ (%)]),[16] and the intraclass correlation coefficient (ICC; classified as follows: less than 0.75 = poor agreement; 0.75 to less than 0.90 = moderate agreement; 0.90 or greater = high agreement).[17] The CV of the individual Zernike coefficients was not computed because the mean values for individual Zernike coefficients can be positive or negative.

A normal distribution of variables was assessed using the Kolmogorov–Smirnov test ($P > .05$ indicated that the data were normally distributed). Differences between normal and keratoconic eyes in all HOA data and between all calculated repeatability coefficients (S_w, precision, repeatability, CV, and ICC) were compared with non-parametric Mann–Whitney *U* tests ($P < .05$ were considered significant). Differences between the aberrometric measurements by the keratoconus stage according to the Amsler–Krumeich classification were also calculated with a non-parametric Kruskal–Wallis analysis of variance ($P < .05$ were considered significant) to assess the diagnostic and classification utility of the HOAs in management of patients with keratoconus. If significant differences between keratoconus stages were detected, a pairwise analysis was conducted (Mann–Whitney *U* with Bonferroni correction was used, and a *P* value of .05/3 = .0017 was used to judge significance).

RESULTS

Intraobserver repeatability was analyzed in 72 eyes of 72 patients divided into two study groups (normal and keratoconus). In the normal group, 36 eyes of 36 patients (28 women, 8 men) were included, with a mean age of 29.4 ± 8.2 years (range: 19 to 50 years) and a mean spherical equivalent refractive error of -1.47 ± 1.75 D (range: +1.50 to -5.00 D). Thirty-six eyes of 36 patients with keratoconus (11 women, 25 men) comprised the keratoconus group (12 keratoconic eyes in stage I, 12 eyes in stage II, and 12 eyes in stage III, according to the Amsler–Krumeich classification); the mean age of this group was 36.9 ± 10.5 years (range: 19 to 58 years) and the mean spherical equivalent refractive error was -4.45 ± 4.25 D (range: -0.50 to -14.00 D). Maximum and minimum anterior corneal powers and their repeatability assessment by group are shown in **Table 1**.

Table A (available in the online version of this article) shows the intraobserver repeatability results for the wavefront aberrations in normal and keratoconic eyes. All modal pairs were significantly different between the normal and keratoconus groups ($P \leq .03$) except in Z^{+1}_3, Z^{+3}_3, Z^{-4}_4, and Z^{+4}_4. In the normal group, the S_w was 0.031 µm or less, the CV ranged from 6.49% for spherical aberration to 37.18% for secondary astigmatism, and the ICC values ranged from 0.502 to 0.982 for Zernike coefficients and from 0.227 to 0.925 for RMS values. In the keratoconus group, the S_w was 0.059 µm or less, the CV ranged from 2.06% for HOA total RMS to 25.82% for tetrafoil, and the ICC values ranged from 0.943 to 0.996 for Zernike coefficients and from 0.839 to 0.996 for RMS values.

Intraobserver repeatability results of the wavefront aberrations analyzed by keratoconus stage are summarized in **Table B** (available in the online version of this article). The mean value of all normalized polar Zernike coefficients and RMS values tended to increase (in absolute magnitude) from stage I to stage III (**Figure 1**). The S_w was 0.064 µm or less in three stages of keratoconus and the CV decreased (better repeatability) with increasing keratoconus stage in coma, trefoil, coma-like, and 3rd- and 4th-order HOAs, and total RMS value (**Figure 2**).

DISCUSSION

In the current study, the repeatability of maximum and minimum corneal powers provided by the Allegro Topolyzer were analyzed, and we found excellent repeatability and agreement measurements in normal and keratoconic eyes (**Table 1**). Only one study of corneal power repeatability using the Allegro Topolyzer has been published and demonstrated similar results to our study in a normal sample of patients ($CV \leq 0.29\%$ and $ICC \geq 0.993$); however, the study did not investigate repeatability in keratoconic eyes.[18]

For the total anterior corneal wavefront measurements, we found that the repeatability tended to be better in keratoconic eyes than in normal eyes (**Table A**). In both groups, the repeatability of Zernike coefficients was better at the center of the Zernike pyramid than for coefficients along the periphery of the Zernike pyramid at the 3rd and 4th order.

TABLE 1

Intraobserver Repeatability for Maximum and Minimum Corneal Power (D) in Normal and Keratoconic Eyes

Parameter	Mean ± SD (D) (Range)	S_w (D)	Precision (D)	Repeatability (D)	CV (%)	ICC (95% CI)
Maximum corneal power (D)						
Keratoconus	47.61 ± 3.16 (42.70 to 55.57)	0.21	0.42	0.59	0.44	0.998 (0.996 to 0.999)
Normal	44.11 ± 1.32 (41.06 to 46.00)	0.13	0.25	0.35	0.29	0.996 (0.992 to 0.998)
P[a]	< .01	.03	.04	.04	.01	–
Stage I	45.55 ± 2.10 (42.70 to 49.10)	0.19	0.38	0.54	0.43	0.994 (0.985 to 0.998)
Stage II	47.74 ± 3.06 (42.90 to 53.80)	0.19	0.37	0.52	0.39	0.998 (0.994 to 0.999)
Stage III	49.54 ± 3.06 (45.70 to 55.57)	0.25	0.49	0.70	0.50	0.997 (0.992 to 0.999)
P[b]	< .01[c]	.51	.51	.51	.66	–
Minimum corneal power (D)						
Keratoconus	45.05 ± 2.79 (40.33 to 51.93)	0.08	0.16	0.23	0.43	0.997 (0.995 to 0.998)
Normal	43.33 ± 1.35 (40.23 to 45.70)	0.11	0.21	0.30	0.25	0.997 (0.994 to 0.998)
P[a]	< .01	.36	.36	.36	.04	–
Stage I	44.13 ± 1.97 (40.33 to 47.87)	0.06	0.12	0.17	0.43	0.994 (0.985 to 0.998)
Stage II	45.17 ± 3.15 (40.43 to 51.00)	0.09	0.17	0.24	0.41	0.997 (0.993 to 0.999)
Stage III	45.86 ± 3.06 (40.70 to 51.93)	0.10	0.20	0.29	0.44	0.998 (0.994 to 0.999)
P[b]	.28	.16	.16	.16	.87	–

D = diopters; SD = standard deviation; S_w = within-subject standard deviation; CV = coefficient of variation; ICC = intraclass correlation coefficient; CI = confidence interval

[a]*Mann–Whitney U analysis of variance between normal and keratoconic eyes.*

[b]*Kruskal–Wallis analysis of variance between stages of keratoconus.*

[c]*Mann–Whitney U analysis of variance. Statistically significant difference between stages I and III.*

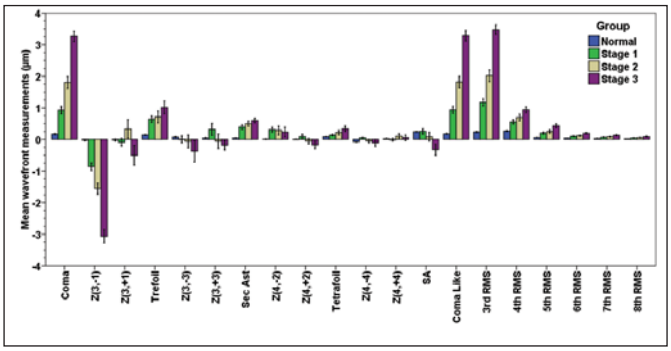

Figure 1. Mean value of corneal wavefront measurements (µm) in keratoconus stages. RMS = root mean square; sec ast = secondary astigmatism; SA = spherical aberration

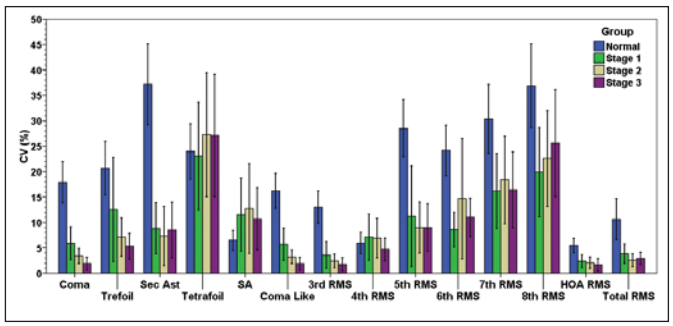

Figure 2. Mean value of coefficient of variation (%) of Zernike coefficients in keratoconus stages. CV = coefficient of variation; sec ast = secondary astigmatism; SA = spherical aberration; RMS = root mean square; HOA = higher order aberration

Comparing the results of wavefront aberration repeatability with previous studies[19-24] is complicated because there is no consensus on how to analyze the data, as shown in **Tables C-D** (available in the online version of this article). Some studies show aberrations as individual values [ie, Z^{-1}_3 and Z^{+1}_3],

whereas others show the normalized polar Zernike coefficients [ie, $Z^{\pm1}_3$] and analyze the anterior cornea surface, the posterior cornea surface, or the entire cornea (both surfaces), depending on the device used. Furthermore, not all published studies calculated the CV of the normalized polar Zernike coefficients, which causes a loss of important information. The advantage of the CV is that it is a unitless number and is consequently independent of the units of observation in which the measurement has been taken. In contrast, the S_w of data (calculated in all studies included in **Tables C-D**) must always be understood in the context of the mean of the Zernike data in the sample analyzed (ie, keratoconic eyes have a higher mean value than normal eyes). Therefore, it is difficult to compare the results of various published studies using different samples and devices, and the same problem occurs with the precision and repeatability values. This comparison of several studies of wavefront aberration repeatability emphasizes the need to establish a consensus to facilitate comparison between the results of various studies and devices; for example, CV of the normalized polar Zernike coefficients should be included to permit a repeatability comparison of various devices. Moreover, all devices should show the Zernike coefficients in the Optical Society of America standard notation to make a comparison between results. A limitation of the Allegro Topolyzer is that it presents the individual Zernike coefficients in Malacara notation and hinders comparison with other studies.

In the normal group (**Table B**), the spherical aberration presented high repeatability (CV = 6.43% and ICC = 0.948) except in Z^{-1}_3 and Z^{+1}_3 (ICCs ≥ 0.917). The trefoil, secondary astigmatism, and tetrafoil (including individual Zernike values) showed poor repeatability. These trends are in agreement with other studies,[19,20,22] in which the spherical aberration and coma shows higher levels of wavefront repeatability than the rest of the Zernike coefficients in normal eyes (**Table C**). Our results were slightly better than other previously reported findings[11] of the Sirius device, which analyzes anterior HOAs in spherical aberration (ICC = 0.824) and coma (ICC = 0.856). In summary, the Allegro Topolyzer presents repeatability values for Zernike coefficients similar to those previously reported in normal eyes with better agreement in coma and spherical aberration than trefoil, secondary astigmatism, and tetrafoil (individual values and normalized polar Zernike coefficients).

In regard to aberration wavefront repeatability in patients with keratoconus, there are few reports on this topic,[11,23,24] and only one study has analyzed the anterior corneal surface wavefront, in which keratoconus classifications were based on the HOAs of the anterior corneal surface[9] (**Table D**). We found a high agreement (ICCs ≥ 0.905) among all Zernike coefficients (individual values and normalized polar Zernike coefficients) except in 7th- and 8th-order HOAs and total RMS that showed moderate agreement (ICCs ≥ 0.839) (**Table B**). Bayhan et al.[11] reported the repeatability of the Sirius topographer in keratoconic eyes (n = 41) and analyzed normalized polar Zernike coefficients and found high agreement in coma, trefoil, secondary astigmatism, and spherical aberration (ICCs ≥ 0.930), with the worst results in tetrafoil (ICC = 0.809). This finding is consistent with our results, in which the tetrafoil presented the highest CV (25.82%).

One of the main contributions of the current study is the analysis of repeatability at various keratoconus stages that, to the best of our knowledge, has not been previously reported. Generally, the Zernike coefficient repeatability tended to be better with increasing keratoconus stage (**Table C**). This finding may be because the HOAs are greater and clearly defined with increasing keratoconus stage, so their measurement could be more repeatable and useful to disease classification.

The Zernike coefficients reveal differences between stages I, II, and III of keratoconus (according to the Amsler–Krumeich classification) in the mean value of coma, vertical coma (Z^{-1}_3), coma-like, 3rd-order RMS, HOA RMS, and total RMS (**Table C**). Further research is necessary to determine if these findings can be used in diagnosing, managing, and classifying keratoconus.[9] Currently, this study demonstrated that coma, coma-like, vertical coma (Z^{-1}_3), and 3rd-order RMS could be the most useful aberration coefficients for keratoconus detection[25,26] and classification[9] because these coefficients show statistical differences between the three keratoconus stages (**Table C**). Alió and Shabayek[9] proposed a modification in the Amsler–Krumeich classification to consider the coma-like (3rd, 5th, and 7th order) values based on the aberrometry analysis of 40 keratoconic eyes (coma-like criteria: stage I > 1.50 to 2.50 µm; stage II > 2.50 to ≤ 3.50 µm; stage III > 3.50 to ≤ 4.50 µm, and stage IV > 4.50 µm). However, we found a lower coma-like value in all studied stages than in the proposed coma-like values in these classification criteria. Our results suggest that this classification should be used with caution in clinical practice because coma-like values could depend on the device. More studies with larger samples of patients with keratoconus would be needed to support a classification rule using corneal wavefront aberrations.

Finally, external factors influenced the measurement of the aberrations and may have significantly reduced the repeatability of corneal HOA measurements; these factors include saccadic eye movements,[27] misalignment of patients' head in the forehead and chin rest that produces variations in pupil center location,[28] and changes in tear film stability after blinking that could not be detected by the operator during topography acquisition. However, a carefully controlled data acquisition could control the quality of the image capture and minimize the effect of these external factors on HOA measurements.[29] Consequently, the difficulty in obtaining highly repeatable HOA measurements might arise from small eye movements and their continuous adaptation in attaining the best optical image rather than the inability of the device to provide repeatable measurements.

CONCLUSIONS

For the first time, a HOA repeatability assessment with the Allegro Topolyzer was conducted and described in keratoconic and normal eyes. The results of this study are important to eye care practitioners and refractive surgeons for management of patients who have undergone refractive surgery or have keratoconus.

Generally, the HOA repeatability was moderate and poor for Zernike coefficients in normal eyes; it was better at the center of the Zernike pyramid than along the periphery of the Zernike pyramid in the 3rd and 4th order.

Keratoconic eyes presented good HOA repeatability, except in tetrafoil and RMS up to the 7th-order, which had moderate repeatability. Coma, vertical coma (Z^{-1}_3), coma-like, 3rd-order RMS, HOA RMS, and total RMS would help in keratoconus detection, management, and future disease stage classification.

AUTHOR CONTRIBUTIONS

Study concept and design (SO-T, GR, VJ, RM); data collection (SO-T, GR, VJ, RM); analysis and interpretation of data (SO-T, GR, VJ); writing the manuscript (SO-T, GR, VJ, RM); critical revision of the manuscript (SO-T, GR, RM); statistical expertise (SO-T, GR, VJ, RM); administrative, technical, or material support (RM); supervision (RM)

REFERENCES

1. McAlinden C, McCartney M, Moore J. Mathematics of Zernike polynomials: a review. *Clin Experiment Ophthalmol.* 2011;39:820-827.
2. Visser N, Berendschot TT, Verbakel F, Tan AN, de Brabander J, Nuijts RM. Evaluation of the comparability and repeatability of four wavefront aberrometers. *Invest Ophthalmol Vis Sci.* 2011;52:1302-1311.
3. Falavarjani KG, Hashemi M, Modarres M, Sanjari MS, Darvish N, Gordiz A. Topography-guided vs Wavefront-optimized surface ablation for myopia using the WaveLight platform: a contralateral eye study. *J Refract Surg.* 2011;27:13-17.
4. Pérez-Merino P, Birkenfeld J, Dorronsoro C, et al. Aberrometry in patients implanted with accommodative intraocular lenses. *Am J Ophthalmol.* 2014;157:1077-1089.
5. Marsack JD, Ravikumar A, Nguyen C, et al. Wavefront-guided scleral lens correction in keratoconus. *Optom Vis Sci.* 2014;91:1221-1230.
6. Allen PM, Radhakrishnan H, Price H, et al. A randomised clinical trial to assess the effect of a dual treatment on myopia progression: the Cambridge Anti-Myopia Study. *Ophthalmic Physiol Opt.* 2013;33:267-276.
7. Smolek MK, Klyce SD. Goodness-of-prediction of Zernike polynomial fitting to corneal surfaces. *J Cataract Refract Surg.* 2005;31:2350-2355.
8. Gobbe M, Guillon M. Corneal wavefront aberration measurements to detect keratoconus patients. *Cont Lens Anterior Eye.* 2005;28:57-66.
9. Alió JL, Shabayek HM. Corneal higher order aberrations: a method to grade keratoconus. *J Refract Surg.* 2006;22:539-545.
10. Zadnik K, Barr JT, Edrington TB, et al. Baseline findings in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study. *Invest Ophthalmol Vis Sci.* 1998;39:2537-2546.
11. Bayhan HA, Aslan Bayhan S, Muhafiz E, Can I. Repeatability of aberrometric measurements in normal and keratoconus eyes using a new Scheimpflug-Placido topographer. *J Cataract Refract Surg.* 2014;40:269-275.
12. Choi JA, Kim MS. Progression of keratoconus by longitudinal assessment with corneal topography. *Invest Ophthalmol Vis Sci.* 2012;53:927-935.
13. Malacara D, DeVore SL. Interferogram evaluation and wavefront fitting. In: Malacara D, ed. *Optical Shop Testing,* 2nd ed. New York: John Wiley & Sons; 1992:455-496.
14. American National Standards Institute. American National Standard for Ophthalmics-Methods for reporting optical aberrations of the eye. ANSI Z80.28-2004 (2004).
15. International Organization for Standardization. Ophthalmic optics and instruments – Reporting aberrations of the human eye. ISO 24157:2008 (2008).
16. Bland M. *An Introduction to Medical Statistics,* 3rd ed. Oxford, United Kingdom: Oxford University Press; 2000:268-275.
17. McGraw KO, Wong SP. Forming inferences about some intraclass correlation coefficients. *Psychol Meth.* 1996;1:30-46.
18. Wang Q, Savini G, Hoffer KJ, et al. A comprehensive assessment of the precision and agreement of anterior corneal power measurements obtained using 8 different devices. *PLoS One.* 2012;7:e45607.
19. Cerviño A, Dominguez-Vicent A, Ferrer-Blasco T, García-Lázaro S, Albarrán-Diego C. Intrasubject repeatability of corneal power, thickness, and wavefront aberrations with a new version of a dual rotating Scheimpflug-Placido system. *J Cataract Refract Surg.* 2015;41:186-192.
20. Wang L, Shirayama M, Koch DD. Repeatability of corneal power and wavefront aberration measurements with a dual-Scheimpflug Placido corneal topographer. *J Cataract Refract Surg.* 2010;36:425-430.
21. López-Miguel A, Martínez-Almeida L, González-García MJ, Coco-Martín MB, Sobrado-Calvo P, Maldonado MJ. Precision of higher-order measurements with a new Placido-disk topographer and Hartmann-Shack wavefront sensor. *J Cataract Refract Surg.* 2013;39:242-249.
22. Aramberri J, Araiz L, Garcia A, et al. Dual versus single

Scheimpflug camera for anterior segment analysis: precision and agreement. *J Cataract Refract Surg*. 2012;38:1934-1949.

23. Sideroudi H, Labiris G, Giarmoulakis A, Bougatsou N, Mikropoulos D, Kozobolis V. Repeatability, reliability and reproducibility of posterior curvature and wavefront aberrations in keratoconic and cross-linked corneas. *Clin Exp Optom*. 2013;96:547-556.
24. Jinabhai A, Radhakrishnan H, O'Donnell C. Repeatability of ocular aberration measurements in patients with keratoconus. *Ophthalmic Physiol Opt*. 2011;31:588-594.
25. Gordon-Shaag A, Millodot M, Ifrah R, Shneor E. Aberrations and topography in normal, keratoconus-suspect, and keratoconic eyes. *Optom Vis Sci*. 2012;89:411-418.
26. Jafri B, Li X, Yang H, Rabinowitz YS. Higher order wavefront aberrations and topography in early and suspected keratoconus. *J Refract Surg*. 2007;23:774-781.
27. Cheng X, Himebaugh N, Kollbaum PS, Thibos LN, Bradley A. Test-retest reliability of clinical Shack-Hartmann measurements. *Invest Ophthalmol Vis Sci*. 2004;45:351-360.
28. Guirao A, Williams DR, Cox IG. Effect of rotation and translation on the expected benefit of an ideal method to correct the eye's higher-order aberrations. *J Opt Soc Am A Opt Image Sci Vis*. 2001;18:1003-1015.
29. Montés-Micó R, Alió JL, Muñoz G, Pérez-Santonja JJ, Charman WN. Postblink changes in total and corneal ocular aberrations. *Ophthalmology*. 2004;111:758-767.

TABLE A

Intraobserver Repeatability for Total Corneal Wavefront Measurements of Allegro Topolyzer (6-mm Optic Diameter)

Parameter	Mean ± SD (μm) (Range)	S_w (μm)	Precision (μm)	Repeatability (μm)	CV (%)	ICC (95% CI)
Coma						
Keratoconus	1.999 ± 1.075 (0.417 to 4.209)	0.055	0.108	0.152	3.74	0.995 (0.992 to 0.998)
Normal	0.174 ± 0.084 (0.036 to 0.350)	0.026	0.050	0.071	17.91	0.884 (0.809 to 0.934)
P[a]	< .01	< .01	< .01	< .01	< .01	–
Z^{-1}_3						
Keratoconus	-1.827 ± 1.058 (-4.150 to -0.352)	0.059	0.115	0.162	–	0.994 (0.990 to 0.997)
Normal	-0.020 ± 0.121 (-0.250 to 0.184)	0.031	0.060	0.085	–	0.917 (0.861 to 0.953)
P[a]	< .01	< .01	< .01	< .01	–	–
Z^{+1}_3						
Keratoconus	-0.088 ± 0.833 (-1.982 to 1.703)	0.041	0.088	0.113	–	0.996 (0.993 to 0.998)
Normal	-0.019 ± 0.147 (-0.258 to 0.341)	0.017	0.048	0.046	–	0.982 (0.969 to 0.990)
P[a]	.95	< .01	< .01	< .01	–	–
Trefoil						
Keratoconus	0.790 ± 0.521 (0.151 to 2.339)	0.042	0.082	0.116	8.33	0.989 (0.981 to 0.994)
Normal	0.148 ± 0.048 (0.038 to 0.232)	0.027	0.054	0.076	20.68	0.633 (0.460 to 0.775)
P[a]	< .01	.17	.17	.17	< .01	–
Z^{-3}_3						
Keratoconus	-0.142 ± 0.718 (-2.065 to 2.029)	0.050	0.098	0.138	–	0.993 (0.988 to 0.996)
Normal	0.075 ± 0.095 (-0.191 to 0.203)	0.029	0.056	0.080	–	0.876 (0.798 to 0.930)
P[a]	< .01	< .01	< .01	< .01	–	–
Z^{+3}_3						
Keratoconus	0.027 ± 0.604 (-1.588 to 1.044)	0.045	0.088	0.124	–	0.990 (0.983 to 0.995)
Normal	0.043 ± 0.086 (-0.127 to 0.187)	0.024	0.048	0.067	–	0.881 (0.805 to 0.933)
P[a]	.717	.04	.04	.04	–	–
Secondary astigmatism						
Keratoconus	0.498 ± 0.235 (0.081 to 0.899)	0.032	0.063	0.089	8.23	0.965 (0.940 to 0.981)
Normal	0.043 ± 0.018 (0.016 to 0.092)	0.014	0.027	0.038	37.18	0.504 (0.308 to 0.682)
P[a]	< .01	< .01	< .01	< .01	< .01	–
Z^{-2}_4						
Keratoconus	0.278 ± 0.370 (-0.720 to 0.870)	0.037	0.072	0.102	–	0.984 (0.972 to 0.991)
Normal	0.011 ± 0.033 (-0.050 to 0.077)	0.015	0.029	0.041	–	0.771 (0.643 to 0.866)
P[a]	< .01	< .01	< .01	< .01	–	–
Z^{+2}_4						
Keratoconus	-0.044 ± 0.297 (-0.665 to 0.679)	0.022	0.044	0.062	–	0.991 (0.985 to 0.995)
Normal	0.003 ± 0.030 (-0.066 to 0.056)	0.011	0.022	0.031	–	0.846 (0.751 to 0.912)
P[a]	.03	< .01	< .01	< .01	–	–
Tetrafoil						
Keratoconus	0.233 ± 0.213 (0.042 to 0.869)	0.041	0.081	0.114	25.82	0.946 (0.909 to 0.970)
Normal	0.088 ± 0.030 (0.031 to 0.176)	0.020	0.039	0.055	24.00	0.577 (0.392 to 0.736)
P[a]	< .01	< .01	< .01	< .01	.69	–
Z^{-4}_4						
Keratoconus	-0.035 ± 0.218 (-0.862 to 0.465)	0.043	0.085	0.120	–	0.943 (0.903 to 0.968)
Normal	-0.074 ± 0.037 (-0.164 to -0.015)	0.022	0.044	0.062	–	0.634 (0.462 to 0.776)
P[a]	.31	< .01	< .01	< .01	–	–
Z^{+4}_4						
Keratoconus	0.049 ± 0.217 (-0.265 to 0.800)	0.037	0.073	0.103	–	0.954 (0.923 − 0.975)
Normal	0.021 ± 0.032 (-0.050 to 0.068)	0.019	0.037	0.052	–	0.640 (0.469 to 0.780)
P[a]	.31	< .01	< .01	< .01	–	–
Z^0_4 spherical aberration						
Keratoconus	0.006 ± 0.479 (-1.102 to 0.746)	0.032	0.063	0.089	11.66	0.993 (0.988 to 0.996)
Normal	0.247 ± 0.065 (0.094 to 0.376)	0.014	0.027	0.038	6.49	0.948 (0.912 to 0.971)
P[a]	< .01	< .01	< .01	< .01	.13	–
Coma like (3rd, 5th, and 7th order)						
Keratoconus	2.013 ± 1.078 (0.410 to 4.225)	0.054	0.106	0.150	3.62	0.996 (0.992 to 0.998)
Normal	0.180 ± 0.082 (0.056 to 0.351)	0.025	0.049	0.070	16.23	0.879 (0.801 to 0.931)
P[a]	< .01	< .01	< .01	< .01	< .01	–

TABLE A (cont'd)

Intraobserver Repeatability for Total Corneal Wavefront Measurements of Allegro Topolyzer (6-mm Optic Diameter)

Parameter	Mean ± SD (μm) (Range)	S_w (μm)	Precision (μm)	Repeatability (μm)	CV (%)	ICC (95% CI)
3rd-order RMS						
Keratoconus	2.222 ± 1.052 (0.752 to 4.327)	0.049	0.096	0.136	2.61	0.996 (0.993 to 0.998)
Normal	0.239 ± 0.070 (0.120 to 0.394)	0.030	0.058	0.082	13.02	0.761 (0.629 to 0.860)
P[a]	< .01	.10	.10	.10	< .01	–
4th-order RMS						
Keratoconus	0.731 ± 0.314 (0.216 to 1.651)	0.040	0.078	0.110	6.24	0.974 (0.956 to 0.986)
Normal	0.269 ± 0.061 (0.151 to 0.393)	0.014	0.027	0.038	5.93	0.925 (0.874 to 0.958)
P[a]	< .01	< .01	< .01	< .01	.81	–
5th-order RMS						
Keratoconus	0.296 ± 0.179 (0.077 to 0.897)	0.025	0.048	0.068	9.76	0.953 (0.920 to 0.974)
Normal	0.057 ± 0.017 (0.025 to 0.092)	0.016	0.032	0.045	28.51	0.281 (0.078 to 0.499)
P[a]	< .01	.34	.34	.34	< .01	–
6th-order RMS						
Keratoconus	0.141 ± 0.066 (0.045 to 0.327)	0.016	0.031	0.044	11.46	0.905 (0.843 to 0.947)
Normal	0.037 ± 0.009 (0.022 to 0.059)	0.013	0.026	0.037	24.17	0.382 (0.177 to 0.587)
P[a]	< .01	.08	.08	.08	< .01	–
7th-order RMS						
Keratoconus	0.097 ± 0.053 (0.021 to 0.289)	0.015	0.029	0.041	17.00	0.896 (0.828 to 0.941)
Normal	0.026 ± 0.009 (0.016 to 0.051)	0.009	0.017	0.024	30.36	0.227 (0.026 to 0.450)
P[a]	< .01	< .01	< .01	< .01	< .01	–
8th-order RMS						
Keratoconus	0.063 ± 0.042 (0.016 to 0.253)	0.014	0.027	0.038	22.69	0.839 (0.741 to 0.908)
Normal	0.019 ± 0.007 (0.009 to 0.043)	0.008	0.015	0.022	36.90	0.235 (0.029 to 0.458)
P[a]	< .01	.02	.02	.02	< .01	–
HOA RMS (3rd to 8th order)						
Keratoconus	2.391 ± 1.052 (0.833 to 4.427)	0.045	0.088	0.125	2.06	0.997 (0.994 to 0.998)
Normal	0.376 ± 0.053 (0.284 to 0.495)	0.020	0.040	0.057	5.46	0.788 (0.666 to 0.877)
P[a]	< .01	< .01	< .01	< .01	< .01	–
Total RMS (1st to 8th order)						
Keratoconus	7.425 ± 3.888 (2.352 to 16.525)	0.217	0.425	0.601	3.62	0.995 (0.991 to 0.997)
Normal	1.093 ± 0.388 (0.467 to 2.039)	0.102	0.201	0.283	16.23	0.865 (0.779 to 0.923)
P[a]	< .01	< .01	< .01	< .01	< .01	–

SD = standard deviation; S_w = within-subject standard deviation; CV = coefficient of variation; ICC = intraclass correlation coefficient; CI = confidence interval; RMS = root mean square; HOA = higher order aberration

[a]*Mann–Whitney* U *analysis of variance.*

The Allegro Topolyzer is manufactured by Alcon Laboratories, Erlangen, Germany.

TABLE B

Intraobserver Repeatability for Total Corneal Wavefront Measurements (6-mm Optic Diameter) in Different Stages of Keratoconus

Parameter	Mean ± SD (μm) (Range)	S_w (μm)	Precision (μm)	Repeatability (μm)	CV (%)	ICC (95% CI)
Coma						
Stage I	0.929 ± 0.382 (0.417 to 1.455)	0.054	0.106	0.150	5.99	0.995 (0.986 to 0.998)
Stage II	1.802 ± 0.564 (0.779 to 2.874)	0.055	0.107	0.152	3.41	0.997 (0.992 to 0.999)
Stage III	3.265 ± 0.487 (2.610 to 4.209)	0.056	0.108	0.154	1.91	0.993 (0.983 to 0.998)
P[a]	< .01[b,c,d]	.56	.56	.56	.01[c]	–
Z^{-1}_3						
Stage I	-0.861 ± 0.393 (-1.388 to -0.352)	0.062	0.121	0.170	–	0.993 (0.980 to 0.998)
Stage II	-1.522 ± 0.543 (-2.846 to -0.573)	0.050	0.098	0.139	–	0.997 (0.991 to 0.999)
Stage III	-3.068 ± 0.619 (-4.156 to -1.973)	0.064	0.126	0.178	–	0.988 (0.968 to 0.996)
P[a]	< .01[b,c,d]	.51	.51	.51	–	–
Z^{+1}_3						
Stage I	-0.088 ± 0.339 (-0.603 to 0.442)	0.039	0.077	0.108	–	0.996 (0.989 to 0.999)
Stage II	0.330 ± 0.879 (-1.746 to 1.703)	0.034	0.066	0.094	–	0.997 (0.993 to 0.999)
Stage III	-0.505 ± 0.932 (-1.982 to 0.865)	0.049	0.096	0.136	–	0.996 (0.989 to 0.999)
P[a]	< .01[b,d]	.23	.23	.23	–	–
Trefoil						
Stage I	0.643 ± 0.288 (0.151 to 1.159)	0.045	0.089	0.129	12.52	0.989 (0.971 to 0.997)
Stage II	0.712 ± 0.288 (0.181 to 2.339)	0.034	0.066	0.094	7.14	0.986 (0.965 to 0.996)
Stage III	1.015 ± 0.048 (0.280 to 2.182)	0.046	0.090	0.127	5.32	0.992 (0.979 to 0.997)
P[a]	< .01[c,d]	.63	.63	.63	.85	–
Z^{-3}_3						
Stage I	0.003 ± 0.323 (-0.557 to 0.502)	0.041	0.082	0.156	–	0.996 (0.988 to 0.999)
Stage II	-0.061 ± 0.605 (-0.575 to 1.716)	0.046	0.090	0.127	–	0.990 (0.974 to 0.997)
Stage III	-0.374 ± 1.008 (-2.065 to 2.029)	0.062	0.122	0.172	–	0.992 (0.979 to 0.998)
P[a]	< .01[c]	.56	.56	.56	–	–
Z^{+3}_3						
Stage I	0.319 ± 0.533 (-0.602 to 1.044)	0.042	0.083	0.017	–	0.991 (0.977 to 0.997)
Stage II	-0.056 ± 0.683 (-1.588 to 0.716)	0.042	0.082	0.117	–	0.984 (0.958 to 0.995)
Stage III	-0.180 ± 0.446 (-0.790 to 0.526)	0.050	0.098	0.138	–	0.994 (0.983 to 0.998)
P[a]	< .01[c]	.34	.34	.34	–	–
Secondary astigmatism						
Stage I	0.394 ± 0.203 (0.097 to 0.787)	0.029	0.058	0.082	8.83	0.938 (0.845 to 0.980)
Stage II	0.498 ± 0.245 (0.081 to 0.871)	0.022	0.043	0.061	7.32	0.987 (0.967 to 0.996)
Stage III	0.601 ± 0.214 (0.194 to 0.899)	0.044	0.087	0.123	8.53	0.954 (0.884 to 0.985)
P[a]	< .01[c]	.37	.37	.37	.72	–
Z^{-2}_4						
Stage I	0.309 ± 0.222 (0.050 to 0.756)	0.033	0.064	0.091	–	0.952 (0.879 to 0.985)
Stage II	0.289 ± 0.411 (-0.586 to 0.870)	0.029	0.057	0.081	–	0.994 (0.986 to 0.998)
Stage III	0.236 ± 0.444 (-0.720 to 0.856)	0.049	0.096	0.135	–	0.976 (0.937 to 0.992)
P[a]	.80	.21	.21	.21	–	–
Z^{+2}_4						
Stage I	0.093 ± 0.212 (-0.219 to 0.407)	0.019	0.037	0.052	–	0.995 (0.985 to 0.995)
Stage II	-0.055 ± 0.239 (-0.570 to 0.399)	0.017	0.033	0.047	–	0.993 (0.981 to 0.998)
Stage III	-0.170 ± 0.363 (-0.665 to 0.679)	0.031	0.061	0.087	–	0.987 (0.966 to 0.996)
P[a]	< .01[c]	.08	.08	.08	–	–
Tetrafoil						
Stage I	0.140 ± 0.058 (0.051 to 0.217)	0.027	0.052	0.074	23.09	0.879 (0.717 to 0.960)
Stage II	0.220 ± 0.206 (0.042 to 0.806)	0.042	0.083	0.117	27.28	0.970 (0.924 to 0.991)
Stage III	0.338 ± 0.270 (0.064 to 0.869)	0.055	0.108	0.153	27.12	0.941 (0.853 to 0.981)
P[a]	.01[c]	.33	.33	.33	.80	–
Z^{-4}_4						
Stage I	0.049 ± 0.062 (-0.091 to 0.164)	0.029	0.057	0.081	–	0.939 (0.848 to 0.980)
Stage II	-0.050 ± 0.153 (-0.323 to 0.168)	0.044	0.087	0.123	–	0.973 (0.930 to 0.991)
Stage III	-0.106 ± 0.324 (-0.862 to 0.465)	0.057	0.111	0.157	–	0.892 (0.744 to 0.964)
P[a]	< .01[b,c]	.20	.20	.20	–	–
Z^{+4}_4						
Stage I	-0.016 ± 0.125 (-0.210 to 0.192)	0.032	0.063	0.089	–	0.947 (0.868 to 0.983)
Stage II	0.108 ± 0.229 (-0.115 to 0.738)	0.037	0.072	0.102	–	0.962 (0.904 to 0.988)
Stage III	0.056 ± 0.026 (-0.027 to 0.800)	0.057	0.083	0.117	–	0.948 (0.870 to 0.983)
P[a]	.06	.27	.27	.27	–	–

TABLE B (cont'd)

Intraobserver Repeatability for Total Corneal Wavefront Measurements (6-mm Optic Diameter) in Different Stages of Keratoconus

Parameter	Mean ± SD (μm) (Range)	S_w (μm)	Precision (μm)	Repeatability (μm)	CV (%)	ICC (95% CI)
Z^0_4 spherical aberration						
Stage I	0.258 ± 0.252 (-0.206 to 0.585)	0.029	0.057	0.081	11.55	0.978 (0.942 to 0.993)
Stage II	0.084 ± 0.423 (-0.421 to 0.716)	0.032	0.062	0.088	12.74	0.998 (0.995 to 0.999)
Stage III	-0.323 ± 0.524 (-1.102 to 0.746)	0.035	0.069	0.098	10.69	0.994 (0.985 to 0.998)
P[a]	< .01[c,d]	.51	.51	.51	.98	–
Coma like (3rd, 5th and 7th order)						
Stage I	0.938 ± 0.397 (0.410 to 1.471)	0.053	0.104	0.147	5.73	0.952 (0.880 to 0.985)
Stage II	1.819 ± 0.567 (0.795 to 2.874)	0.054	0.105	0.149	3.28	0.988 (0.968 to 0.996)
Stage III	3.287 ± 0.505 (2.614 to 4.225)	0.056	0.110	0.156	1.90	0.981 (0.950 to 0.994)
P[a]	< .01[b,c,d]	.56	.56	.56	.02[c]	–
3rd-order RMS						
Stage I	1.175 ± 0.344 (0.752 to 1.644)	0.044	0.086	0.121	3.61	0.997 (0.991 to 0.999)
Stage II	2.019 ± 0.555 (1.338 to 2.930)	0.047	0.091	0.129	2.43	0.996 (0.989 to 0.999)
Stage III	3.473 ± 0.446 (2.805 to 4.327)	0.057	0.111	0.157	1.78	0.994 (0.984 to 0.998)
P[a]	< .01[b,c,d]	.27	.27	.27	.30	–
4th-order RMS						
Stage I	0.555 ± 0.204 (0.216 to 0.839)	0.036	0.071	0.100	7.13	0.943 (0.958 to 0.982)
Stage II	0.695 ± 0.314 (0.342 to 1.386)	0.163	0.072	0.101	6.92	0.990 (0.973 to 0.997)
Stage III	0.941 ± 0.286 (0.709 to 1.651)	0.046	0.091	0.128	4.68	0.962 (0.903 to 0.988)
P[a]	<.01[c,d]	.55	.55	.55	.86	–
5th-order RMS						
Stage I	0.204 ± 0.092 (0.081 to 0.348)	0.027	0.053	0.074	11.24	0.972 (0.927 to 0.991)
Stage II	0.252 ± 0.147 (0.077 to 0.539)	0.017	0.033	0.047	9.01	0.950 (0.875 to 0.984)
Stage III	0.433 ± 0.193 (0.145 to 0.897)	0.030	0.059	0.083	9.02	0.950 (0.874 to 0.984)
P[a]	< .01[c,d]	.06	.06	.06	.99	–
6th-order RMS						
Stage I	0.103 ± 0.031 (0.045 to 0.149)	0.001	0.017	0.026	8.63	0.951 (0.876 to 0.984)
Stage II	0.123 ± 0.052 (0.048 to 0.243)	0.016	0.031	0.043	14.72	0.892 (0.745 to 0.965)
Stage III	0.199 ± 0.067 (0.110 to 0.327)	0.022	0.043	0.061	11.03	0.773 (0.519 to 0.921)
P[a]	<.01[c,d]	.05	.05	.05	.68	–
7th-order RMS						
Stage I	0.067 ± 0.031 (0.021 to 0.137)	0.011	0.021	0.029	16.21	0.861 (0.680 to 0.954)
Stage II	0.089 ± 0.049 (0.034 to 0.188)	0.015	0.029	0.040	18.37	0.946 (0.866 to 0.983)
Stage III	0.135 ± 0.052 (0.081 to 0.289)	0.019	0.038	0.053	16.41	0.816 (0.594 to 0.937)
P[a]	<.01[c,d]	.08	.08	.08	.96	–
8th-order RMS						
Stage I	0.044 ± 0.024 (0.016 to 0.082)	0.008	0.016	0.023	19.90	0.943 (0.857 to 0.982)
Stage II	0.054 ± 0.031 (0.021 to 0.121)	0.013	0.025	0.035	22.58	0.702 (0.406 to 0.892)
Stage III	0.092 ± 0.052 (0.049 to 0.253)	0.020	0.039	0.055	25.60	0.403 (0.045 to 0.743)
P[a]	< .01[c,d]	.03[c]	.03[c]	.03[c]	.67	–
HOA RMS						
Stage I	1.347 ± 0.359 (0.833 to 1.812)	0.034	0.067	0.094	2.40	0.998 (0.994 to 0.999)
Stage II	2.178 ± 0.568 (1.430 to 3.276)	0.043	0.084	0.119	2.09	0.996 (0.989 to 0.999)
Stage III	3.649 ± 0.411 (3.057 to 4.427)	0.058	0.114	0.165	1.70	0.995 (0.987 to 0.998)
P[a]	< .01[b,c,d]	.33	.33	.33	.60	–
Total RMS						
Stage I	3.788 ± 1.295 (2.352 to 5.827)	0.154	0.301	0.426	3.86	0.991 (0.977 to 0.997)
Stage II	6.427 ± 1.324 (3.516 to 8.841)	0.163	0.320	0.453	2.56	0.998 (0.995 to 0.999)
Stage III	12.060 ± 2.459 (8.247 to 16.525)	0.334	0.654	0.925	2.39	0.993 (0.981 to 0.998)
P[a]	< .01[b,c,d]	.02[c]	.02[c]	.02[c]	.45	–

SD = standard deviation; S_w = within-subject standard deviation; CV = coefficient of variation; ICC = intraclass correlation coefficient; CI = confidence interval; RMS = root mean square; HOA = higher order aberration

[a]*Statistically significant differences between the three study groups (Kruskal–Wallis analysis of variance).*

[b]*Statistically significant differences between keratoconus stages I and II (Mann–Whitney U analysis of variance).*

[c]*Statistically significant differences between keratoconus stages I and III (Mann–Whitney U analysis of variance).*

[d]*Statistically significant differences between keratoconus stages II and III (Mann–Whitney U analysis of variance).*

The Allegro Topolyzer is manufactured by Alcon Laboratories, Erlangen, Germany.

TABLE C

Summary of Previous Reports of Corneal Wavefront Repeatability in Healthy Eyes

Parameter	Current Study	Wang et al.[20]	Cerviño et al.[19]	Aramberri et al.[22]	Aramberri et al.[22]	Bayhan et al.[11]	López-Miguel et al.[21]
Device	Allegro Topolyzer	Galilei G3	Galilei G4	Pentacam HR	Galilei G2	Sirius	Topcon KR-1W
Corneal surface	Anterior	Total	Total	Total	Total	Anterior	Total
No. of eyes	36	20	25	35	35	30	75
Coma							
Mean	0.174 ± 0.084	0.33 ± 0.15	–	–	–	0.24 ± 0.08	0.181
S_w	0.026	0.08	–	–	–	0.04	0.041
CV	17.91%	29%	–	–	–	–	–
ICC	0.884	0.897	–	–	–	0.856	0.869
Z^{-1}_3							
Mean	-0.020 ± 0.121	-0.06 ± 0.24	-0.068 ± 0.231	-0.04 ± 0.15	-0.04 ± 0.22	–	–
S_w	0.031	0.08	0.076	0.009	0.09	–	–
CV	–	–	–	–	–	–	–
ICC	0.917	0.966	0.849	0.740	0.809	–	–
Z^{+1}_3							
Mean	-0.019 ± 0.147	0.04 ± 0.26	0.013 ± 0.361	0.00 ± 0.11	0.00 ± 0.34	–	–
S_w	0.017	0.10	0.093	0.02	0.13	–	–
CV	–	–	–	–	–	–	–
ICC	0.982	0.945	0.915	0.961	0.868	–	–
Trefoil							
Mean	0.148 ± 0.048	0.23 ± 0.10	–	–	–	0.16 ± 0.07	–
S_w	0.027	0.09	–	–	–	0.04	–
CV	20.68%	37%	–	–	–	–	–
ICC	0.633	0.714	–	–	–	0.750	–
Z^{-3}_3							
Mean	0.075 ± 0.095	-0.11 ± 0.15	-0.051 ± 0.164	0.01 ± 0.06	-0.13 ± 0.15	–	–
S_w	0.029	0.12	0.070	0.08	0.13	–	–
CV	–	–	–	–	–	–	–
ICC	0.876	0.775	0.811	0.478	0.477	–	–
Z^{+3}_3							
Mean	0.043 ± 0.086	-0.07 ± 0.11	-0.011 ± 0.128	0.00 ± 0.05	0.00 ± 0.15	–	–
S_w	0.024	0.011	0.076	0.05	0.15	–	–
CV	–	–	–	–	–	–	–
ICC	0.881	0.667	0.552	0.509	0.510	–	–
Secondary astigmatism							
Mean	0.043 ± 0.018	0.09 ± 0.05	–	–	–	0.04 ± 0.02	–
S_w	0.014	0.04	–	–	–	0.05	–
CV	37.18%	40%	–	–	–	–	–
ICC	0.504	0.695	–	–	–	0.678	–
Z^{-2}_4							
Mean	0.011 ± 0.033	-0.02 ± 0.05	–	–	–	–	–
S_w	0.015	0.05	–	–	–	–	–
CV	–	–	–	–	–	–	–
ICC	0.771	0.682	–	–	–	–	–
Z^{+2}_4							
Mean	0.003 ± 0.030	-0.02 ± 0.08	–	–	–	–	–
S_w	0.011	0.05	–	–	–	–	–
CV	–	–	–	–	–	–	–
ICC	0.846	0.864	–	–	–	–	–
Tetrafoil							
Mean	0.088 ± 0.030	0.15 ± 0.09	–	–	–	0.06 ± 0.03	–
S_w	0.020	0.09	–	–	–	0.05	–
CV	24%	53%	–	–	–	–	–
ICC	0.577	0.669	–	–	–	0.568	–
Z^{-4}_4							
Mean	-0.074 ± 0.037	0.01 ± 0.06	–	–	–	–	–
S_w	0.022	0.09	–	–	–	–	–
CV	–	–	–	–	–	–	–
ICC	0.634	0.162	–	–	–	–	–

TABLE C (cont'd)

Summary of Previous Reports of Corneal Wavefront Repeatability in Healthy Eyes

Parameter	Current Study	Wang et al.[20]	Cerviño et al.[19]	Aramberri et al.[22]	Aramberri et al.[22]	Bayhan et al.[11]	López-Miguel et al.[21]
Z^{+4}_{4}							
Mean	0.021 ± 0.032	-0.07 ± 0.13	–	–	–	–	–
S_w	0.019	0.10	–	–	–	–	–
CV	–	–	–	–	–	–	–
ICC	0.640	0.819	–	–	–	–	–
Spherical aberration							
Mean	0.247 ± 0.065	0.27 ± 0.08	0.121 ± 0.077	0.21 ± 0.06	0.22 ± 0.08	-0.22 ± 0.04	0.085
S_w	0.014	0.02	0.022	0.03	0.04	0.01	0.033
CV	6.49%	7%	–	13.55%	16.26%	–	–
ICC	0.948	0.981	0.857	0.814	0.833	0.824	0.939
Coma-like							
Mean	0.179 ± 0.081	–	–	–	–	–	–0.283[a]
S_w	0.025	–	–	–	–	–	0.029
CV	16.23%	–	–	–	–	–	–
ICC	0.879	–	–	–	–	–	0.883
3rd-order RMS							
Mean	0.239 ± 0.070	0.42 ± 0.16	–	–	–	–	0.246
S_w	0.030	0.09	–	–	–	–	0.038
CV	13.02%	23%	–	–	–	–	–
ICC	0.761	0.878	–	–	–	–	0.883
4th-order RMS							
Mean	0.269 ± 0.061	0.34 ± 0.09	–	–	–	–	0.168
S_w	0.014	0.06	–	–	–	–	0.029
CV	5.93%	14%	–	–	–	–	–
ICC	0.925	0.825	–	–	–	–	0.876
5th-order RMS							
Mean	0.057 ± 0.017	0.09 ± 0.04	–	–	–	–	–
S_w	0.016	0.03	–	–	–	–	–
CV	28.51%	24%	–	–	–	–	–
ICC	0.281	0.806	–	–	–	–	–
6th-order RMS							
Mean	0.037 ± 0.009	0.06 ± 0.02	–	–	–	–	–
S_w	0.013%	0.02	–	–	–	–	–
CV	24.17%	29%	–	–	–	–	–
ICC	0.382	0.787	–	–	–	–	–
7th-order RMS							
Mean	0.026 ± 0.009	–	–	–	–	–	–
S_w	0.009	–	–	–	–	–	–
CV	30.36%	–	–	–	–	–	–
ICC	0.227	–	–	–	–	–	–
8th-order RMS							
Mean	0.019 ± 0.007	–	–	–	–	–	–
S_w	0.008	–	–	–	–	–	–
CV	36.90%	–	–	–	–	–	–
ICC	0.235	–	–	–	–	–	–
HOAs RMS							
Mean	0.376 ± 0.053	0.56 ± 0.14[b]	–	0.11 ± 0.03	0.59 ± 0.20	0.41 ± 0.06[c]	-
S_w	0.020	0.09	–	0.03	0.12	0.07	–
CV	5.46%	14%	–	23.96%	20.26%	–	–
ICC	0.788	0.858	–	0.564	0.687	0.824	–
Total RMS							
Mean	1.093 ± 0.388	–	–	–	–	0.91 ± 0.37[c]	–
S_w	0.102	–	–	–	–	0.07	–
CV	16.23%	–	–	–	–	–	–
ICC	0.865	–	–	–	–	0.976	–

S_w = within-subject standard deviation; CV = coefficient of variation; ICC = intraclass correlation coefficient; RMS = root mean square; HOA = higher order aberration

[a]Coma-like 3rd and 5th Zernike order.

[b]Up to the 7th Zernike order.

[c]3rd to 6th Zernike order.

TABLE D

Summary of Previous Reports of Corneal Wavefront Repeatability in Keratoconic Eyes

Parameter	Current Study	Bayhan et al.[11]	Sideroudi et al.[23]	Jinabhai et al.[24]
Device	Allegro Topolyzer	Sirius	Pentacam	IRX-3 aberrometer
Cornea surface	Anterior	Anterior	Posterior	Ocular
No. of eyes	36	41	33	31
Coma				
Mean	1.999 ± 1.075	2.22 ± 1.33	7.6 ± 4.6	0.85
S_w	0.055	0.03	0.258	0.06
CV	3.74%	–	–	–
ICC	0.995	0.988	0.997	–
Z^{-1}_3				
Mean	-1.827 ± 1.058	–	-6.653 ± 3.939	–
S_w	0.059	–	0.209	–
CV	–	–	–	–
ICC	0.994	–	0.997	–
Z^{+1}_3				
Mean	-0.088 ± 0.833	–	-0.154 ± 3.697	–
S_w	0.041	–	0.236	–
CV	–	–	–	–
ICC	0.996	–	0.993	–
Trefoil				
Mean	0.790 ± 0.521	0.70 ± 0.36	–	0.54
S_w	0.042	0.05	–	0.07
CV	8.33%	–	–	–
ICC	0.989	0.930	–	–
Z^{-3}_3				
Mean	-0.142 ± 0.718	–	0.064 ± 1.208	–
S_w	0.050	–	0.216	–
CV	–	–	–	–
ICC	0.993	–	0.672	–
Z^{+3}_3				
Mean	0.027 ± 0.604	–	-0.178 ± 0.427	–
S_w	0.045	–	0.127	–
CV	–	–	–	–
ICC	0.990	–	0.846	–
Secondary astigmatism				
Mean	0.498 ± 0.235	0.45 ± 0.28	–	0.40
S_w	0.032	0.04	–	0.07
CV	8.23%	–	–	–
ICC	0.965	0.976	–	–
Z^{-2}_4				
Mean	0.278 ± 0.370	–	0.007 ± 0.220	–
S_w	0.037	–	0.263	–
CV	–	–	–	–
ICC	0.984	–	0.952	–
Z^{+2}_4				
Mean	-0.044 ± 0.297	–	-0.187 ± 0.183	–
S_w	0.022	–	0.232	–
CV	–	–	–	–
ICC	0.991	–	0.878	–
Tetrafoil				
Mean	0.233 ± 0.213	0.18 ± 0.09	–	0.33
S_w	0.041	0.04	–	0.08
CV	25.82%	–	–	–
ICC	0.946	0.809	–	–
Z^{-4}_4				
Mean	-0.035 ± 0.218	–	-0.002 ± 0.411	–
S_w	0.043	–	0.207	–
CV	–	–	–	–
ICC	0.943	–	0.806	–

TABLE D (cont'd)

Summary of Previous Reports of Corneal Wavefront Repeatability in Keratoconic Eyes

Parameter	Current Study	Bayhan et al.[11]	Sideroudi et al.[23]	Jinabhai et al.[24]
Z^{+4}_{4}				
Mean	0.049 ± 0.217	–	0.273 ± 0.238	–
S_w	0.037	–	0.260	–
CV	–	–	–	–
ICC	0.954	–	0.988	–
Spherical aberration				
Mean	0.006 ± 0.479	0.15 ± 0.38	-0.376 ± 1.125	0.34
S_w	0.032	0.03	0.127	0.09
CV	11.63%	–	–	–
ICC	0.993	0.956	0.956	–
Coma-like				
Mean	2.013 ± 1.078	–	7.677 ± 4.615[a]	–
S_w	0.054	–	0.262	–
CV	3.62%	–	–	–
ICC	0.996	–	0.997	–
3rd-order RMS				
Mean	2.222 ± 1.052	–	–	–
S_w	0.049	–	–	–
CV	2.61%	–	–	–
ICC	0.996	–	–	–
4th-order RMS				
Mean	0.731 ± 0.314	–	–	–
S_w	0.040	–	–	–
CV	6.24%	–	–	–
ICC	0.974	–	–	–
5th-order RMS				
Mean	0.296 ± 0.179	–	–	–
S_w	0.025	–	–	–
CV	9.76%	–	–	–
ICC	0.953	–	–	–
6th-order RMS				
Mean	0.141 ± 0.066	–	–	–
S_w	0.016	–	–	–
CV	11.46%	–	–	–
ICC	0.905	–	–	–
7th-order RMS				
Mean	0.097 ± 0.053	–	–	–
S_w	0.015	–	–	–
CV	17.00%	–	–	
ICC	0.896	–	–	–
8th-order RMS				
Mean	0.063 ± 0.042	–	–	–
S_w	0.014	–	–	–
CV	22.69%	–	–	–
ICC	0.839	–	–	–
HOAs RMS				
Mean	2.391 ± 1.052	2.49 ± 1.32[b]	7.94 ± 0.43[b]	0.93[a]
S_w	0.045	0.03	0.275	0.07
CV	22.69%	–	–	–
ICC	0.839	0.979	0.996	–
Total RMS				
Mean	7.425 ± 3.888	4.41 ± 1.77[c]	–	–
S_w	0.217	0.09	–	–
CV	3.62%	–	–	–
ICC	0.865	0.986	–	–

S_w = within-subject standard deviation; CV = coefficient of variation; ICC = intraclass correlation coefficient; RMS = root mean square; HOA = higher order aberration

[a]3rd to 5th Zernike order.

[b]3rd to 6th Zernike order.

[c]Up to the 6th Zernike order.

5.3. Intercambiabilidad de tecnologías (Plácido versus Scheimpflug) en queratocono

Ortiz-Toquero S[1,2,3], Rodriguez G[1,2,3], De Juan V[3,4], Martin R[1,2,3,5]

Agreement of corneal measurements between dual rotation Scheimpflug-Placido system and Placido-based topography device in normal and keratoconus eyes.

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ARTICLE

Agreement of corneal measurements between dual rotating Scheimpflug–Placido system and Placido-based topography device in normal and keratoconus eyes

Sara Ortiz-Toquero, MSc, Virginia Zuñiga, OD, Guadalupe Rodriguez, MSc, Victoria de Juan, PhD, Raul Martin, PhD

PURPOSE: To compare the anterior corneal measurements between Placido-based topography and dual-Scheimpflug topography in healthy and keratoconus eyes.

SETTING: Optometry Research Group, Instituto Universitario de Oftalmobiología Aplicada, University of Valladolid, Valladolid, Spain.

DESIGN: Comparative case series.

METHODS: The mean simulated keratometry (K), flat K, steep K, astigmatism power, corneal astigmatism axis, J0, J45, maximum corneal power point, and white-to-white (WTW) distance were collected and compared between healthy eyes and keratoconus eyes.

RESULTS: The study evaluated in 56 healthy eyes and 56 keratoconus eyes. Placido-based topography underestimated all topographic values except J45 and WTW in healthy eyes and J0, maximum corneal power point, and WTW in keratoconus eyes, with statistically significant differences in astigmatism (healthy), flat K (keratoconus), axis (keratoconus), J0, J45, and WTW ($P < .05$). Healthy eyes showed better agreement (95% limits of agreement: simulated K −0.13 to 0.40; steep K −0.30 to 0.59; flat K −0.29 to 0.51; astigmatism −0.60 to 0.64; J0 −1.15 to 1.13; J45 −1.10 to 1.20; maximum corneal power point −0.70 to 1.17; WTW −0.96 to 0.76 mm) than keratoconic eyes (simulated K −2.84 to 4.55; steep K −2.80 to 5.21; flat K −3.68 to 4.70; astigmatism −1.90 to 2.95; J0 −2.85 to 3.20; J45 −3.21 to 3.05; maximum corneal power point −7.00 to 4.51 D; WTW −1.00 to 0.88).

CONCLUSIONS: Healthy eyes showed better agreement than keratoconus eyes between Placido-based and dual-Scheimpflug topography. Both instruments could be used interchangeably with caution in healthy eyes, but not in keratoconus management.

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Precise measurements of the anterior corneal surface are very important in various clinical situations such as corneal refractive surgery practice, calculation of intraocular lens (IOL) power in phakic or pseudophakic planning surgery, contact lens fitting, and corneal disease detection and follow-up.[1,2] The screening of patients having corneal refractive surgery in preoperative assessment is particularly important to exclude keratoconus or other corneal disease and to avoid potentially undesirable side effects.[3,4]

Today, multiple imaging techniques for anterior corneal assessment are available. Placido disk–based videokeratography analyzes concentric light rings reflected on the anterior corneal surface, and it is the most extensively used technique among corneal topographic assessments of corneal curvature.[5] Scheimpflug

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tomography relies on the reconstruction of corneal images from a rotating camera and allows analysis of the anterior corneal surface as well as the posterior surface.[3,5] At present, mixed devices combining Placido disk with Scheimpflug tomography are available.[2] However, most agreement studies compare different Placido-disk and Scheimpflug techniques in healthy eyes[1,5–10] To our knowledge, no previous reports have evaluated the agreement between the 2 techniques in cases of corneal diseases, such as in keratoconus for which corneal topography is mandatory for early diagnosis, classification, management, and follow-up.[3,11,12]

This study evaluated the interdevice agreement between Placido topography (Allegro-Topolyzer, Wavelight Technologie AG [Alcon Laboratories, Inc.]) and dual rotating Scheimpflug–Placido topography (Galilei G4, Ziemer Group) for anterior corneal assessment in keratoconus eyes and compare the data with those from healthy eyes.

PATIENTS AND METHODS

In this prospective clinic-based observational single-masked study, patients were divided into 2 groups: healthy and keratoconus. Informed consent was obtained from each patient after the Human Sciences Ethics Committee, University of Valladolid, granted approval for the study. All patients were treated in accordance with the tenets of the Declaration of Helsinki.

Healthy patients with active ocular surface disease, corneal opacities, glaucoma, use of medication that could affect ocular physiology, a history of any type of ocular surgery, and refractive error (spherical equivalent [SE]) greater than 6.00 diopters (D) were excluded. Soft and rigid contact lenses wear was discontinued for at least 2 weeks and 4 weeks, respectively, before the eye examination. A single eye of each patient was randomly chosen for the study.

Independent corneal specialists diagnosed keratoconus patients after a complete eye examination that included topographic analysis and anterior eye biomicroscopy assessment based on slitlamp findings (stromal thinning, conical protrusion, Fleischer ring, and Vogt striae).[12,13] Eyes with previous acute corneal hydrops or a history of ocular surgery were excluded. Because keratoconus is a bilateral and asymmetric disease, both eyes of the same patient were included in the study.

Instrumentation

The Allegro-Topolyzer (Examination Software version 1.76r45 FW1.19) is a noninvasive diagnostic device based on the Placido disk system supported by 22 rings and generates high-resolution data of the corneal surface with 22 000 data points. The corneal measurements provided by this Placido topographer have been shown to have excellent repeatability in healthy eyes and keratoconus eyes.[7,14]

The Galilei-G4 (software version V6.0.3) is a noninvasive optical diagnostic device that has a rotating dual-Scheimpflug camera integrated (located 180 degrees apart to compensate for error associated with scans at an oblique angle) with a Placido disk (20 monochrome rings, 200 mm diameter) to measure the anterior and posterior corneal surfaces. It is a topographer and tomographer that integrates data simultaneously obtained from the Placido and Scheimpflug components to measure the anterior corneal surface.[15] It analyzes more than 122 000 data points per complete scan. This device uses a hypothetical keratometric index of 1.3375 for the anterior corneal curvature calculation and has good repeatability of measurements in healthy eyes and keratoconic eyes.[16]

Measurements

Corneal topography was performed in all patients using the Placido topographer and the dual rotating Scheimpflug–Placido topographer during the same visit. Both devices were calibrated before the study. The same experienced operator performed all measurements in a darkened room following the manufacturer's guidelines.

Corneal Topographical Outcomes

The following corneal parameters were collected from both devices and compared: mean central corneal dioptric power (simulated keratometry [K]), corneal dioptric power in the flattest meridian (flat K) and steepest meridian (steep K) of the simulated K, maximum corneal dioptric power point of the anterior corneal surface, corneal diameter or white-to-white distance (WTW), and corneal astigmatism (diopters and axis of corneal astigmatism). The conversion to power vectors components J0 and J45, as suggested by Thibos et al.,[17] was performed with the following equations:

$$J0 = (-C/2)\cos(2\alpha)$$

$$J45 = (-C/2)\sin(2\alpha)$$

where J0 is the Jackson cross-cylinder, axes at 0 degrees and 90 degrees; J45 is the Jackson cross-cylinder, axes at 45 degrees

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and 135 degrees; C is the astigmatism (difference in diopters between the higher and the lower simulated K readings); and α is the meridian, expressed in degrees, of the higher simulated K reading. These measures were also calculated and compared. Because vectorial analysis of corneal astigmatism can be nonclinically intuitive,[6] axis data were transformed to ensure that the difference in each pair of measurements was corrected by adding or subtracting 180 degrees to the axis difference value following the recommendations of Delrivo et al.[6]

Statistical Analysis

Statistical analysis was performed using SPSS for Windows software (version 15.0, SPSS, Inc.). A normal distribution of variables was assessed using the Kolmogorov-Smirnov test; P values greater than 0.05 indicated the data were normally distributed. The mean values of the measurements between healthy eyes and keratoconus eyes were compared with analysis of variance; P values less than 0.05 were considered statistically significant. The mean values of the measurements between the Placido topographer and the dual rotating Scheimpflug–Placido topographer were compared with the paired t test; P values less than 0.05 were considered statistically significant. Linear regression was used to quantify the r^2 correlation coefficient between measurements of both devices; P values less than 0.05 were considered statistically significant.

The degree of agreement between the Placido topographer and the dual rotating Scheimpflug–Placido topographer in healthy eyes and keratoconus eyes was evaluated using Bland-Altman analysis.[18] The differences between the measurements of both devices were plotted against the means of both techniques, and 95% limits of agreement (LoA) were calculated (mean difference ± 1.96 SD).

RESULTS

One hundred twelve eyes were included in the study. The healthy group comprised 56 eyes of 56 patients (30 women, 26 men) with a mean age of 30.8 years ± 6.2 (SD) (range 18 to 44 years) and a mean SE refractive error of −3.26 ± 2.19 D (range +1.50 to −6.00 D). The keratoconus group comprised 56 eyes of 33 keratoconus patients (11 women, 22 men) with a mean age of 35.1 ± 10.7 years (range 19 to 58 years) and a mean SE refractive error of −4.85 ± 4.35 D (range −0.50 to −14.00 D).

Table 1 shows the Placido topographer and dual rotating Scheimpflug–Placido topographer measurements in healthy eyes and keratoconus eyes. The simulated K, flat K, steep K, corneal astigmatism, and maximum corneal power point values were significantly different between healthy eyes and keratoconus eyes with both devices ($P < .05$). The Placido topographer underestimated all topographic values compared with the dual rotating Scheimpflug–Placido topographer in healthy eyes (except J45 and WTW) and in keratoconus eyes (except J0, J45, maximum corneal power point, and WTW). All measurements were significantly different between the 2 devices in healthy eyes (except astigmatism, J0, J45, and WTW) and in keratoconus eyes (except flat K, axis, J0, J45, and WTW) (both $P < .05$). Healthy eyes showed better agreement than keratoconic eyes in all topographic parameters; that is, in simulated K, flat K, steep K, maximum corneal power point (Figure 1); mean corneal astigmatism, axis corneal astigmatism, J0, and J45 (Figures 2 and 3); and WTW (Figure 4).

There was a low, but significant correlation between the mean simulated K ($r^2 = 0.191$, $P < .01$), steep K ($r^2 = 0.132$, $P < .01$), and flat K ($r^2 = 0.166$, $P < .01$) values with a difference in the keratoconus group measured with both devices. However, there was a nonsignificant correlation between the difference and the mean value in healthy eyes. The difference (in absolute value) in the corneal axis between devices was inversely significantly correlated with corneal astigmatism in healthy eyes ($r^2 = 164$, $P < .01$) and keratoconus eyes ($r^2 = .139$, $P < .01$) (Figure 5).

DISCUSSION

Accurate anterior corneal curvature is essential to diagnose and manage keratoconus in conjunction with a clinical examination.[4] This study analyzed the agreement of the anterior corneal topography in healthy eyes and keratoconus eyes between 2 commercially available imaging systems; that is, the Allegro-Topolyzer Placido topographer and the Galilei-G4 dual rotating Scheimpflug–Placido topographer. To our knowledge, this study is the first in the literature to compare these 2 devices in healthy eyes and in keratoconus eyes.

The Placido topographer measured significantly lower corneal curvature values in healthy eyes and keratoconic eyes, and the discrepancy in the agreement between the 2 devices was greater in the keratoconus eyes, with values that could be clinically relevant in keratoconus patient management (classification, contact lens fitting, intracorneal ring surgery, or topography-guided treatments).[19–21] In contrast, healthy eyes showed good agreement (Figure 1) that could be clinically equivalent in the management of these patients (refraction, contact lens fitting, or traditional IOL calculation).[6]

To our knowledge, no previous reports have compared Scheimpflug topography and Placido topography in keratoconus eyes. However, the agreement between a Scheimpflug device (Pentacam, Oculus Optikgeräte GmbH) and a combined Placido optical coherence tomography device (Visante Omni, Carl Zeiss Meditec) was recently described.[4] The study found poor agreement in flat K and steep K between keratoconus eyes (range 95% LoA −1.35 to 1.92 D and −1.38 to 1.99 D, respectively) and healthy eyes (range 95% LoA −0.32 to 0.59 D and −0.41 to 0.74 D, respectively), which is similar to our results.

Table 1. Corneal measurements of the 2 devices and agreement between then in healthy eyes and keratoconus eyes.

	Scheimpflug–Placido Device		Placido Device		Correlation		Difference		
Parameter/Group	Mean ± SD	95% CI	Mean ± SD	95% CI	r^2 Value	*P* Value	Mean ± SD	95% LoA	*P* Value*
SimK (D)									
Healthy	43.73 ± 1.40	43.36, 44.10	43.60 ± 1.45	43.21, 43.98	0.992	<.01	0.13 ± 0.13	−0.13, 0.40	<.01
Keratoconus	47.39 ± 3.67	46.40, 48.37	46.53 ± 2.88	45.76, 47.30	0.742	<.01	0.86 ± 1.89	−2.84, 4.55	<.01
Flat K (D)									
Healthy	43.23 ± 1.49	42.83, 43.63	43.12 ± 1.52	42.72, 43.53	0.982	<.01	0.11 ± 0.20	−0.29, 0.51	<.01
Keratoconus	45.89 ± 3.53	44.95, 46.84	45.38 ± 2.79	44.64, 46.13	0.633	<.01	0.51 ± 2.14	−3.68, 4.70	.08
Steep K (D)									
Healthy	44.22 ± 1.38	43.85, 44.59	44.07 ± 1.88	43.69, 44.44	0.975	<.01	0.15 ± 0.23	−0.30, 0.59	<.01
Keratoconus	48.88 ± 4.02	47.80, 49.95	47.68 ± 3.21	46.82, 48.54	0.745	<.01	1.20 ± 2.04	−2.80, 5.21	<.01
Corneal astigmatism (D)									
Healthy	0.97 ± 0.60	0.81, 1.13	0.95 ± 0.54	0.80, 1.09	0.723	<.01	0.02 ± 0.32	−0.60, 0.64	.56
Keratoconus	2.98 ± 1.77	2.51, 3.46	2.46 ± 1.52	2.05, 2.87	0.530	<.01	0.52 ± 1.24	−1.90, 2.95	<.01
Corneal axis (°)									
Healthy	91.61 ± 34.31	82.42, 100.80	87.23 ± 34.15	78.09, 96.38	0.894	<.01	4.37 ± 11.32	−17.81, 26.56	<.01
Keratoconus	92.36 ± 45.63	80.12, 104.58	92.52 ± 41.35	81.45, 103.60	0.904	<.01	−0.17 ± 14.31	−28.22, 27.89	.93
J0 (D)									
Healthy	0.02 ± 0.35	−0.51, 1.15	0.01 ± 0.42	−1.06, 1.20	0.023	.27	0.01 ± 0.58	−1.13, 1.15	.89
Keratoconus	−0.14 ± 1.26	−3.08, 2.38	0.03 ± 0.93	−2.29, 2.32	0.001	.79	−0.17 ± 1.54	−3.19, 2.85	.40
J45 (D)									
Healthy	−0.07 ± 0.45	−0.91, 1.36	−0.01 ± 0.45	−0.78, 0.74	0.003	.69	−0.05 ± 0.59	−1.20, 1.10	.50
Keratoconus	0.00 ± 1.20	−0.31, 3.44	−0.08 ± 1.11	−3.20, 2.53	0.002	.74	0.08 ± 1.60	−3.05, 3.21	.72
MCPP (D)									
Healthy	44.64 ± 1.44	44.26, 45.03	44.41 ± 1.52	44.02, 44.80	0.895	<.01	0.23 ± 0.48	−0.70, 1.17	<.01
Keratoconus	52.56 ± 5.28	51.15, 53.97	53.81 ± 5.09	52.44, 55.17	0.706	<.01	−1.25 ± 2.94	−7.00, 4.51	<.01
WTW (mm)									
Healthy	11.93 ± 0.33	11.84, 12.02	12.03 ± 0.40	45.76, 47.30	0.087	.03	−0.10 ± 0.44	−0.96, 0.76	.10
Keratoconus	11.90 ± 0.38	11.80, 12.00	11.96 ± 0.39	11.86, 12.07	0.059	.08	−0.06 ± 0.48	−1.00, 0.88	.35

CI = confidence interval; J0 = Jackson cross-cylinder, axes at 0 degrees and 90 degrees; J45 = Jackson cross-cylinder, axes at 45 degrees and 135 degrees; K = keratometry; MCPP = maximum corneal power point; SimK = simulated keratometry; WTW = with the rule
*Difference between the 2 devices

The agreement in corneal power between these 2 devices in healthy eyes is consistent results with in previous reports that compared the corneal power obtained with the Galilei dual rotating Scheimpflug–Placido topographer[9,10] and the Allegro-Topolyzer Placido topographer[7] with that obtained with other corneal assessment devices. For example, previous studies compared the simulated K value provided by Galilei dual rotating Scheimpflug–Placido topography with those of Placido disk devices and found good agreement with Corneal Map Placido-based topographer (Costruzione Strumenti Oftalmici) (range 95% LoA −1.11 to 0.58 D)[10] and the Humphrey Atlas corneal topographer (Carl Zeiss) (range 95% LoA −0.35 to 0.19 D)[9]; however, in these studies, the Galilei dual rotating Scheimpflug–Placido topographer underestimated the corneal power compared with Placido-based devices, in contrast with our results. In addition, the Allegro-Topolyzer Placido topographer measured a lower corneal power (underestimation) with good agreement with various Scheimpflug camera devices (Pentacam) (range 95% LoA: simulated K −0.28 to 0.27 D, flat K −0.23 to 0.22 D, steep K −0.38 to 0.36 D)[7] and Sirius (Costruzione Strumenti Oftalmici) (range 95% LoA: simulated K −0.31 to 0.18 D, flat K −0.31 to 0.17 D, steep K −0.36 to 0.24 D),[7] agreeing with our results.

Corneal astigmatism is an important value in the management of healthy eyes (in corneal refractive surgery, toric IOL calculation, or astigmatic contact lens fitting) and in keratoconus eyes (eg, clinical classification, intracorneal rings calculation). We found good agreement in healthy eyes with a low value (mean 0.02 ± 0.32 D; LoA −0.60 to 0.64 D) compared with that reported by Karimian et al.[10] (mean 0.09 ± 0.34 D; LoA −0.75 to 0.58 D). Karimian et al. compared corneal astigmatism with the Galilei dual rotating Scheimpflug–Placido device and Corneal Map Placido-based device. Delrivo et al.[6] concluded

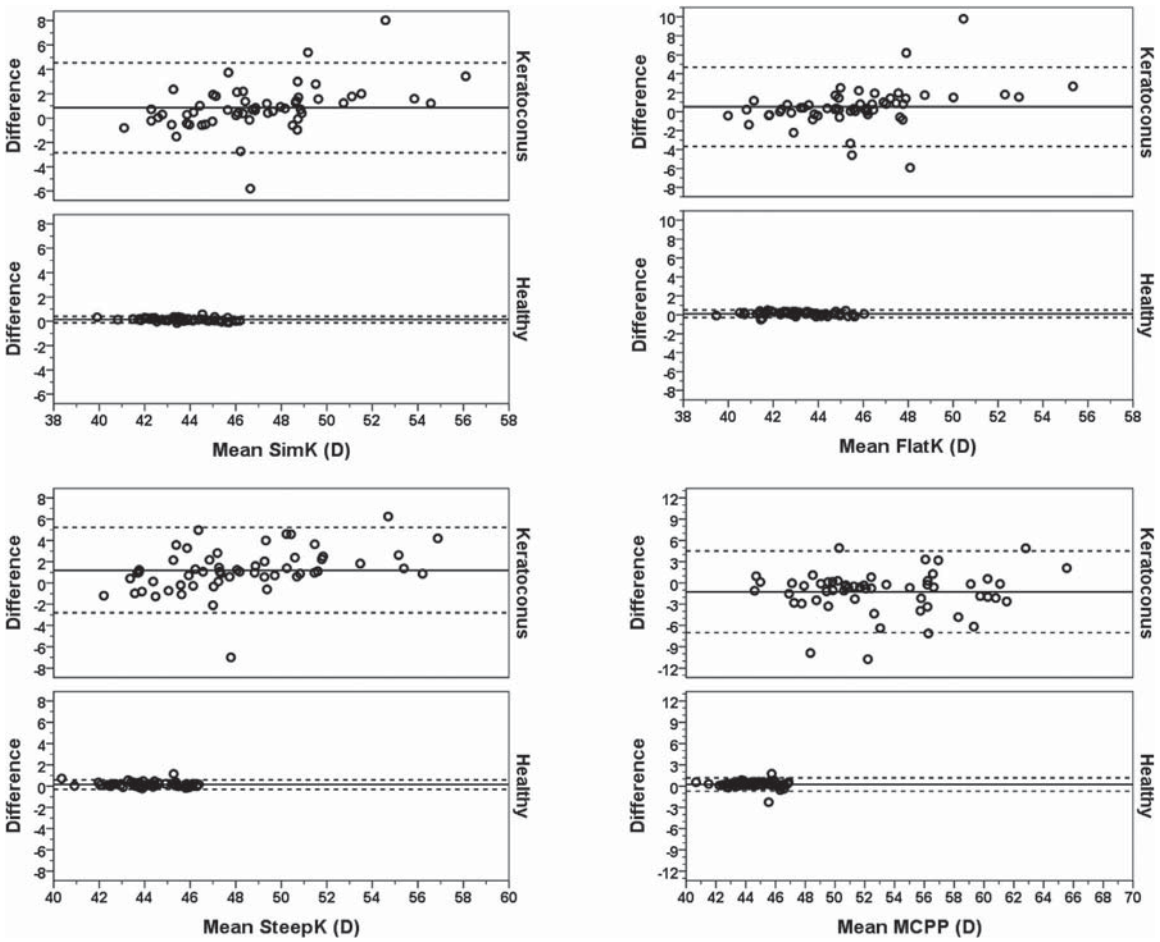

Figure 1. Bland-Altman plots of the agreement in simulated K, flat K, steep K, and maximum corneal power point between the Placido topographer and dual rotating Scheimpflug–Placido topographer in healthy eyes and keratoconus eyes. The mean difference (*solid line*) and 95% LoA (*discontinuous lines*) are represented (K = keratometry; MCPP = maximum corneal power point; SimK = simulated keratometry).

that Pentacam Scheimpflug tomography and iTrace Placido topography (Tracey Technologies) are interchangeable in eyes with astigmatism less than 2.0 D because they found higher agreement between devices in eyes with low astigmatism. The discrepancies in the astigmatism value might not be clinically relevant, such as in the final choice of IOL power (usually available in 0.50 D increments[6]); therefore, both devices could be used interchangeably with caution in healthy eyes with previous cataract surgery or high myopia management with IOL implantation. Hence, in keratoconus eyes, we found moderate agreement that suggests that the 2 devices we studied are not interchangeable in the management of keratoconus because the difference could be clinically significant.

In contrast, there was poor agreement in the corneal astigmatism axis measurements in both groups. In healthy eyes, this finding is important because in toric IOL implantation, each 1-degree error in corneal axis determination produces a 3% reduction in astigmatism correction.[6] The absolute difference in the astigmatism axis between the 2 devices was negatively correlated with corneal astigmatism in both study groups. Thus, a higher agreement of axis measurements between the devices was found when astigmatism was more severe. Delrivo et al.[6] reported the same correlation between the Pentacam device and the iTrace Placido-based device. The accepted statistical analysis for corneal astigmatism is the decomposition in vector components (J0 and J45); however, the clinical interpretation of these data is more difficult and less clinically intuitive. We found a poor correlation of vector components between the 2 devices. Nevertheless, the highest J0 difference was 1.57 D in healthy eyes and −4.60 D in keratoconus eyes; however, the axis differed only by 5.10 degrees and 1.30 degrees, respectively. The same situation occurred with J45; the difference was −1.43 D in the healthy group and 6.64 D in the keratoconus group. However, these results translate to 4.90 degrees and 4.60 degrees of difference in the

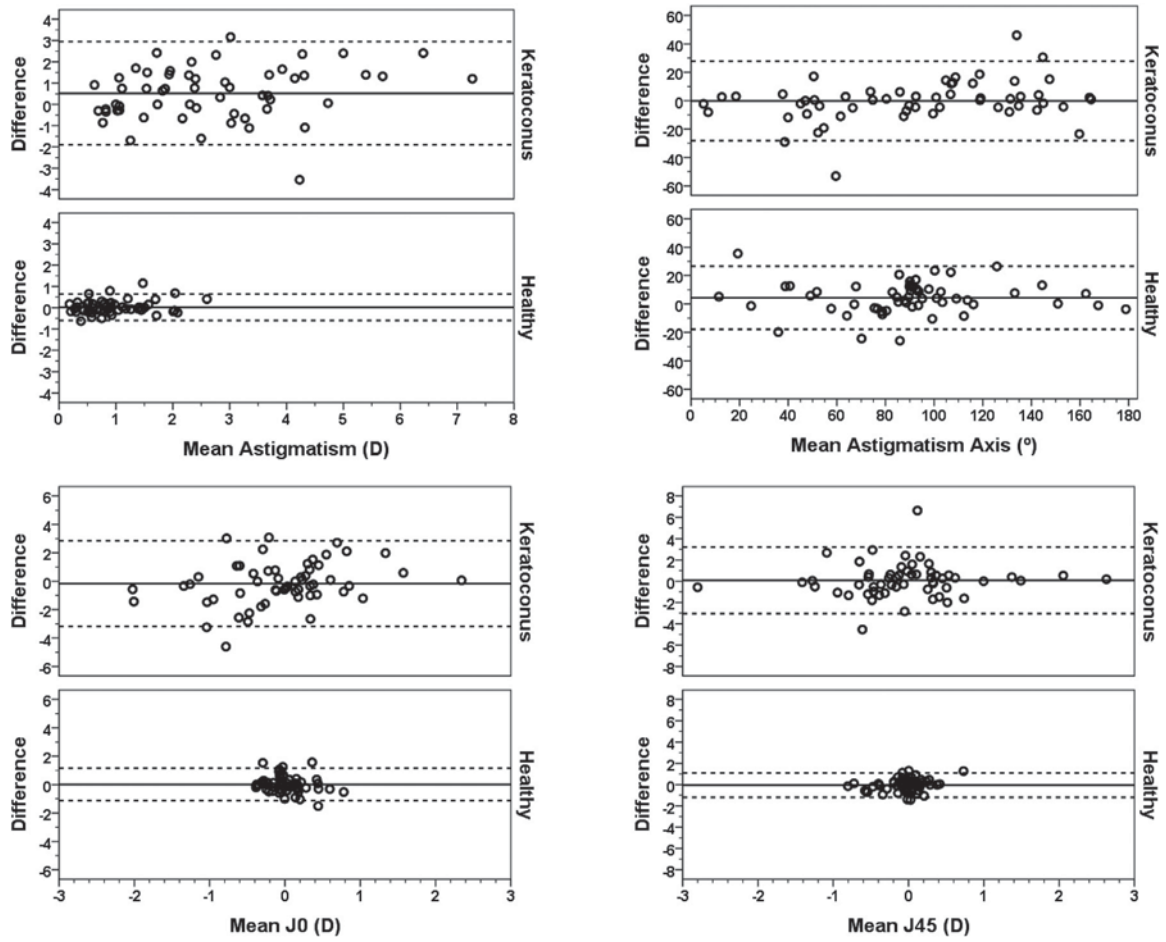

Figure 2. Bland-Altman plots of the agreement in corneal astigmatism, astigmatism axis, J0, and J45 between the Placido topographer and dual rotating Scheimpflug–Placido topographer in healthy eyes and keratoconus eyes. The mean difference (*solid line*) and 95% LoA (*discontinuous lines*) are represented (J0 = Jackson cross-cylinder, axes at 0 degrees and 90 degrees; J45 = Jackson cross-cylinder, axes at 45 degrees and 135 degrees).

astigmatism axis, respectively, between devices. However, our polar plots improved the data presentation and showed less difference in corneal astigmatism in healthy eyes than in keratoconus eyes, providing a better understanding of the J0 and J45 results.

A keratoconus cornea with cone protrusion has a focal steepening with a maximum corneal power point

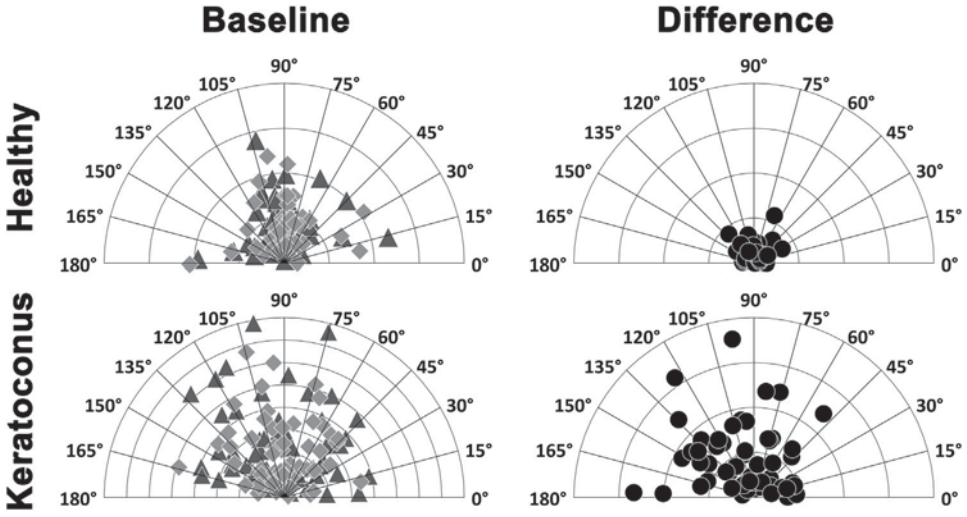

Figure 3. Polar-plot representation of the astigmatism data. Baseline data (*left*) of the dual rotating Scheimpflug–Placido topographer (*solid triangles*) and Placido topographer (*solid diamonds*) and (*right*) the difference (*solid circles*) between both devices plotted for healthy eyes and keratoconus eyes. The step size between rings represents 1.0 D.

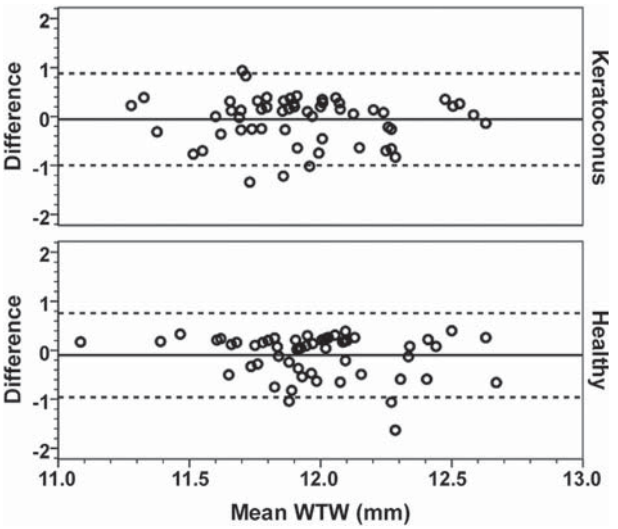

Figure 4. Bland-Altman plot of the agreement in the WTW distance between the Placido topographer and dual rotating Scheimpflug–Placido topographer in healthy eyes and keratoconus eyes. The mean difference (*solid line*) and 95% LoA (*discontinuous lines*) are represented (WTW = white to white).

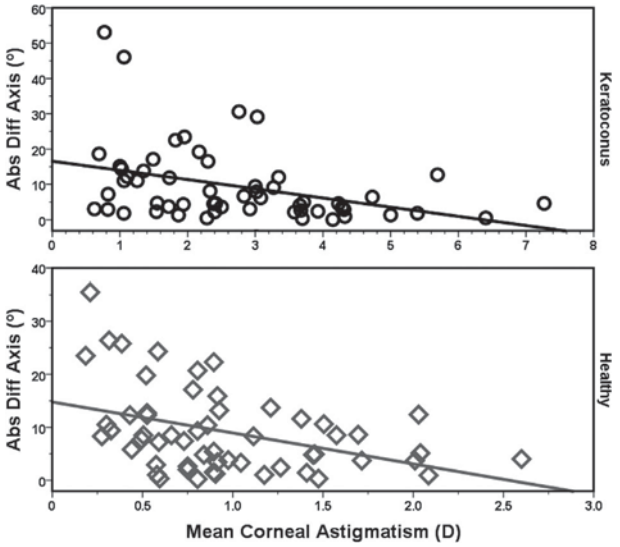

Figure 5. Correlation between corneal astigmatism and absolute difference in axis of corneal astigmatism (degrees) in healthy eyes and keratoconus eyes (Abs Diff = absolute difference).

surrounded by concentric decreasing power zones.[11] This focal steepening in the cone should help confirm the diagnosis of keratoconus and in general has values greater than 46.0 to 47.0 D.[11] In our study, the disagreement in the maximum corneal power point in keratoconus eyes between dual rotating Scheimpflug–Placido topography and Placido topography was greater; therefore, their measurements are not interchangeable in keratoconus diagnosis, management, and follow-up.

The horizontal corneal diameter or WTW distance did not differ between groups or devices. This finding was expected because keratoconus does not affect the corneal diameter. Nevertheless, the WTW distance is an important parameter in phakic IOL calculation and implantation in myopic eyes and even in keratoconus eyes.[22] The WTW values provided by the 2 devices would be not interchangeable because the LoA were approximately 1.0 mm between devices in both group, which have an effect in phakic IOL calculation and postsurgical follow-up. This difference has not been previously reported.

The major limitations of this study might be related to the clinical implication of the differences in keratoconus management because these differences do not imply that any device could be considered better than the other or that the use of 1 device would lead to better patient management than the other. Underestimation of corneal measurements by the Allegro-Topolyzer Placido topographer and overestimation by the Galilei-G4 dual rotating Scheimpflug–Placido topographer must be clarified in further studies. However, a strength of our study was that to our knowledge, it is the first to show agreement in keratoconus eyes and healthy eyes between Placido topography and dual Scheimpflug–Placido topography because the Galilei-G4 dual rotating Scheimpflug–Placido topographer integrates data from Placido and Scheimpflug technology for the anterior curvature analysis using a proprietary method[15] that takes into account more data from the Scheimpflug cameras in cases of irregular corneas, for which the Placido disk's information is less accurate. Another limitation of this study is related to the use of both eyes in the keratoconus group. However, because keratoconus is an asymmetric disease with great differences between the eyes of the same patient, this use would have a negligible impact on the study results and conclusions. Further studies should be performed to determine the accuracy of corneal power measurements in keratoconus eyes obtained with various technologies, such as manual or automated keratometry, scanning-slit tomography, optical coherence tomography, partial coherence interferometry, and point-source color light-emitting diode topography.[23]

In conclusion, in this study, the discrepancy between Allegro-Topolyzer Placido topography and Galilei-G4 dual rotating Scheimpflug–Placido topography measurements was higher in keratoconus eyes than in healthy eyes, probably because of the irregular corneal surface associated with keratoconus. Therefore, these 2 devices are not interchangeable in the

management of keratoconus patients. However, in healthy eyes, the corneal curvature measurements provided by the 2 devices could be used interchangeably with caution.

WHAT WAS KNOWN

- In conjunction with a clinical examination, accurate anterior corneal curvature assessment is essential to diagnose and manage keratoconus patients because steepening of the anterior corneal curvature is of great importance in the early detection, severity, and progression of the disease.
- Both Placido-disk and Scheimpflug–Placido imaging systems have been proposed for corneal assessment in healthy eyes and keratoconus eyes with accurate and clinically accepted data.

WHAT THIS PAPER ADDS

- Assessment of the anterior cornea showed better agreement between Placido-disk topography and dual rotating Scheimpflug–Placido topography in healthy eyes than in keratoconus eyes, suggesting that these 2 devices are not interchangeable in the management of keratoconus.

REFERENCES

1. Nanavaty MA, Favor MP, Lake DB. Comparison of equivalent keratometric indices on Scheimpflug tomography with Placido-based topography system at different optical zones. Br J Ophthalmol 2013; 97:350–356
2. Wang X, Dong J, Wu Q. Comparison of anterior corneal curvature measurements using a Galilei dual Scheimpflug analyzer and Topcon auto kerato-refractometer. J Ophthalmol 2014:140628. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4055652/pdf/JOPH2014-140628.pdf. Accessed June 9, 2016
3. Holladay JT. Keratoconus detection using corneal topography. J Refract Surg 2009; 25:S958–S962. Available at: http://www.hicsoap.com/publications/102%20Keratoconus%20Detection%20Using%20Corneal%20Topography%20JRS2009.pdf. Accessed June 9, 2016
4. Viswanathan D, Kumar NL, Males JJ, Graham SL. Comparative analysis of corneal measurements obtained from a Scheimpflug camera and an integrated Placido-optical coherence tomography device in normal and keratoconic eyes. Acta Ophthalmol 2015; 93:e488–e594
5. Gonen T, Cosar CB, Sener B, Keskinbora KH. Comparison of keratometric data obtained by automated keratometer, Dicon CT 200, Allegro-Topolyzer, and Pentacam. J Refract Surg 2012; 28:557–561
6. Delrivo M, Ruiseñor Vázquez PR, Galletti JD, Garibotto M, Fuentes Bonthoux F, Pförtner T, Galletti JG. Agreement between Placido topography and Scheimpflug tomography for corneal astigmatism assessment. J Refract Surg 2014; 30:49–53
7. Wang Q, Savini G, Hoffer KJ, Xu Z, Feng Y, Wen D, Hua Y, Yang F, Pan C, Huang J. A comprehensive assessment of the precision and agreement of anterior corneal power measurements obtained using 8 different devices. PLoS One 2012; 7:e45607. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3458095/pdf/pone.0045607.pdf. Accessed June 9, 2016
8. Savini G, Carbonelli M, Sbreglia A, Barboni P, Deluigi G, Hoffer KJ. Comparison of anterior segment measurements by 3 Scheimpflug tomographers and 1 Placido corneal topographer. J Cataract Refract Surg 2011; 37:1679–1685
9. Shirayama M, Wang L, Weikert MP, Koch DD. Comparison of corneal powers obtained from 4 different devices. Am J Ophthalmol 2009; 148:528–535
10. Karimian F, Feizi S, Doozandeh A, Faramarzi A, Yaseri M. Comparison of corneal tomography measurements using Galilei, Orbscan II, and Placido disk-based topographer systems. J Refract Surg 2011; 27:502–508
11. Piñero DP, Nieto JC, Lopez-Miguel A. Characterization of corneal structure in keratoconus. J Cataract Refract Surg 2012; 38:2167–2183
12. Gomes JAP, Tan D, Rapuano CJ, Belin MW, Ambrósio R Jr, Guell JL, Malecaze F, Nishida K, Sangwan VS; the Group of Panelists for the Global Delphi Panel of Keratoconus and Ectatic Diseases. Global consensus on keratoconus and ectatic diseases. Cornea 2015; 34:359–369
13. Romero-Jiménez M, Santodomingo-Rubido J, Wolffsohn JS. Keratoconus: A review. Cont Lens Anterior Eye 2010; 33:157–166
14. Ortiz-Toquero S, Rodriguez G, de Juan V, Martin R. Repeatability of wavefront aberration measurements with a Placido-based topographer in normal and keratoconic eyes. J Refract Surg 2016; 32:338–344
15. Huang J, Ding X, Savini G, Jiang Z, Pan C, Hua Y, Wu F, Feng Y, Yu Y, Wang Q. Central and midperipheral corneal thickness measured with Scheimpflug imaging and optical coherence tomography. PLoS One 2014; 9:e98316. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4031212/pdf/pone.0098316.pdf. Accessed June 9, 2016
16. Güler E, Yağcı R, Akyol M, Arslanyılmaz Z, Balcı M, Hepşen İF. Repeatability and reproducibility of Galilei measurements in normal keratoconic and postrefractive corneas. Cont Lens Anterior Eye 2014; 37:331–336
17. Thibos LN, Wheeler W, Horner D. Power vectors: an application of Fourier analysis to the description and statistical analysis of refractive error. Optom Vis Sci 1997; 74:367–375. Available at: http://journals.lww.com/optvissci/Abstract/1997/06000/Power_Vectors__An_Application_of_Fourier_Analysis.19.aspx. Accessed June 9, 2016
18. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986; 1:307–310. Available at: http://www-users.york.ac.uk/~mb55/meas/ba.pdf. Accessed June 9, 2016
19. Ertan A, Colin J. Intracorneal rings for keratoconus and keratectasia. J Cataract Refract Surg 2007; 33:1303–1314
20. Choi JA, Kim M-S. Progression of keratoconus by longitudinal assessment with corneal topography. Invest Ophthalmol Vis Sci 2012; 53:927–935. Available at: http://iovs.arvojournals.org/article.aspx?articleid=2188463. Accessed June 9, 2016
21. Kanellopoulos AJ, Asimellis G. Comparison of Placido disc and Scheimpflug image-derived topography-guided excimer laser surface normalization combined with higher fluence CXL: the Athens Protocol, in progressive keratoconus. Clin Ophthalmol 2013; 7:1385–1396. Available at: http://www.ncbi.nlm.nih.gov/

pmc/articles/PMC3720663/pdf/opth-7-1385.pdf. Accessed June 9, 2016
22. Kamiya K, Shimizu K, Kobashi H, Igarashi A, Komatsu M, Nakamura A, Kojima T, Nakamura T. Three-year follow-up of posterior chamber toric phakic intraocular lens implantation for the correction of high myopic astigmatism in eyes with keratoconus. Br J Ophthalmol 2015; 99: 177–183
23. Ventura BV, Wang L, Ali SF, Koch DD, Weikert MP. Comparison of corneal power, astigmatism, and wavefront aberration measurements obtained by a point-source color light-emitting diode-based topographer, a Placido-disk topographer, and a combined Placido and dual Scheimpflug device. J Cataract Refract Surg 2015; 41:1658–1671

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5.4. Clasificación de la severidad del queratocono con topografía corneal

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The usefulness of the anterior coma aberration in keratoconus severity classification.

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Abstract

Purpose: The aim of this study was to analyse anterior coma aberration provided by Placido disk-based videokeratography to improve the Amsler-Krumeich classification and provide new cut-off values between different stages of severity in keratoconus. Methods: Corneal topography of 70 normal and 77 keratoconus eyes [divided according to Amsler-Krumeich classification (n=21 stage 1; n=30 stage 2 and n=26 stage 3)] was assessed using the Oculus Keratograph. Receiver operating characteristic curve analysis was used to compare the mean values of coma aberration [Z(3,±1)] to calculate cut-off values, sensitivity and specificity to discriminate between normal and keratoconus eyes and between keratoconus stages. Results: Keratoconus eyes showed (2.294±0.137 μm, CI95% 2.020-2.567) higher coma value (P<0.001) than normal group (0.173±0.009 μm, CI95% 0.154-0.193). A cut-off value of 0.377 μm shows 100% sensitivity and 100% specificity to discriminate between keratoconus or normal eyes. Moreover, coma value increases with keratoconus severity; stage 1 (0.948±0.069 μm, CI95% 0.803-1.093), stage 2 (2.062±0.103 μm, CI95% 1.853-2.279) and stage 3 (3.646±0.135 μm, CI95% 3.368-3.925) (P<0.01 post hoc comparison) with cut-off values of 1.466 μm to discriminate between stage 1 or 2 (90% sensitivity and 100% specificity) and 2.790 μm between stage 2 or 3 (92% sensitivity and 83.3% specificity). Conclusion: These results suggest that anterior coma value could be useful in keratoconus classification, improving topographical classification of keratoconus and facilitating keratoconus patients' assessment by eye care practitioners and refractive surgeons. Current Amsler-Krumeich classification could be improved with this new coma values.

Keywords	keratoconus; coma; aberration; classification

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Title Page

Title: The usefulness of the anterior coma aberration in keratoconus severity classification.

Running head: Coma aberration in keratoconus classification.

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None of the authors has a financial or proprietary interest in any material or method mentioned.

Introduction

Keratoconus is a corneal disorder progressive characterized by thinning and steepening of the central and paracentral cornea, which leads to protrusion [1,2]. This ectatic condition is bilateral and asymmetric, and it induces high myopia and irregular astigmatism resulting in impairment in quality of vision [1,2]. Keratoconus commonly appears during the second decade of life and puberty, and it progresses until the fourth decade of life, when it generally stabilizes. This corneal disease affects approximately 1/2000 people in the general population [1,2].

Currently, Placido disk-based videokeratography is one of the most extensively used to corneal topographic assessments in keratoconus [3-5]. Several topographic indices have been developed to introduce objectivity in diagnosis, detection, grading the disease severity and monitoring progression of the keratoconus [3-5]. Some of these indices are K-Value and I-S Value (based on the central keratometry and the inferior-superior asymmetry), SRAX (skewed radial axis; angle between the steepest superior meridian and steepest inferior meridian), KSS (based on slit-lamp findings, corneal power and higher order first corneal surface wavefront root mean square error), KPI (derived from 8 quantitative videokeratography indices), KISA% (based on K-Value, I-S Value, the degree of regular corneal astigmatism and SRAX index) or CLMI (determined by the location and magnitude of the curvature of the cone) between others [2,3,6]. However, most of these indexes have been not extensively used in clinical practice.

Amsler–Krumeich classification permits to classify the keratoconus severity in four levels using refractive (amount of myopia and astigmatism), topography (eccentric steepening, central K readings), pachymetry, and biomicroscopic corneal signs (presence of Vogt's striae, corneal opacities and corneal scars) (Table 1) [7,8]. Despite to be a commonly used classification there is some controversial with its clinical use, because it is possible that the same patient shows keratoconus signs of different stages making difficult an objective use and a practitioner's full judgment is necessary [9]. To improve Amsler–Krumeich classification Alió and Shabayek [10] proposed its modification including coma-like (3rd, 5th, and 7th order) values based on the aberrometry analysis of 40 keratoconic eyes, however this study lacks of an exhaustive analysis of sensitivity and specificity.

Meanwhile, anterior corneal wavefront analysis has been demonstrated to be an effective tool to management keratoconus eyes, due to larger values of vertical coma, coma and coma-like root mean square (RMS) founded in these patients [3,10-13]. This increase of anterior high order aberrations, especially coma, is caused by the irregular steepening and protrusion of the keratoconus anterior corneal surface [3,12].

The aim of this study was to analyse anterior coma aberration provided by Placido disk-based videokeratography to improve the Amsler-Krumeich classification and provide new cut-off values between different stages of severity in keratoconus.

Materials and methods

Subjects

The subjects included in this study were divided into the following two groups: normal subjects and keratoconus patients. Informed consent was obtained from each subject after the Human Sciences Ethics Committee of the University of Valladolid granted approval of the study. All subjects were treated in accordance with the Declaration of Helsinki.

Independent corneal specialists confirmed the diagnosis of keratoconus after a complete eye examination, which included topographical analysis (Placido and Scheimpflug) and anterior eye assessment based on slit lamp findings (stromal thinning, conical protrusion, Fleischer ring and Vogt striae) [2]. Eyes with previous acute corneal hydrops or history of ocular surgery were excluded. Because keratoconus is a bilateral and asymmetric disease, both eyes of the same patient were included in the study. Keratoconus eyes were classified according to the Amsler-Krumeich classification [8]. Eyes with stage 4 were also excluded from the study to guarantee an optimal quality of corneal topography due to that the eyes included in this group have corneal scarring.

Healthy patients with any active ocular-surface disease, corneal opacities, glaucoma, use of medication that could affect ocular physiology and a history of any type of ocular surgery and refractive error (equivalent spherical) greater than 6.00 diopters were excluded. Soft and rigid contact lenses wear was discontinued for at least 2 and 4 weeks, respectively, before eye examination. A random single eye of each subject was chosen for the study.

Measurement procedure

The Oculus Keratograph (Examination Software Version 1.76r45 FW1.19) is a diagnostic device based on the Placido disc system supported by 22 measurement rings with 22,000 elevation points (Oculus Optikgeräte GmbH, Wetzlar, Germany). The corneal measurements provided by the Oculus Keratograph which is identical Allegro-Topolyzer in terms of hardware and software (WaveLight Technologie AG, Alcon Laboratories, Erlangen, Germany) have been shown to have excellent repeatability in normal and keratoconus eyes [5, 13].

Three successive corneal topographies of all eyes included in the study were taken with the Oculus Keratograph following the manufacturer's guidelines in a darkened room. The subject's chin was placed on the chin rest, and the forehead was pressed against the forehead strap; the eye was aligned to the visual axis, and patients were asked to perform a complete blink just before each measurement to spread an optically smooth tear film over the cornea. Poor quality topographies with an "Analyze Area" value less than 70% were deleted (these included artefacts from tear film or movement and shadows from eyelids, eyelashes, or nose). The same experienced operator performed all measurements and the device was calibrated before the study.

The normalized polar Zernike coefficient of coma [Z(3,±1); 6-mm optic diameter) was recorder for each eye (Option Display – Zernike Analysis) to determine the cut-off values to distinguish between normal and keratoconus corneas as well as to define

severity stages of keratoconus. Oculus Keratograph has demonstrated good repeatability in coma value measurement in keratoconus patients showing statistically differences between keratoconus stages (Amsler Krumeich) [13].

Statistical Analysis

Statistical analysis was performed using the SPSS 15.0 (SPSS, Chicago, IL, USA) statistical package for Windows. A normal distribution of variables was assessed using the Kolmogorov–Smirnov test (P values >0.05 indicated that the data were normally distributed). Independent Student t-test was used to compare coma value between healthy and keratoconus eyes (P values <0.05 were considered significant). Differences between the keratoconus stage according to the Amsler-Krumeich classification were calculated with an analysis of variance (ANOVA; P values <0.05 were considered significant) with Games-Howell post hoc comparison after homogeneity of variance analysis with Levene test (P<0.05 rejects the hypothesis that the variances are equal).

Receiver-operating-characteristic (ROC) curves of coma value were calculated to obtain the area under the curve (AUC) that provides a single metric that can be used to judge the overall discriminative ability of a classification method. Based on the magnitude of the AUC, the accuracy of a diagnostic test is classified as perfect test (AUC 1.0), excellent (AUC 0.9 to 0.99), good (AUC 0.8 to 0.89), fair (AUC 0.7 to 0.79) and non-useful test (AUC <0.7) [14]. Sensitivity [true positive/(true positive + false negative)], specificity [true negative/(true negative + false positive)], and cutoff value that corresponded to the maximum AUC were calculated.

Results

One hundred and forty-seven eyes were included in the study and divided into two groups (normal and keratoconus eyes). In normal group, 70 eyes of 70 subjects (48 women, 22 men) were included, with a mean age of 28.9 ± 7.6 years (range, 19 to 50 years) and a mean spherical equivalent refractive error of -3.12 ± 2.10 D (range, +1.50 D to -6.00 D). Seventy-seven eyes of 45 keratoconus patients (17 women, 28 men) comprised the keratoconus group (21 keratoconus eyes in stage I, 30 eyes in stage II, and 26 eyes in stage III, according to the Amsler-Krumeich classification) with a mean age of 30.3 ± 7.1 years (range, 18 to 51 years) and a mean spherical equivalent refractive error of -5.77 ± 3.93 D (range, +1.75 D to -13.75 D).

The coma value in the keratoconus group (2.294 ± 0.137 μm; CI95% from 2.020 to 2.567 μm) was statistically significantly higher (P<0.001) from the value found in the normal group (0.173 ± 0.009 μm; CI95% from 0.154 to 0.193 μm). Moreover, statistically significant differences (P<0.01, Post Hoc pairwise) between the coma value between stage 1 (0.948 ± 0.069 μm; CI95% from 0.803 to 1.093 μm), stage 2 (2.062 ± 0.103 μm; CI95% from 1.853 to 2.273 μm) and stage 3 (3.646 ± 0.135 μm; CI95% from 3.368 to 3.925 μm) were found (Figure 1).

ROC curves (Figure 2) and the AUC (Table 2) shows excellent discriminant ability for coma measurement in all pairwise. In discriminating keratoconus eyes from normal eyes, coma value presented a cut-off value of 0.377 μm that provided 100% sensitivity and 100% specificity (Figure 2-A and Table 2). In discriminating severity keratoconus

stages, coma value showed a cut-off value of 1.466 µm between stage 1 and 2 (90% sensitivity and 100% specificity, Figure 2-B and Table 2) and 2.790 µm between stage 2 and 3 (92% sensitivity and 83.3% specificity, Figure 2-C and Table 2).

Discussion

Topographic analysis of the anterior corneal surface is an excellent tool that has been used for the keratoconus diagnosis, characterization and progression of the disease [3,6,15]. Several indices, decision trees, and neural networks based on the corneal topographic data have been developed to detect suspect corneas affected by ectasia and grading of the severity of the disease [6,16].

Amsler-Krumeich classification (Table 1) is commonly used in research and clinical practice, nevertheless practitioner's full judgment is necessary because the same patient could be classifies into two different stages [9] and this classification fails to address current information and technological advances nowadays available [1]. Keratoconus Severity Score (KSS) (proposed by McMahon et al. for grading the severity of keratoconus) [17] utilizes corneal signs (Vogt´s striae, Fleischer ring and corneal scarring), average corneal power, higher-order first corneal surface wavefront root mean square error and subjective interpretation of the pattern topography map, resulting in severity score grading system (between 0 to 5). Smolek, et al. developed the Keratoconus Severity Index (KSI; also known as Smolek/Klyce index) with a combination of a neural network and a binary decision-making tree assessing data collected from TMS-1 videokeratoscope corneal topography (Tomey Technology, Waltham, MA) [18]. KSI index classifies in three levels: normal cornea (score less than 15%), suspected keratoconus (between 15% to 30%), and manifest keratoconus (score higher than 30%) [18] Keratoconus Classification Index proposed by Maeda et al. (KCI; also known as Maeda/Klyce index) combined eight topographic indices derived from TMS-1 that provide a classification tree being KCI 0–5% a sign for suspecting keratoconus, and KCI>5% a sign for manifest keratoconus [19].

Another option for classification of keratoconus into stages is provided by several Scheimpflug devices. For example, Pentacam (Oculus Optikgeräte GmbH, Wetzlar, Germany) has integrated the Belin/Ambrósio Enhanced Ectasia Display that combine data from anterior and posterior elevation, maximum corneal curvature, and pachymetry to facilitate the keratoconus diagnosis [20] and recently has included the "Belin ABCD Keratoconus Classification" that uses the anterior and posterior radius of curvature taken from the 3 mm zone centred on the thinnest point, the corneal thickness at the thinnest point and the best corrected distance visual acuity proposing 5 stages (between 0 to 4) [21]. Other devices such as Ocular Response Analyzer using the Keratoconus Match Index (KMI) and the Keratoconus Match Probability (KMP) to estimate the probability of the measurement being classified into stages 0–4 based in biomechanical diagnosis [22]. GALILEI dual Scheimpflug analyzer system use a full range of corneal indices [surface indices including inferior-superior index (I-S), standard deviation of corneal power (SDP), surface regularity index (SRI), surface asymmetry index (SAI), irregular astigmatism index (IAI), differential sector index (DSI), opposite sector index (OSI), center/surround index (CSI), keratoconus prediction index (KPI), and keratoconus probability (KProb)] derived from Placido-disc, Scheimpflug technology and wavefront to distinguish keratoconus from normal corneas [23].

However, these grading classifications present several problems due to a high grade of dependency for the corneal topographer or device for which it has been developed (TMS, Pentacam, ORA, GALILEI, etc.) and use huge number of data that make difficult their application in clinical practice without the software designed to data analysis. This makes difficult to establish an easy keratoconus severity classification to be used for all eye care practitioners; in primary care (helping in early detection and diagnosis) and in specialist units (keratoconus management, special contact lens fitting, surgery, etc.).

In summary, there is not an accepted clinical classification for keratoconus severity [1], so new classifications proposals based in current data and technology are necessary to improve keratoconus diagnosis and patient care. The cut-off values of anterior coma aberration proposed in this study could permits to improve the classification of keratoconus stage in a simple and quickly way, with an excellent sensitivity and specificity that improve previous reports [10,24-26]. Alió and Shabayek [10] modified previously the Amsler–Krumeich classification introducing coma-like values in a study involved 40 eyes, founded cut-off values lacking of sensitivity and specificity analysis, and consequently, without sound evidence of its useful clinical practice.

The discriminative ability of anterior corneal wavefront data in keratoconus disease is consistent in the literature [24,26,27]. We found a cut-off coma value of 0.377 µm to distinguish normal corneas to early keratoconus with 100% sensibility and 100% specificity. Other authors have analysed the cut-off value of the vertical coma or coma-like to detect keratoconus showing different results. For example, Bühren et al. [24] reported a cut-off vertical coma of -0.385 µm (100% sensibility and 100% specificity) and a cut-off coma-like of 0.555 µm (100% sensibility and 98.4% of specificity). The same author in posterior study founded a cut-off vertical coma of -0.275 µm with poor results (81.3% sensibility and 80.8% specificity) [27]. Reddy et al. [26] reported a very different cut-off value of vertical coma of -0.540 µm with 57% of sensibility and 90% of specificity. However, in these studies analysis were conducted comparing normal against wide sample of keratoconus eyes, without an independent analysis between advanced and early cases as we propose in our study. Including advanced keratoconus eyes allow find high sensitivity and specificity values, but clinically relevant issue in keratoconus detection is be able to differentiate between healthy and early keratoconus[1] (stage 1), as we find in our study.

Our results could be of interest in feature studies involving several therapeutic choices for the management of keratoconus, such as special contact lens fitting, thermokeratoplasty procedures, corneal collagen cross-linking (CXL), intracorneal ring segment (ICRS) implantation, and lamellar and penetrating keratoplasty due to a proposal of simply classification of the severity disease. For example, in selection of the adequate patient for ICRS implantation full ophthalmic examination should be performed including corneal aberrometry however there are not a cut-off value that help in this clinical decision [28]. Moreover, there are nomograms to decide the number, arc length, thickness, and position of the ICRS based on anecdotic clinical data or variables that are subjectively assessed for example subjective refraction or cone pattern classification [28].

Meanwhile, corneal collagen cross-linking is a treatment strategy for progressive keratoconus, however, currently there is no consistent or accepted definition of

progression of the disease [1]. For this reason, our results could be the initial line of investigation providing objective assessment in keratoconus management and follow up that could permit an objective assessment of the disease progression.

The major limitations of this study may be related with the use of a single anterior Placido-based topographer (Oculus Keratograph). However, the small differences between different devices in coma value (<0.21 microns in healthy eyes) [29] or in corneal topography data in keratoconus eyes (ICC >0.930) [30] suggest that this factor could has a limited effect in our cut off values. The use of an anterior Placido based topographer could controversial because corneal tomography (Scheimpflug or optical coherence tomography devices) is the most widely accepted to diagnose early keratoconus [1]. But, anterior Placido-based corneal topographers are widely used to corneal topographic assessment [3-5] so the cut off values proposed could be of great utility in keratoconus screening and early keratoconus diagnosis but never replace a complete exam that involve corneal tomography and full corneal thickness assessment to provide a definitive diagnosis [1]. Moreover, we have included a stratified analysis with different keratoconus stages to guarantee that the classification rule is able to differentiate between healthy and early keratoconus stage - following the recommendations of the Global Consensus on Keratoconus and Ectatic Diseases panel [1] - and to guarantee that advanced stage does not produce any effect in our early diagnosis cut-off value, as previous reports included. For this reason, severe keratoconus eyes (Amsler-Krumeich 4 stage) were not included in this study because eyes in this stage, have corneal scarring that could be influenced in the results and a good diagnosis criterion may allow early detection and diagnosis as our classification rule propose. More research with high sample size of keratoconus patients and different topographers or tomographers could be necessary to support the applicability of this new keratoconus classification rule with other devices.

Conclusions

These results suggest that coma value could be useful to improve Amsler-Krumeich keratoconus classification and could be of high interest to eye care practitioners and refractive surgeons, who use wavefront assessment to support clinical decisions in keratoconus patient management. Therefore, the use of anterior coma aberration may improve the topographical diagnosis of keratoconus and facilitate keratoconus patients' assessment and follow up.

Figure Legends

Figure 1. Differences in anterior coma (microns) between healthy and all keratoconus eyes, (P<0.01) and between healthy with each keratoconus grade (Amsler-Krumeich) (P<0.01). Moreover, statistically significant differences between stage 1-2 (P<0.001), stage 1-3 (P<0.01) and stage 2-3 (P<0.01) have been found in coma value, as well.

Figure 2. Receiver operating characteristic (ROC) curves of coma value for the discrimination between normal corneas and keratoconus (A); stage 1 and stage 2 (B); and stage 2 and stage 3 (C).

References

[1] J.A. Gomes, D. Tan, C.J. Rapuano CJ, R.Jr. Ambrósio, Group of Panelists for the Global Delphi Panel of Keratoconus and Ectatic Diseases, Global consensus on keratoconus and ectatic diseases, Cornea. 34 (2015) 359–69.

[2] M. Romero-Jiménez, J. Santodomingo-Rubido, J.S. Wolffsohn, Keratoconus: a review, Cont. Lens Anterior Eye. 33 (2010) 157–66.

[3] D.P. Piñero, J.C. Nieto, A. Lopez-Miguel, Characterization of corneal structure in keratoconus, J. Cataract Refract. Surg. 38 (2012) 2167–83.

[4] D. Ramos-López, A. Martínez-Finkelshtein, G.M. Castro-Luna, N. Burguera-Gimenez, A. Vega-Estrada, D. Piñero, J.L. Alió JL, Screening subclinical keratoconus with placido-based corneal indices, Optom. Vis. Sci. 90 (2013) 335–43.

[5] S. Ortiz-Toquero, G. Rodriguez, V. de Juan, R. Martin, Repeatability of placido-based corneal topography in keratoconus, Optom. Vis. Sci. 91 (2014) 1467–73.

[6] F. Cavas-Martínez, E. De la Cruz Sánchez, J. Nieto Martínez, F.J. Fernández Cañavate, D.G. Fernández-Pacheco, Corneal topography in keratoconus: state of the art, Eye Vis. (Lond). 3 (2016) 5.

[7] M. Amsler, Kératocõne classique et kératocône fruste; arguments unitaires, Ophthalmologica, 111 (1946) 96–101.

[8] J.H. Krumeich, J. Daniel, A. Knülle, Live-epikeratophakia for keratoconus, J. Cataract Refract. Surg. 24 (1998) 456–63.

[9] M.M. Sinjab, Keratoconus: when, why and why not, A step by step sistematic approach. 1st ed. New Delhi: JP Medical Ltd (2012) 22.

[10] J.L. Alió, M.H. Shabayek, Corneal higher order aberrations: a method to grade keratoconus, J. Refract. Surg. 22 (2006) 539–45.

[11] M. Gobbe, M. Guillon, Corneal wavefront aberration measurements to detect keratoconus patients, Cont. Lens Anterior Eye. 28 (2005) 57–66.

[12] S. Barbero, S. Marcos, J. Merayo-Lloves, E. Moreno-Barriuso, Validation of the estimation of corneal aberrations from videokeratography in keratoconus, J. Refract. Surg. 18 (2002) 263–70.

[13] S. Ortiz-Toquero, G. Rodriguez, V. de Juan, R. Martin, Repeatability of Wavefront Aberration Measurements With a Placido-Based Topographer in Normal and Keratoconic Eyes, J. Refract. Surg. 32 (2016) 338–44.

[14] J.V. Carter, J. Pan, S.N. Rai, S. Galandiuk, ROC-ing along: Evaluation and interpretation of receiver operating characteristic curves, Surgery. 159 (2016) 1638–45.

[15] Y.S. Rabinowitz, Keratoconus, Surv. Ophthalmol. 42 (1998) 297–319.

[16] E. Sykakis, R. Karim, J.R. Evans, C. Bunce, K.N. Amissah-Arthur, S. Patwary, P.J. McDonnell, S. Hamada, Corneal collagen cross-linking for treating keratoconus, Cochrane Database Syst. Rev. 3 (2015) CD010621.

[17] T.T. McMahon, L. Szczotka-Flynn, J.T. Barr JT, R.J. Anderson, M.E. Slaughter, J.H. Lass, S.K. Iyengar, CLEK Study Group, A new method for grading the severity of keratoconus: the Keratoconus Severity Score (KSS), Cornea. 25 (2006) 794–800.

[18] M.K. Smolek, S.D. Klyce, Current keratoconus detection methods compared with a neural network approach, Invest. Ophthalmol. Vis. Sci. 38 (1997) 2290–9.

[19] N. Maeda, S.D. Klyce, M.K. Smolek, H.W. Thompson, Automated keratoconus screening with corneal topography analysis, Invest. Ophthalmol. Vis. Sci. 35 (1994) 2749–57.

[20] M.W. Belin, R. Ambrósio, Scheimpflug imaging for keratoconus and ectatic disease, Indian J. Ophthalmol. 61 (2013) 401–6.

[21] J.K. Duncan, M.W. Belin, M. Borgstrom, Assessing progression of keratoconus: novel tomographic determinants, Eye Vis. (Lond) 3 (2016) 6.

[22] G. Labiris, Z. Gatzioufas, H. Sideroudi, A. Giarmoukakis, V. Kozobolis, B. Seitz, Biomechanical diagnosis of keratoconus: evaluation of the keratoconus match index and the keratoconus match probability, Acta Ophthalmol, 91 (2013) e258–62.

[23] S. Feizi, M. Yaseri, B. Kheiri, Predictive Ability of Galilei to Distinguish Subclinical Keratoconus and Keratoconus from Normal Corneas, J. Ophthalmic Vis. Res. 11 (2016) 8–16.

[24] J. Bühren, C. Kühne, T. Kohnen, Defining subclinical keratoconus using corneal first-surface higher-order aberrations, Am. J. Ophthalmol. 143 (2007) 381–9.

[25] J. Bühren, D. Kook, G. Yoon, T. Kohnen, Detection of subclinical keratoconus by using corneal anterior and posterior surface aberrations and thickness spatial profiles, Invest. Ophthalmol. Vis. Sci. 51 (2010) 3424–32.

[26] J.C. Reddy, C.J. Rapuano, J.R. Cater, K. Suri, P.K. Nagra, K.M. Hammersmith, Comparative evaluation of dual Scheimpflug imaging parameters in keratoconus, early keratoconus, and normal eyes, J. Cataract Refract. Surg. 40 (2014) 582–92.

[27] J. Bühren, T. Schäffeler, T. Kohnen, Validation of metrics for the detection of subclinical keratoconus in a new patient collective, J. Cataract Refract. Surg. 40 (2014) 259–68.

[28] A. Vega-Estrada, J.L. Alio, The use of intracorneal ring segments in keratoconus, Eye Vis. (Lond) 3 (2016) 8.

[29] T. de Jong, M.T. Sheehan, M. Dubbelman, S.A. Koopmans, N.M. Jansonius, Shape of the anterior cornea: comparison of height data from 4 corneal topographers, J. Cataract Refract. Surg. 39 (2013) 1570–80.

[30] H. Hashemi, A. Yekta, M. Khabazkhoob, Effect of keratoconus grades on repeatability of keratometry readings: Comparison of 5 devices, J. Cataract Refract. Surg. 41 (2015) 1065–72.

Highlights

1. Videokeratography is the most extensively used to corneal topography in keratoconus

2. Topographic indices have been developed to detect and grading keratoconus

3. The clinical use of Amsler-Krumeich classification is controversial

4. Coma has been demonstrated to be an effective value to management keratoconus

5. Anterior coma could be useful in keratoconus classification

Figure 1

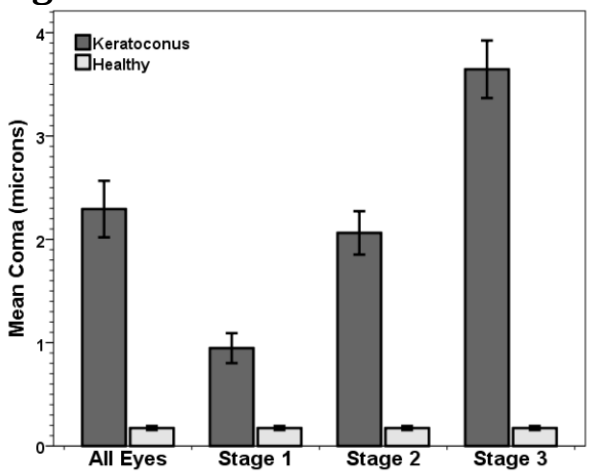

Figure 2

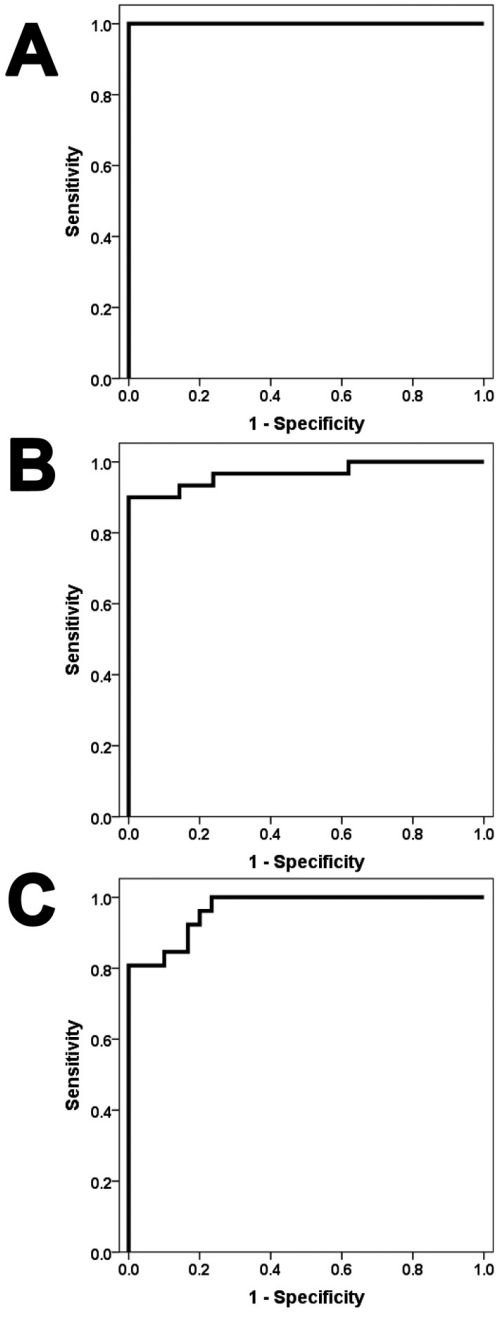

Table 1: Amsler-Krumeich keratoconus classification

Stage I	Eccentric steepening Myopia and/or astigmatism < 5.00 D Mean central K readings < 48.00 D Vogt's striae, no corneal opacities
Stage II	Myopia and/or astigmatism from 5.00-8.00 D Mean central K readings < 53.00 D Absence of scarring Minimum corneal thickness ≥ 400 µm
Stage III	Myopia and/or astigmatism from 8.00-12.00 D Mean central K readings > 53.00 D Absence of scarring Minimum corneal thickness from 200-400 µm
Stage IV	Refraction not measurable Mean central K readings > 55.00 D Central corneal scarring Minimum corneal thickness < 200 µm

Table 2. Results of ROC analysis of sensitivity and specificity of coma value to discriminate between keratoconus and normal eyes and between keratoconus stages.

Pairwise	AUC	95% CI	SE	Cutoff Value (µm)	Sensitivity (%)	Specificity (%)
Normal – Keratoconus	1	1 – 1	0.00	0.377	100%	100%
Normal – Stage 1	1	1 – 1	0.00	0.377	100%	100%
Stage 1 – 2	0.97	0.92 – 1.01	0.02	1.466	90%	100%
Stage 2 – 3	0.97	0.93 – 1	0.02	2.790	92%	83.3%

5.5. Detección del queratocono en atención primaria

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Keratoconus screening in primary eye care – A general overview.

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Keratoconus Screening in Primary Eye Care – A General Overview

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Keratoconus early detection (screening) and diagnosis requires an in-deep corneal analysis with different techniques; slip lamp assessment, corneal topography and corneal tomography are the most commonly accepted to detect clinical signs and assess anterior and posterior corneal surface and global corneal pachymetry. However, keratoconus early detection and definitive diagnosis are two different clinical procedures that require a different approach and goals. The aim of this review is to provide some general information about different corneal assessment technology, useful in keratoconus patient assessment; highlighting the differences in the adequate investigation techniques to its detection in primary eye care clinic and to conduct the definitive diagnosis (usually in a cornea specialist clinic). Information of most extensively available commercial devices and the advantages and disadvantages of their use in keratoconus early detection and diagnosis are described. In conclusion, corneal topography (Placido-based keratographers) plays a significant role in keratoconus detection, especially in primary eye care clinics. However, corneal tomography (with different slit scanning and/or rotational imaging devices) including posterior corneal surface assessment and global corneal pachymetry investigation, is critical in definitive keratoconus diagnosis.

Keywords

Keratoconus, early detection, screening, corneal topography, corneal tomography, primary eye care

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Keratoconus early detection (screening) and diagnosis requires an in-deep corneal analysis with different techniques available.[1] Slip lamp assessment and corneal topography/tomography are the most commonly accepted techniques in eye examination.

Corneal topography and corneal tomography are useful terms that distinguish between two different types of corneal examination, so both will coexist and be complementary.[2] In fact, hybrid systems, combining Placido disk-based videokeratography and slit-scan images provide reliable corneal measurements in keratoconus assessment.[3,4]

The aim of this review is to provide general information about different corneal assessment technologies useful in keratoconus assessment; highlighting the different investigative techniques from its detection in the primary eye care clinic to definitive diagnosis, usually in the cornea specialist clinic. Information of most extensively available commercial devices, and the advantages and disadvantages of their use in keratoconus early detection and diagnosis, are described.

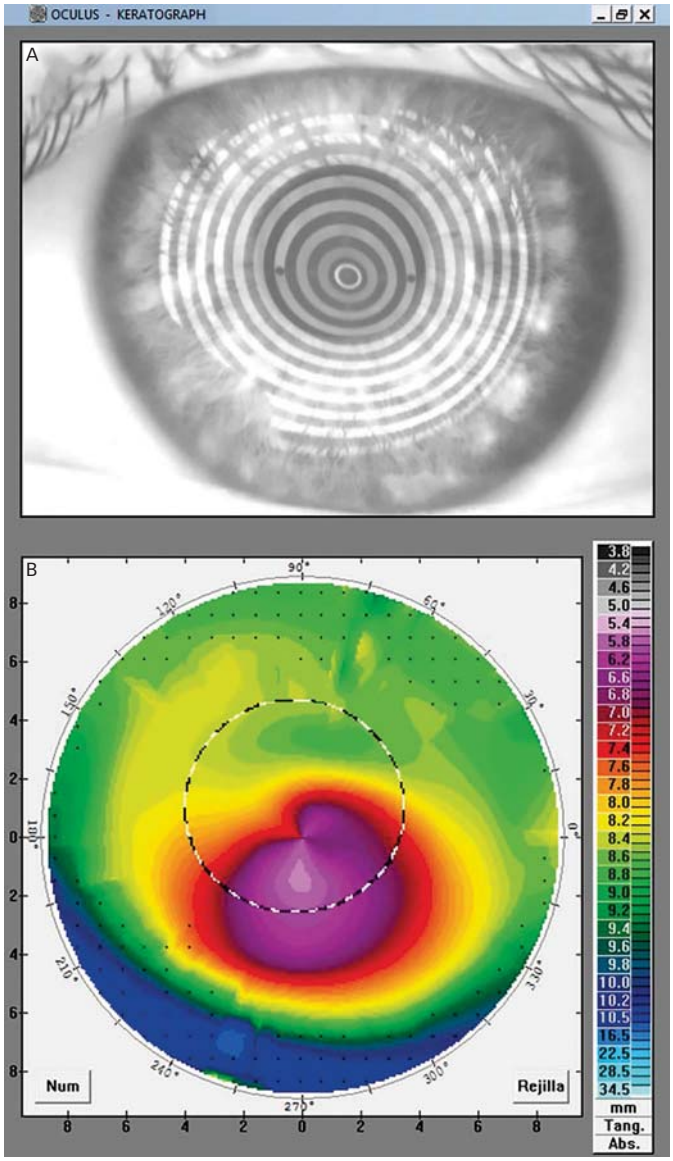
Method of literature search

We performed an extensive electronic search of the Medline and PubMed databases using individual and combinations of key words (keratoconus, keratoconus fustre, subclinical keratoconus, keratoconus treatment, keratoconus topography, keratoconus tomography, scheimpflug, keratoconus biomechanical properties, and keratoconus anterior OCT) in May 2016 to identify the relevant publications in this field. We included the references if they focused on assessment techniques of the cornea in keratoconus patients. We excluded techniques that are considered experimental, non-English publications and case reports.

Keratoconus

Keratoconus is a multifactorial disease with genetic, biochemical, biomechanical, and environmental pathophysiology,[5] characterised by a thinning and steepening of the central and paracentral cornea, affecting approximately 1/2000 people in the general population.[6–8] Commonly, this bilateral and asymmetric ectatic condition appears during the second decade of life and puberty and it progresses until the fourth decade of life, causing high myopia and irregular astigmatism.[5–8] Keratoconus patient management requires a multi-professional approach for early detection, correct diagnosis, follow up, monitoring and adequate management that involve: primary eye care practitioners, optometrists, contact lens (CL) practitioners and ophthalmologists with the last aim to provide better care and improve patients' quality of life.[9,10]

Figure 1: Placido-based topography in a keratoconus patient



A. Placido image; B. Tangential (power) map. Keratograph (OCULUS, Optikgeräte GmbH, Wetzlar, Germany).

Keratoconus detection, diagnosis and classification

Keratoconus diagnosis is a challenge.[5,7] Early stages of keratoconus, where clinical signs are not manifest on biomicroscopy (stromal thinning, conical protrusion, Fleischer corneal epithelial iron ring, Munson sign, Rizzuti sign, or Vogt striae)[7,8] but the cornea demonstrates subtle topographic features comparable to those of clinical keratoconus receive the name of fruste keratoconus, subclinical keratoconus or keratoconus suspect.[3,11–13] Therefore, distinguishing between healthy cornea and early keratoconus (in opposition to moderate or advanced stages), of subclinical keratoconus or other ectatic diseases imposes greater diagnostic challenge.[5,7] It is of paramount clinical importance in primary eye care and in screening refractive surgical patients to avoid iatrogenic corneal ectasia after laser surgery.[14–16]

Clinical keratoconus is reliably detected with Placido disk-based corneal topography and even sometimes at slit-lamp examination.[16] Other technologies, such as: corneal tomography (Scheimpflug or dual Scheimpflug devices),[3,13,17] anterior segment optical coherence tomography (AS-OCT),[18,19] biomechanical devices[20,21] that analyse the anterior and posterior corneal surface, full corneal thickness map, epithelial mapping, or corneal biomechanical properties are necessary to complete keratoconus diagnosis.[5,22]

Currently, there is no clinically accepted classification allowing eye-care practitioners to clearly differentiate between healthy and keratoconus cornea (especially in early stages), and that could be used in patients' follow-up in suspect (or diagnosed) cases. The most common classifications were the Amsler-Krumeich,[23] and Collaborative Longitudinal Evaluation of Keratoconus (CLEK)[24] classifications. However, both classifications fail to address current information and technological advances5 and a new classification criterion is necessary.

The Amsler-Krumeich classification proposes four different stages using refractive, topographic and biomicroscopic corneal signs. The CLEK classification proposes to use the average corneal power and root mean square (RMS) error for higher-order Zernike terms (derived from the first corneal surface wavefront) combined with clinical biomicroscopic signs. Because larger values of vertical coma have been found in keratoconic corneas, high-order corneal aberration analysis could play a relevant role in future keratoconus classification[24–28] Therefore, future keratoconus classifications will be directly dependent on the accuracy and reliability of the corneal device used in patient assessment.[27,29]

Corneal topography

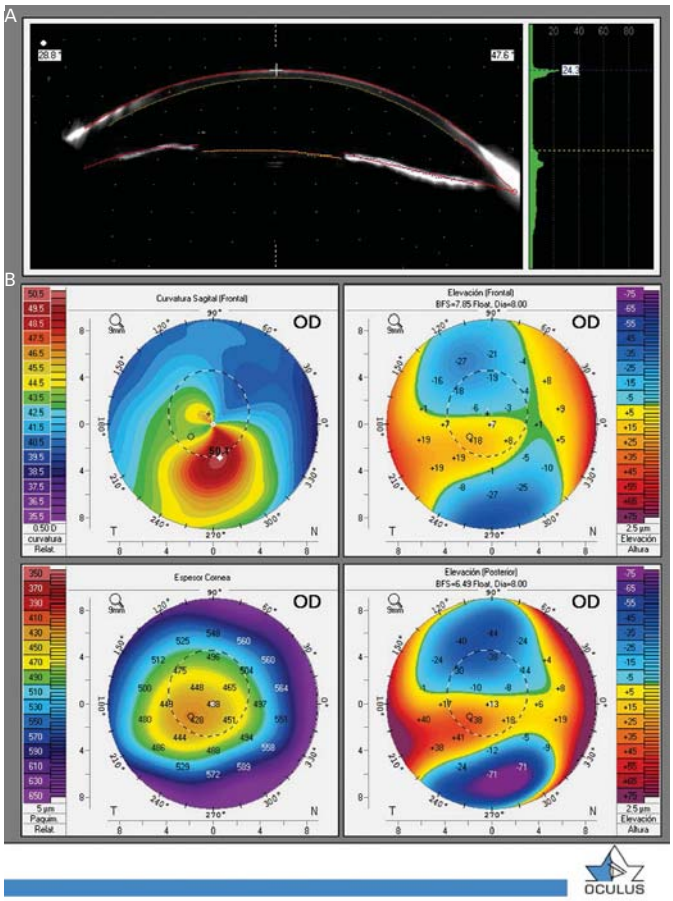
Corneal topography is a method of computer-assisted, non-invasive examination of the anterior surface of the cornea. It provides a qualitative and quantitative description of the morphology of the cornea in a topographical map after analysing the reflected image of illuminated rings (Placido disk) onto the corneal surface (*Figure 1*).[30]

Corneal topography was introduced in the mid-1980s with the developing of different algorithms to analyse the Placido photokeratoscope's images, and has represented a true revolution in the diagnosis and management of corneal disease,[2] including keratoconus. Nowadays, corneal topographers are one of the most extensively used devices in clinical practice.[26,29]

In fact, several mathematical indices have been developed with the aim of helping with keratoconus detection, grading the disease and monitoring its progression.[26,31] For example; central keratometry (K-value)[32] with different cut-off values to keratoconus suspect (>47.2 D); inferior-superior asymmetry (I-S value)[32] with a cut-off value of 1.4 D difference between average inferior and superior corneal powers at 3 mm from the centre of the cornea; the steepest radial axes (SRAX)[32] calculated with the angle between the steepest superior meridian and steepest inferior meridian; surface asymmetry index (SAI)[33,34]; keratoconus severity score (KSS)[24] calculated with some corneal topography features (axial pattern, average corneal power and higher-order RMS) and slit-lamp signs (including scarring); keratoconus prediction index (KPI)[35] calculated after a discriminant analysis of eight quantitative videokeratography indices (Simulated K1, Simulated K2, opposite sector index [OSI], centre/surround index [CSI], differential sector index [DSI], SAI, irregular astigmatism index [IAI] and analysed area [AA]); keratoconus percentage index (KISA%)[36] based on K-value, I-S value, keratometric astigmatism (AST), and SRAX indices; or cone location and magnitude index (CLMI),[37] calculated with the axial and tangential curvature data.

However, most of these indices depend on the topography software, but with sensitivity and specificity controversial, they may be difficult to understand[38] and have not been extensively used in clinical practice.

Figure 2: Corneal tomography in a keratoconus patient



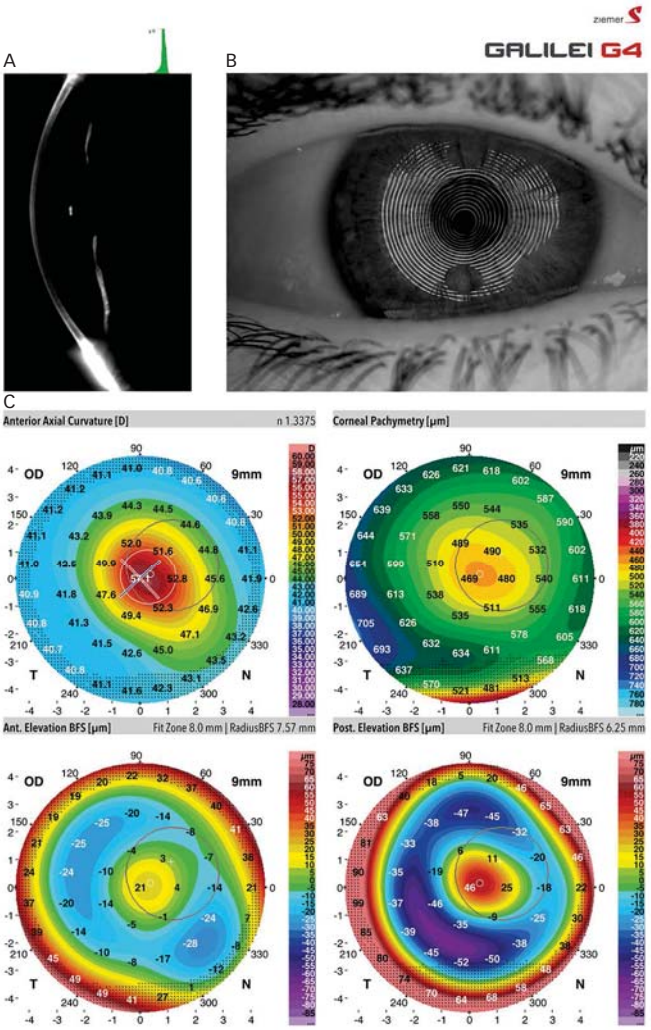
A. Scan image (Scheimpflug image); B. Axial (power) map, anterior and posterior elevation maps, and global pachymetry map. Pentacam (OCULUS Optikgeräte GmbH, Wetzlar, Germany).

Therefore, new criteria, easy to use and non-device dependent methods would be necessary to improve keratoconus detection, diagnosis and classification.[27,29]

Gas permeable (GP) CL fitting is the primary keratoconus management option.[6–8,39] However, fitting of GP lenses in keratoconus patients is challenging because the irregular cornea often requires several diagnostic lenses to achieve a final acceptable GP lens fit, which prolongs practitioner and patient chair time.[40–45] However, GP CL fitting could be improved with different CL fitting software that analyses Placido-based corneal topography curvature data to propose the lens parameters, mainly base optic zone radius and lens diameter.[40,41,46–49] Using these software could decrease the number of diagnostic lenses necessary to achieve an acceptable CL fit and reduce the chair time in keratoconus patients.[10,40,41,46]

Although, corneal topography is probably the most commonly used tool for the diagnosis of keratoconus, it is accepted that this technique may lead to false negatives in the subclinical phase. That means that Placido-based videokeratographers cannot identify very mild forms of keratoconus (fruste keratoconus) that would require to be identified, assessing corneal thickness and anterior/posterior curvature measurements over the entire cornea provided with corneal tomography.[22,50] Standard corneal topography could be an acceptable technique in primary care but not in speciality clinics or in screening refractive surgical patients,[14–16] where a complete diagnosis is necessary and complete corneal assessment with corneal tomography.

Figure 3: Anterior and posterior corneal elevation and global pachymetry maps achieved with Galilei corneal tomographer in a keratoconus patient

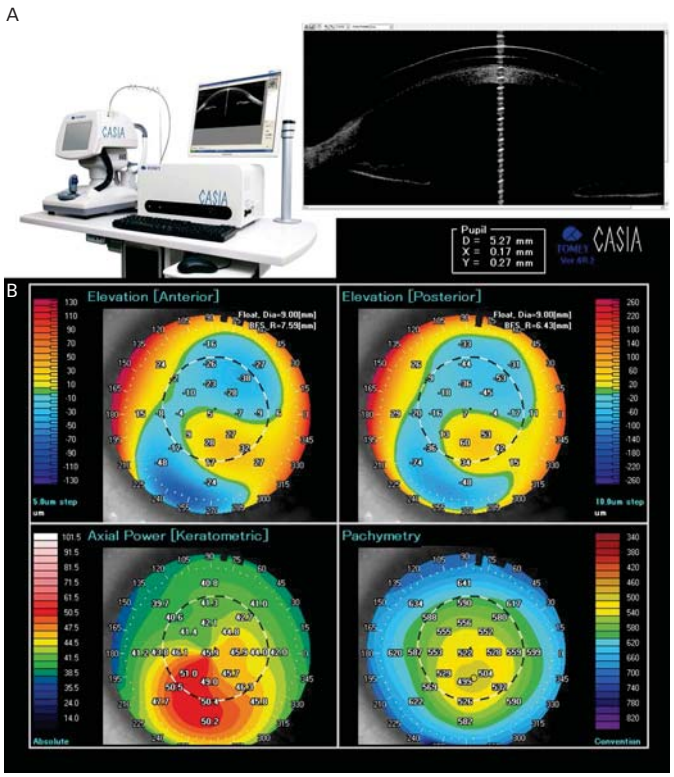


A. Scan image (Scheimpflug image); B. Placido image; C. Axial (power) map, global pachymetry map, anterior and posterior elevation maps.

Corneal tomography

The term computed tomography is classically used in medicine, for referring to the radiographic technique for imaging a section of an internal solid organ, producing a three-dimensional image. Corneal tomography allows three-dimensional characterisation of the cornea (*Figure 2*) after anterior and posterior corneal surface analysis, using different slit-imaging technologies,[2,51,52] such as vertical slit scanning, [53,54] rotational Scheimpflug imaging,[55] arc scanning with very high-frequency ultrasound, and optical coherence tomography.[56] The first device that permitted imaging of the anterior and posterior corneal surfaces, was the Orbscan II (Bausch + Lomb, New York, US).[53,54] This has since been replaced by rotational Scheimpflug devices, such as: Pentacam® (OCULUS Optikgeräte GmbH, Wetzlar Germany),[57] WaveLight® Oculyzer™ (Alcon, Texas, US)[56] and Preciso (Ivis Technologies, Taranto, Italy). Finally, other devices combine Placido-based topography with slit-image analysis and are collectively named hybrid systems, hybrid topographers or dual Scheimpflug-Placido tomographers. Highlight Galilei G4 (Ziemer, Port, Switzerland),[58] TMS-5 (Tomey, Aichi, Japan) and SIRIUS (CSO, Firenze, Italy)[59] are examples of these devices. In summary, corneal tomography defines the spatial relationship between the anterior and posterior corneal surfaces and provides a global thickness corneal map (*Figure 3*).

Figure 4: Anterior segment optical coherence tomography in a keratoconus patient (OCT-SA- Casia; Tomey, Aichi, Japan)



A. Scan image with a scleral lens; B. Anterior and posterior elevation maps, axial (power) map and global pachymetry map.

Corneal tomography has been recognised as a critical diagnostic component in keratoconus patients' assessment,[5] helping in diagnosis (differentiating between fustre and clinical keratoconus) and monitoring progression, because it is necessary to confirm changes on the posterior corneal surface and corneal thickness alteration in order to diagnose (and monitor) keratoconus.[5,13,50,60,61]

Anterior segment optical coherence tomography

The first report of AS-OCT imaging appeared in 1994.62 OCT compares the time delay of infrared light (1310 nm) reflected from the anterior segment structures against a reference reflection, achieving a high resolution cross-sectional image of the anterior segment of the eye (from 2 to 20 µm).[63]

There are three commercial AS-OCT devices; Visante (Carl Zeiss Meditec, Jena, Germany), RTVue-OCT (Optovue, California, US) and Casia SS-1000 (Tomey, Aichi, Japan).[64,65] AS-OCT has been proposed to assess keratoconus patients (*Figure 4*);[66] helping to investigate corneal thickness asymmetry,[67] epithelial thickness-distribution characteristics[68] and monitoring progression.[19] AS-OCT could be a promise tool in keratoconus diagnosis (helping to differentiate between fustre and clinical forms of keratoconus of healthy corneas).

Biomechanical devices

Keratoconus corneas show abnormalities in biomechanical response when they are compared to normal corneas in ex-vivo studies.[69,70] However, in-vivo measurement of corneal biomechanics remains a difficult task, and just two commercially available instruments have been proposed;[1,71,72] the Ocular Response Analyzer® (ORA; Reichert, New York, US) and the Corneal Visualization Scheimpflug Technology (Corvis® ST; Oculus Optikgeräte GmbH, Wetzlar, Germany).

Table 1: Commercially available methods and instruments for corneal assessment

Technology	Method	Product (manufacturer)
Keratometry	Javal-Schiotz principle	Two position keratometer*
	Bausch & Lomb principle	One position keratometer*
Corneal topography	Videokeratoscope	ATLAS 9000™ (Carl Zeiss Meditec, Jena, Germany) Keratograph (OCULUS Optikgeräte GmbH, Wetzlar, Germany) CA-800 (Topcon, Tokyo, Japan) Medmont E300 (Medmont, Victoria, Australia) TMS-4a (Tomey, Aichi, Japan) OPD-Scan III (Nidek Technologies, Padua, Italy) EyeSys 2000 (EyeSys Vision Inc, Texas, US)
Corneal tomography	Vertical slit-scan	Orbscan II (Bauch&Lomb, EE.UU.)
	Rotating Scheimpflug	Pentacam® (OCULUS Optikgeräte GmbH, Wetzlar, Germany) WaveLight® Oculyzer™ (Alcon, Texas, US) Preciso (Ivis Technologies, Taranto, Italy)
	Hybrid system	Galilei G4 (Ziemer, Port, Switzerland) TMS-5 (Tomey, Aichi, Japan) SIRIUS (CSO, Firenze, Italy)
	Anterior segment optical coherence tomography (AS-OCT)	Visante (Carl Zeiss Meditec, Jena, Germany) RTVue-OCT (Optovue, California, US) Casia SS-1000 (Tomey, Aichi, Japan)
	Arc scanning with very high-frequency ultrasound	Artemis 3 (ArcScan, Colorado, US)
Corneal biomechanical	Bi-directional applanation process	Ocular Response Analyzer® (ORA; Reichert, New York, US)
	Ultra-high speed Scheimpflug camera	Corneal Visualization Scheimpflug Technology (Corvis® ST; Oculus Optikgeräte GmbH, Wetzlar, Germany)

** Different manufacturers. Non-exhaustive list.*

The ORA employs a dynamic bi-directional applanation process with an air-pulse, similar to that of traditional air-puff tonometers.[1,71–73] The Corvis ST is a non-contact tonometer with a dual Scheimpflug, high-speed camera that takes more than 4,300 frames per second of the horizontal meridian of the cornea, and captures approximately 140 cross-sectional images of the cornea during the air-puff induced deformation.[1,71,72,74] Both devices determine different corneal biomechanical metrics, mainly corneal hysteresis (CH) and corneal resistance factor (CRF) with ORA -including 37 parameters that describe the waveform of the applanation signal- and deformation amplitude respectively with CorVis. Intraocular pressure (IOP) and IOP value corrected with corneal thickness value is also provided.

Corneal biomechanical metrics are statistically significant between keratoconic and healthy corneas using both ORA[71,75–77] (keratoconus showed lower CH and CRF value) and Corvis[71,78–80] (keratoconus showed higher deformation amplitude), which could be useful to detect subclinical keratoconus.[81]

Unfortunately, data provide for these devices have not proven to be a definitive keratoconus diagnostic value (able to differentiate between

keratoconus, forme fruste and normal eyes)[71] because a substantial overlap exists with normal corneas,[82,83] and further research is necessary to obtain valid cut-off values to use in combination with more clinical data.[20,72,75,77,80,84,85] In summary, further clinical validation is necessary to understand the meaning of these biomechanical parameters obtainied with ORA and Corvis before they can be used in clinical practice.[71]

Other technologies or devices have been proposed to measure corneal biomechanical properties, for example: acoustic radiation force (ARF),[86] applanation resonance tonometry (ART),[87] confocal microscopy,[88] optical coherence elastography,[89] scanning acoustic microscopy (SAM),[90] supersonic shear wave imaging (SSI)[91] that must be validated in human.[71]

Discussion

Keratoconus early detection, diagnosis and classification are a challenge.[5] Both early detection and final diagnosis require a complete eye exam and in-depth corneal assessment using different technologies, such as: corneal topography, corneal tomography, corneal biomechanics and others. However, it is necessary to differentiate between early detection of keratoconus and the final or definitive diagnosis. Early detection is of paramount importance in primary eye care, when a definitive diagnosis is not always required and referral to cornea specialist is necessary to conduct final keratoconus diagnosis. In fact, both procedures are slightly different and should follow different criteria.

Unfortunately, primary eye care service is not easy to define,[92] but there is a reasonable consensus accepting that primary care is the provision of first contact care for ophthalmic conditions and the follow up, preventive, and rehabilitative care of selected eye conditions,[92] in contrast with secondary or referral specialist services.[93] Related with keratoconus screening and diagnosis, in primary eye care, one of the most important purposes should be the detection potential keratoconus indicator (mainly related with patient's corneal shape) in a large population generally asymptomatic or with unspecific symptoms. This practice requires the use of cheap techniques accepted by patients and eye care practitioners with a reasonable sensitivity and specificity. The most commonly used in these clinics are Placido-based corneal topography. In future, if the price of corneal tomographers is reduced, these devices could be introduced in primary eye care clinics. A survey to optometrists in Australia showed that near of 45% of practitioners have a corneal topographic unit.[94] This percentage is lower in United Kingdom (26%) and higher in Spain (60%) (Author unpublished data).

Primary eye care practitioners play a relevant role in early detection of eye disorders and pathologies.[92,95–97] Keratoconus could be suspected in risk patients (Down syndrome, relatives of affected patients, ocular allergy, Asian or Arabian ethnicity, eye rubbing, floppy eyelid syndrome, atopy, connective tissue disorders [Marfan syndrome] and others)5,98,99 or when certain clinical signs are found in the eye exam, such as: scissors reflex during retinoscopy exam, "oil-droplet" reflex (Charleux sign), change in astigmatism refraction (in axe or power) or myopia increase with asymmetry between both eyes.[7,100–103]

In opposition, a definitive diagnose is usually done in specialist clinics, for example in cornea units, refractive surgery, etc. This practice requires establish keratoconus presence using the necessary techniques, which may be expensive but justifiable, such as: corneal tomography, AS-OCT and others devices that allow the characterisation of corneal biomechanical properties.

Conclusions

In summary, corneal topography plays a significant role in keratoconus detection in primary eye care, because anterior Placido-based corneal topographers are cheaper devices with great utility in keratoconus management (fitting GP CL) and follow up. However, a definitive keratoconus diagnosis requires anterior and posterior corneal assessment (with corneal tomography and other techniques) and global pachymetry investigation able to distinguish between healthy cornea, fustre keratoconus and keratoconus. So, corneal tomography is compulsory to conduct a definitive diagnosis or in refractive surgery patients screening. ❑

1. Rio-Cristobal A, Martin R, Corneal assessment technologies: current status, *Surv Ophthalmol*, 2014;59:599–614.
2. Ambrósio R, Belin MW, Imaging of the cornea: topography vs tomography, *J Refract Surg*, 2010;26:847–9.
3. Feizi S, Yaseri M, Kheiri B, Predictive ability of galilei to distinguish subclinical keratoconus and keratoconus from normal corneas, *J Ophthalmic Vis Res*, 2016;11:8–16.
4. Zemova E, Eppig T, Seitz B, et al., Interaction between topographic/tomographic parameters and dry eye disease in keratoconus patients, *Curr Eye Res*, 2014;39:1–8.
5. Gomes JAP, Tan D, Rapuano CJ, et al., Global consensus on keratoconus and ectatic diseases, *Cornea*, 2015;34:359–69.
6. Barnett M, Mannis MJ, Contact lenses in the management of keratoconus, *Cornea*, 2011;30:1510–6.
7. Rabinowitz YS, Keratoconus, *Surv Ophthalmol*, 1998;42:297–319.
8. Romero-Jiménez M, Santodomingo-Rubido J, Wolffsohn JS, Keratoconus: a review, *Cont Lens Anterior Eye*, 2010;33:157–66.
9. Ortiz-Toquero S, Perez S, Rodriguez G, et al., The influence of the refractive correction on the vision-related quality of life in keratoconus patients, *Qual Life Res*, 2016;25:1043–51.
10. Ortiz-Toquero S, Martin R, Fitting Gas Permeable Contact Lens in Keratoconus; Still a Challenge?, *Ophthalmol Open J*, 2016;1:e9–e12.
11. Sanctis U de, Loiacono C, Richiardi L, et al., Sensitivity and specificity of posterior corneal elevation measured by Pentacam in discriminating keratoconus/subclinical keratoconus, *Ophthalmology*, 2008;115:1534–9.
12. Schlegel Z, Hoang-Xuan T, Gatinel D, Comparison of and correlation between anterior and posterior corneal elevation maps in normal eyes and keratoconus-suspect eyes, *J Cataract Refract Surg*, 2008;34:789–95.
13. Smadja D, Touboul D, Cohen A, et al., Detection of subclinical keratoconus using an automated decision tree classification, *Am J Ophthalmol*, 2013;156:237–246.e1.
14. Randleman JB, Russell B, Ward MA, et al., Risk factors and prognosis for corneal ectasia after LASIK, *Ophthalmology*, 2003;110:267–75.
15. Martin R, Rachidi H, Stability of posterior corneal elevation one year after myopic laser in situ keratomileusis, *Clin Exp Optom*, 2012;95:177–86.
16. Santhiago MR, Giacomin NT, Smadja D, Bechara SJ, Ectasia risk factors in refractive surgery, *Clin Ophthalmol*, 2016;10:713–20.
17. Gilani F, Cortese M, Ambrósio RR, et al., Comprehensive anterior segment normal values generated by rotating Scheimpflug tomography, *J Cataract Refract Surg*, 2013;39:1707–12.
18. Xu Z, Jiang J, Yang C, et al., Value of corneal epithelial and Bowman's layer vertical thickness profiles generated by UHR-OCT for sub-clinical keratoconus diagnosis, *Sci Rep*, 2016;6:31550.
19. Fujimoto H, Maeda N, Shintani A, et al., Quantitative evaluation of the natural progression of keratoconus using three-dimensional optical coherence tomography, *Invest Ophthalmol Vis Sci*, 2016;57:169–75.
20. Steinberg J, Katz T, Lücke K, et al., Screening for keratoconus with new dynamic biomechanical in vivo scheimpflug analyses, *Cornea*, 2015;34:1404–12.
21. Roy AS, Shetty R, Kummelil MK, Keratoconus: a biomechanical perspective on loss of corneal stiffness, *Indian J Ophthalmol*, 2013;61:392–3.
22. Saad A, Gatinel D, Topographic and tomographic properties of forme fruste keratoconus corneas, *Invest Ophthalmol Vis Sci*, 2010;51:5546–55.
23. Krumeich JH, Daniel J, Knülle A, Live-epikeratophakia for keratoconus, *J Cataract Refract Surg*, 1998;24:456–63.
24. McMahon TT, Szczotka-Flynn L, Barr JT, et al., A new method for grading the severity of keratoconus: the Keratoconus Severity Score (KSS), *Cornea*, 2006;25:794–800.
25. Sideroudi H, Labiris G, Georgatzoglou K, et al., Fourier analysis of videokeratography data: Clinical usefulness in grade I and subclinical keratoconus, *J Cataract Refract Surg*, 2016;42:731–7.
26. 26. Piñero DP, Nieto JC, Lopez-Miguel A, Characterization of corneal structure in keratoconus, *J Cataract Refract Surg*, 2012;38:2167–83.
27. Ortiz-Toquero S, Rodriguez G, Juan V de, Martin R, Repeatability of wavefront aberration measurements with a placido-based topographer in normal and keratoconic eyes, *J Refract Surg*, 2016;32:338–44.
28. Alió JL, Shabayek MH, Corneal higher order aberrations: a method to grade keratoconus, *J Refract Surg*, 2006;22:539–45.
29. Ortiz-Toquero S, Rodriguez G, Juan V de, Martin R, Repeatability of placido-based corneal topography in keratoconus, *Optom Vis Sci*, 2014;91:1467–73.
30. Cavas-Martínez F, De la Cruz Sánchez E, Nieto Martínez J, et al., Corneal topography in keratoconus: state of the art, *Eye and Vision*, 2016;3:5.
31. Ramos-López D, Martínez-Finkelshtein A, Castro-Luna GM, et al., Screening subclinical keratoconus with placido-based corneal indices, *Optom Vis Sci*, 2013;90:335–43.
32. Schwiegerling J, Greivenkamp JE, Keratoconus detection based on videokeratoscopic height data, *Optom Vis Sci*, 1996;73:721–8.
33. Dingeldein SA, Klyce SD, Wilson SE, Quantitative descriptors of corneal shape derived from computer-assisted analysis of photokeratographs, *Refract Corneal Surg*, 5:372–8.
34. Wilson SE, Klyce SD, Quantitative descriptors of corneal topography. A clinical study, *Arch Ophthalmol*, 1991;109:349–53.
35. Maeda N, Klyce SD, Smolek MK, Thompson HW, Automated keratoconus screening with corneal topography analysis, *Invest Ophthalmol Vis Sci*, 1994;35:2749–57.
36. Sedghipour MR, Sadigh AL, Motlagh BF, Revisiting corneal topography for the diagnosis of keratoconus: use of Rabinowitz's KISA% index, *Clin Ophthalmol*, 2012;6:181–4.
37. Mahmoud AM, Roberts CJ, Lembach RG, et al., CLMI: the cone location and magnitude index, *Cornea*, 2008;27:480–7.
38. Dumitrica DM, Colin J, Indices for the detection of keratoconus, *Oftalmologia*, 2010;54:19–29.
39. Nejabat M, Khalili MR, Dehghani C, Cone location and correction of keratoconus with rigid gas-permeable contact lenses, *Cont Lens Anterior Eye*, 2012;35:17–21.
40. Nosch DS, Ong GL, Mavrikakis I, Morris J, The application of a computerised videokeratography (CVK) based contact lens fitting software programme on irregularly shaped corneal surfaces, *Cont Lens Anterior Eye*, 2007;30:239–48.
41. Mandathara PS, Fatima M, Taureen S, et al., RGP contact lens fitting in keratoconus using FITSCAN technology, *Cont Lens Anterior Eye*, 2013;36:126–9.
42. Pullum K, A keratoconus fitting system using the axial profile to establish optimum lens parameters, *Cont Lens Anterior Eye*, 2003;26:77–84.
43. Zhou AJ, Kitamura K, Weissman BA, Contact lens care in keratoconus, *Cont Lens Anterior Eye*, 2003;26:171–4.

44. Romero-Jiménez M, Santodomingo-Rubido J, González-Méijome JM, An assessment of the optimal lens fit rate in keratoconus subjects using three-point-touch and apical touch fitting approaches with the rose K2 lens, *Eye Contact Lens*, 2013;39:269–72.
45. Mandathara Sudharman P, Rathi V, Dumapati S, Rose K lenses for keratoconus--an Indian experience, *Eye Contact Lens*, 2010;36:220–2.
46. Ortiz-Toquero S, Rodriguez G, Juan V de, Martin R, Rigid Gas Permeable Contact Lens Fitting Using New Software in Keratoconic Eyes, *Optom Vis Sci*, 2016;93:286–92.
47. Bhatoa NS, Hau S, Ehrlich DP, A comparison of a topography-based rigid gas permeable contact lens design with a conventionally fitted lens in patients with keratoconus, *Cont Lens Anterior Eye*, 2010;33:128–35.
48. Jani BR, Szczotka LB, Efficiency and accuracy of two computerized topography software systems for fitting rigid gas permeable contact lenses, *CLAO J*, 2000;26:91–6.
49. Siddireddy JS, Mahadevan R, Comparison of conventional method of contact lens fitting and software based contact lens fitting with Medmont corneal topographer in eyes with corneal scar, *Cont Lens Anterior Eye*, 2013;36:176–81.
50. Wolf A, Abdallat W, Kollias A, et al., Mild topographic abnormalities that become more suspicious on Scheimpflug imaging, *Eur J Ophthalmol*, 2009;19:10–7.
51. Konstantopoulos A, Hossain P, Anderson DF, Recent advances in ophthalmic anterior segment imaging: a new era for ophthalmic diagnosis?, *Br J Ophthalmol*, 2007;91:551–7.
52. Swartz T, Marten L, Wang M, Measuring the cornea: the latest developments in corneal topography, *Curr Opin Ophthalmol*, 2007;18:325–33.
53. Auffarth GU, Wang L, Völcker HE, Keratoconus evaluation using the Orbscan Topography System, *J Cataract Refract Surg*, 2000;26:222–8.
54. Kampfer T, Wegener A, Dragomirescu V, Hockwin O, Improved biometry of the anterior eye segment, *Ophthalmic Res*, 1989;21:239–48.
55. Rosales P, Marcos S, Pentacam Scheimpflug quantitative imaging of the crystalline lens and intraocular lens, *J Refract Surg*, 2009;25:421–8.
56. Kanellopoulos AJ, Asimellis G, Comparison of high-resolution Scheimpflug and high-frequency ultrasound biomicroscopy to anterior-segment OCT corneal thickness measurements, *Clin Ophthalmol*, 2013;7:2239–47.
57. Rabsilber TM, Khoramnia R, Auffarth GU, Anterior chamber measurements using Pentacam rotating Scheimpflug camera, *J Cataract Refract Surg*, 2006;32:456–9.
58. Cerviño A, Dominguez-Vicent A, Ferrer-Blasco T, et al., Intrasubject repeatability of corneal power, thickness, and wavefront aberrations with a new version of a dual rotating Scheimpflug-Placido system, *J Cataract Refract Surg*, 2015;41:186–92.
59. Montalbán R, Alió JL, Javaloy J, Piñero DP, Intrasubject repeatability in keratoconus-eye measurements obtained with a new Scheimpflug photography-based system, *J Cataract Refract Surg*, 2013;39:211–8.
60. Muftuoglu O, Ayar O, Ozulken K, et al., Posterior corneal elevation and back difference corneal elevation in diagnosing forme fruste keratoconus in the fellow eyes of unilateral keratoconus patients, *J Cataract Refract Surg*, 2013;39:1348–57.
61. Smadja D, Santhiago MR, Mello GR, et al., Influence of the reference surface shape for discriminating between normal corneas, subclinical keratoconus, and keratoconus, *J Refract Surg*, 2013;29:274–81.
62. Izatt JA, Hee MR, Swanson EA, et al., Micrometer-scale resolution imaging of the anterior eye in vivo with optical coherence tomography, *Arch Ophthalmol*, 1994;112:1584–9.
63. Ramos JLB, Li Y, Huang D, Clinical and research applications of anterior segment optical coherence tomography - a review, *Clin Experiment Ophthalmol*, 2009;37:81–9.
64. Wang C, Xia X, Tian B, Zhou S, Comparison of Fourier-Domain and Time-Domain Optical Coherence Tomography in the Measurement of Thinnest Corneal Thickness in Keratoconus, *J Ophthalmol*, 2015;2015:402925.
65. Szalai E, Berta A, Hassan Z, Módis L, Reliability and repeatability of swept-source Fourier-domain optical coherence tomography and Scheimpflug imaging in keratoconus, *J Cataract Refract Surg*, 2012;38:485–94.
66. Nakagawa T, Maeda N, Higashiura R, et al., Corneal topographic analysis in patients with keratoconus using 3-dimensional anterior segment optical coherence tomography, *J Cataract Refract Surg*, 2011;37:1871–8.
67. Kanellopoulos AJ, Asimellis G, OCT-derived comparison of corneal thickness distribution and asymmetry differences between normal and keratoconic eyes, *Cornea*, 2014;33:1274–81.
68. Kanellopoulos AJ, Asimellis G, OCT corneal epithelial topographic asymmetry as a sensitive diagnostic tool for early and advancing keratoconus, *Clin Ophthalmol*, 2014;8:2277–87.
69. 69. Nash IS, Greene PR, Foster CS, Comparison of mechanical properties of keratoconus and normal corneas, *Exp Eye Res*, 1982;35:413–24.
70. 70. Andreassen TT, Simonsen AH, Oxlund H, Biomechanical properties of keratoconus and normal corneas, *Exp Eye Res*, 1980;31:435–41.
71. Bao F, Geraghty B, Wang Q, Elsheikh A, Consideration of corneal biomechanics in the diagnosis and management of keratoconus: is it important?, *Eye Vis*, 2016;3:18.
72. Piñero DP, Alcón N, In vivo characterization of corneal biomechanics, *J Cataract Refract Surg*, 2014;40:870–87.
73. Luce DA, Determining in vivo biomechanical properties of the cornea with an ocular response analyser, *J Cataract Refract Surg*, 2005;31:156–62.
74. Valbon BF, Ambrósio R, Fontes BM, et al., Ocular biomechanical metrics by CorVis ST in healthy Brazilian patients, *J Refract Surg*, 2014;30:468–73.
75. Shah S, Laiquzzaman M, Bhojwani R, et al., Assessment of the biomechanical properties of the cornea with the ocular response analyzer in normal and keratoconic eyes, *Invest Ophthalmol Vis Sci*, 2007;48:3026–31.
76. Schweitzer C, Roberts CJ, Mahmoud AM, et al., Screening of forme fruste keratoconus with the ocular response analyser, *Invest Ophthalmol Vis Sci*, 2010;51:2403–10.
77. Fontes BM, Ambrósio R, Jardim D, et al., Corneal biomechanical metrics and anterior segment parameters in mild keratoconus, *Ophthalmology*, 2010;117:673–9.
78. Tian L, Huang Y-F, Wang L-Q, et al., Corneal biomechanical assessment using corneal visualization scheimpflug technology in keratoconic and normal eyes, *J Ophthalmol*, 2014;2014:147516.
79. Ali NQ, Patel D V, McGhee CNJ, Biomechanical responses of healthy and keratoconic corneas measured using a noncontact scheimpflug-based tonometer, *Invest Ophthalmol Vis Sci*, 2014;55:3651–9.
80. Tian L, Ko MWL, Wang L, et al., Assessment of ocular biomechanics using dynamic ultra high-speed Scheimpflug imaging in keratoconic and normal eyes, *J Refract Surg*, 2014;30:785–91.
81. Pniakowska Z, Jurowski P, Detection of the early keratoconus based on corneal biomechanical properties in the refractive surgery candidates, *Indian J Ophthalmol*, 2016;64:109–13.
82. Fontes BM, Ambrósio R, Velarde GC, Nosé W, Ocular response analyzer measurements in keratoconus with normal central corneal thickness compared with matched normal control eyes, *J Refract Surg*, 2011;27:209–15.
83. Johnson RD, Nguyen MT, Lee N, Hamilton DR, Corneal biomechanical properties in normal, forme fruste keratoconus, and manifest keratoconus after statistical correction for potentially confounding factors, *Cornea*, 2011;30:516–23.
84. Kirwan C, O'Malley D, O'Keefe M, Corneal hysteresis and corneal resistance factor in keratoectasia: findings using the Reichert ocular response analyzer, *Ophthalmologica*, 2008;222:334–7.
85. Luz A, Lopes B, Hallahan KM, et al., Discriminant Value of Custom Ocular Response Analyzer Waveform Derivatives in Forme Fruste Keratoconus, *Am J Ophthalmol*, 2016;164:14–21.
86. Urs R, Lloyd HO, Silverman RH, Acoustic radiation force for noninvasive evaluation of corneal biomechanical changes induced by cross-linking therapy, *J Ultrasound Med*, 2014;33:1417–26.
87. Beckman Rehnman J, Behndig A, Hallberg P, Lindén C. Increased corneal hysteresis after corneal collagen crosslinking: a study based on applanation resonance technology, *JAMA Ophthalmol*, 2014;132:1426–32.
88. Scarcelli G, Besner S, Pineda R, et al., In vivo biomechanical mapping of normal and keratoconus corneas, *JAMA Ophthalmol*, 2015;133:480–2.
89. Ford MR, Dupps WJ, Rollins AM, et al., Method for optical coherence elastography of the cornea, *J Biomed Opt*, 16:16005.
90. Beshtawi IM, Akhtar R, Hillarby MC, et al., Biomechanical Changes of Collagen Cross-Linking on Human Keratoconic Corneas Using Scanning Acoustic Microscopy, *Curr Eye Res*, 2016;41:609–15.
91. Touboul D, Gennisson J-L, Nguyen T-M, et al., Supersonic shear wave elastography for the in vivo evaluation of transepithelial corneal collagen cross-linking, *Invest Ophthalmol Vis Sci*, 2014;55:1976–84.
92. Riad SF, Dart JKG, Cooling RJ, Primary care and ophthalmology in the United Kingdom, *Br J Ophthalmol*, 2003;87:493–9.
93. Starfield B, Is primary care essential?, *Lancet*, 1994;344:1129–33.
94. Hodge C, Chan C, Zantos S, et al., Therapeutic treatment of keratoconus: a survey of local optometric practice criteria, *Clin Exp Optom*, 2015;98:312–8.
95. Duenas MR, Public health and optometry--an eye on prevention, *J Am Optom Assoc*, 1997;68:211–3.
96. Fingeret M, Therapeutics and the profession of optometry-a look back, *Optom Vis Sci*, 2012;89:372.
97. Kalloniatis M, Ly C, The role of optometry in collaborative eye care, *Clin Exp Optom*, 2016;99:201–3.
98. McGhee CNJ, 2008 Sir Norman McAlister Gregg Lecture: 150 years of practical observations on the conical cornea-what have we learned?, *Clin Experiment Ophthalmol*, 2009;37:160–76.
99. Gordon-Shaag A, Millodot M, Shneor E, Liu Y, The genetic and environmental factors for keratoconus, *Biomed Res Int*, 2015;2015:795738.
100. Goebels S, Käsmann-Kellner B, Eppig T, et al., Can retinoscopy keep up in keratoconus diagnosis?, *Cont Lens Anterior Eye*, 2015;38:234–9.
101. Naderan M, Shoar S, Kamaleddin MA, et al., Keratoconus Clinical Findings According to Different Classifications, *Cornea*, 2015;34:1005–11.
102. Vazirani J, Basu S, Keratoconus: current perspectives, *Clin Ophthalmol*, 2013;7:2019–30.
103. Henriquez MA, Izquierdo L, Belin MW, Intereye Asymmetry in Eyes With Keratoconus and High Ammetropia: Scheimpflug Imaging Analysis, *Cornea*, 2015;34 Suppl 1:S57-60.

Capítulo 6

Desarrollo de un nuevo algoritmo para simplificar la adaptación de LC RPG en queratocono

CHAPTER 6: Development of a new algorithm to simplify the GP CL fitting in keratoconus

6.1. Nuevo algoritmo para mejorar la adaptación de LC RPG en queratocono

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New web-based algorithm to improve rigid gas permeable contact lens fitting in keratoconus.

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New web-based algorithm to improve rigid gas permeable contact lens fitting in keratoconus

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ABSTRACT

Purpose: To calculate and validate a new web-based algorithm for selecting the back optic zone radius (BOZR) of spherical gas permeable (GP) lens in keratoconus eyes.
Methods: A retrospective calculation (n = 35; multiple regression analysis) and a posterior prospective validation (new sample of 50 keratoconus eyes) of a new algorithm to select the BOZR of spherical KAKC design GP lenses (Conoptica) in keratoconus were conducted. BOZR calculated with the new algorithm, manufacturer guidelines and APEX software were compared with the BOZR that was finally prescribed. Number of diagnostic lenses, ordered lenses and visits to achieve optimal fitting were recorded and compared those obtained for a control group [50 healthy eyes fitted with spherical GP (BIAS design; Conoptica)].
Results: The new algorithm highly correlated with the final BOZR fitted ($r^2 = 0.825$, $p < 0.001$). BOZR of the first diagnostic lens using the new algorithm demonstrated lower difference with the final BOZR prescribed (-0.01 ± 0.12 mm, p = 0.65; 58% difference ≤ 0.05 mm) than with the manufacturer guidelines (+0.12 ± 0.22 mm, $p < 0.001$; 26% difference ≤ 0.05 mm) and APEX software (-0.14 ± 0.16 mm, p = 0.001; 34% difference ≤ 0.05 mm). Close numbers of diagnostic lens (1.6 ± 0.8, 1.3 ± 0.5; p = 0.02), ordered lens (1.4 ± 0.6, 1.1 ± 0.3; $P < 0.001$), and visits (3.4 ± 0.7, 3.2 ± 0.4; p = 0.08) were required to fit keratoconus and healthy eyes, respectively.
Conclusion: This new algorithm (free access at www.calculens.com) improves spherical KAKC GP fitting in keratoconus and can reduce the practitioner and patient chair time to achieve a final acceptable fit in keratoconus. This algorithm reduces differences between keratoconus GP fitting (KAKC design) and standard GP (BIAS design) lenses fitting in healthy eyes.

1. Introduction

Keratoconus is a progressive corneal disorder that is characterized by a thinning and steepening of the central and paracentral cornea [1–4]. This ectatic condition is bilateral and asymmetric, and it causes high refractive myopia and irregular astigmatism. Keratoconus affects approximately 1/2000 people in the general population [1–4]. Keratoconus commonly appears during the second decade of life and puberty, and it progresses until the fourth decade of life, when it generally stabilizes [1–4].

The refractive error can be managed with spectacles or soft contact lenses (CLs) in the early stages of this disease, but corneal irregularities induce higher-order aberrations that cannot be corrected with traditional ophthalmic lenses as keratoconus progresses [2,4]. Gas permeable (GP) CLs represent the best option for visual rehabilitation of keratoconus [1–4]. This type of CLs generally improve best corrected visual acuity (BCVA) better than spectacles or soft CL because the tear layer between the GP CL and the anterior surface of the cornea reduces visual distortion and forms a new regular optical surface [2,5,6].

The fitting of GP lenses in keratoconus patients is challenging for eye care practitioners because the irregular cornea often requires several diagnostic lenses to achieve a final acceptable GP lens fit, which prolongs practitioner and patient chair time [7–12]. Manufacturers of GP lenses generally provide guidelines for

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selecting the back optic zone radius (BOZR) of the CL to fit in keratoconus eyes based on the anterior corneal curvature, but changes in the parameters of the lens are still needed, which increases the number of diagnostic and ordered CLs required for these patients [11].

This study describe the development of a new web-based algorithm (called Calculens.com) to select the BOZR, peripheral geometry and total diameter of the initial diagnostic lens in keratoconus eyes, which will enable practitioners to decrease the number of diagnostic and ordered lenses that are required to complete the final GP lens fitting in keratoconus patients.

2. Materials and methods

2.1. Methods

The study was divided into two phases: a retrospective study to calculate the new algorithm to select the BOZR, peripheral geometry and total diameter of the initial diagnostic lens and a second prospective phase to validate the use of this algorithm in a different sample of keratoconus patients. All patients enrolled in the study were attended in the Optometry Group of the IOBA Eye Institute (University of Valladolid, Spain), which is a tertiary referral clinic that treats patients with irregular corneas and other eye disorders. The Human Sciences Ethics Committee of the University of Valladolid approved the study. Informed consent was obtained from each subject, and all subjects were treated in accordance with the Declaration of Helsinki.

A complete eye examination was conducted in all participating subjects, and the following data were collected: demographic information; CL information (BOZR, power, diameter, design, manufacturer) in previous CL wearers; BCVA with spectacles and CLs; topographic assessment (Orbscan II; Bausch & Lomb, Rochester, NY, USA, version 3.12; Oculus Keratograph, Oculus Optikgeräte GmbH, Wetzlar, Germany and Galilei-G4, Ziemer Group, Port, Switzerland) when available; keratometry (OM-4 Topcon, Japan) and anterior eye biomicroscopy.

Patients with any active ocular-surface disease (except keratoconus), medication use that could affect ocular physiology or with a history of acute corneal hydrops, any type of ocular surgery or any other ocular disease were excluded. Patients with GP intolerance, unsatisfactory fitting of GP CLs or toric GP CLs were also excluded.

2.2. Lens design parameters (retrospective and prospective study phases)

All keratoconus patients were fitted with spherical tetra-curve GP CLs that were specifically designed for keratoconus eyes (KAKC GP, Conoptica-Hecht Contactlinsen, Germany). BOZR, periphery geometry [available in two geometries: N or normal and F or Flat (with a peripheral curve 0.60 mm flatter than N design according manufacturer's instructions)] and total diameter values were collected to statistical comparison (in cases fitted with different lens diameter the equivalent lens was calculated to guarantee same sagittal height and allow BOZR statistical comparison) [13].

A rotationally symmetric bi-aspheric GP lens design (BIAS-GP; Conoptica-Hecht Contactlinsen, Germany) was fitted in healthy eyes in prospective phase.

2.3. Retrospective phase: calculation of the new algorithm to select the first diagnostic lens parameters

Thirty-five GP lenses that were successfully fitted in keratoconus eyes were retrospectively analysed.

The patients' age, refraction, BCVA with spectacles and CL, corneal topography data (simulated keratometry, astigmatism power, axis of astigmatism, eccentricity, maximum corneal power point, central corneal thickness, anterior best fit sphere and posterior best fit sphere), manual keratometry readings and the

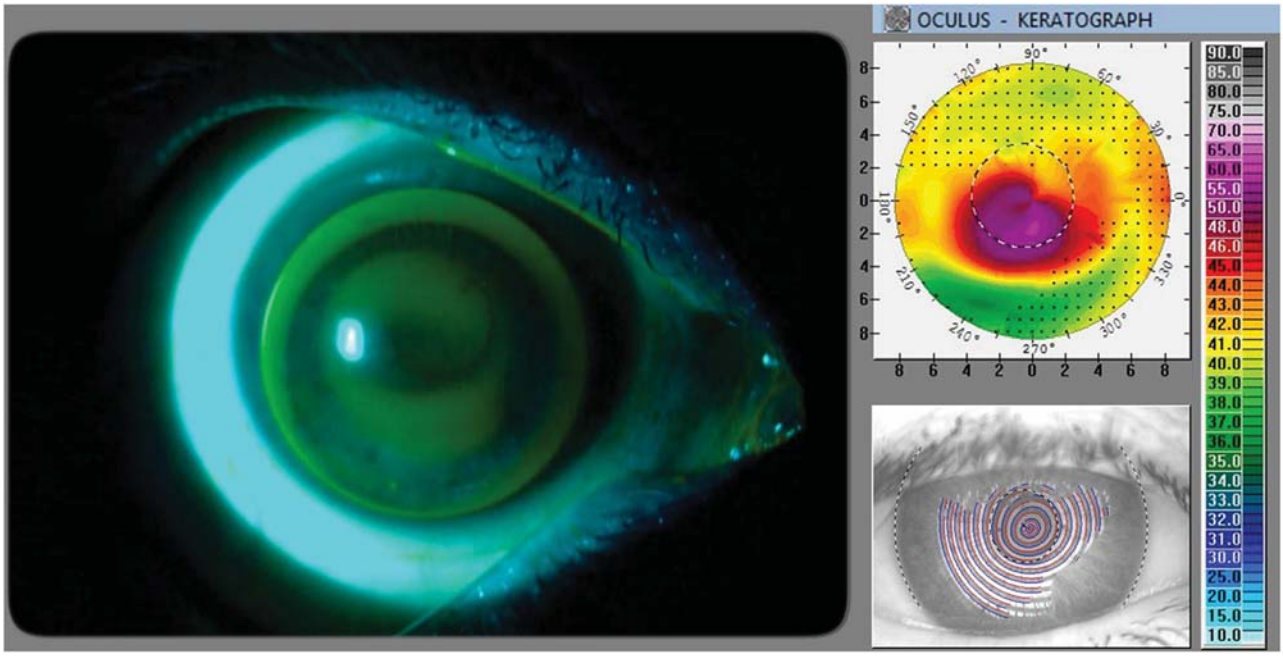

Fig. 1. Fluorescein pattern (left) of the lens proposal by Calculens.com (BOZR 7.00 mm; Diameter 9.20 mm and peripheral geometry N) in a keratoconus patient. OCULUS Keratograph anterior corneal topography is showed at right top and Placido image at right bottom. Final fitted GP lens was BOZR 7.00 mm; Diameter 9.20 mm and peripheral geometry N with a back vertex power of +4.00 D that achieved a visual acuity of 1.0 (6/6).

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definitive parameters of GP lens fitted were collected for statistical analyses.

2.4. Prospective phase: validation of the new predicting algorithm to select the first diagnostic lens

A new sample of keratoconus eyes was included in the prospective clinical validation of the new algorithm.

2.4.1. GP fitting procedure in prospective phase

The first diagnostic lens was calculated using the new algorithm (developed in the retrospective study phase) and it was inserted into the patient's eye, and the lens fitting assessment was evaluated (static and dynamic fit) after an adaptation period of approximately 30 min using the instillation of sodium fluorescein (Fig. 1). An acceptable fit was achieved when a well-centred lens with adequate movement with blinking provided a correct fluorescein pattern (divided support or three-point-touch: lightly touch the apex with peripheral alignment in keratoconus) was obtained [5]. The BOZR was changed if the BOZR of diagnostic lens was inadequate. The BOZR of the next diagnostic lens was decreased in 0.10 mm steps if the BOZR of the lens was flattened (apical touch). In contrast, the BOZR of the next diagnostic lens was increased in 0.10 mm steps if the BOZR was steepened (apical bearing). Overall CL diameter and peripheral geometry were modified to improve CL stability and peripheral fluorescein pattern if was necessary. The number of diagnostic lens was recorded when an acceptable BOZR was achieved, and over-refraction was performed to determine the power of the GP lens that provided the BCVA. The GP lens was ordered from the manufacturer once the lens parameters were determined (BOZR, diameter, periphery geometry and power).

The ordered GP lens was provided in the second visit (i.e., the dispensing visit), and lens fitting visual acuity and patient comfort were evaluated. Patients were instructed in CL management and care if the GP fit was optimal, and a follow-up visit was scheduled after 2–3 weeks of lens wear. However, GP CL specifications (BOZR, diameter, edge lift and/or power) were modified if the GP fit was not adequate, and a second GP was ordered. This process was repeated until the optimal GP CL fit was achieved, and the number of ordered CL was recorded.

A follow-up visit was conducted after three weeks of CL wear to assess whether the GP provided a BCVA that was not improvable with over-refraction, the GP provided at least 6–8 h of comfortable

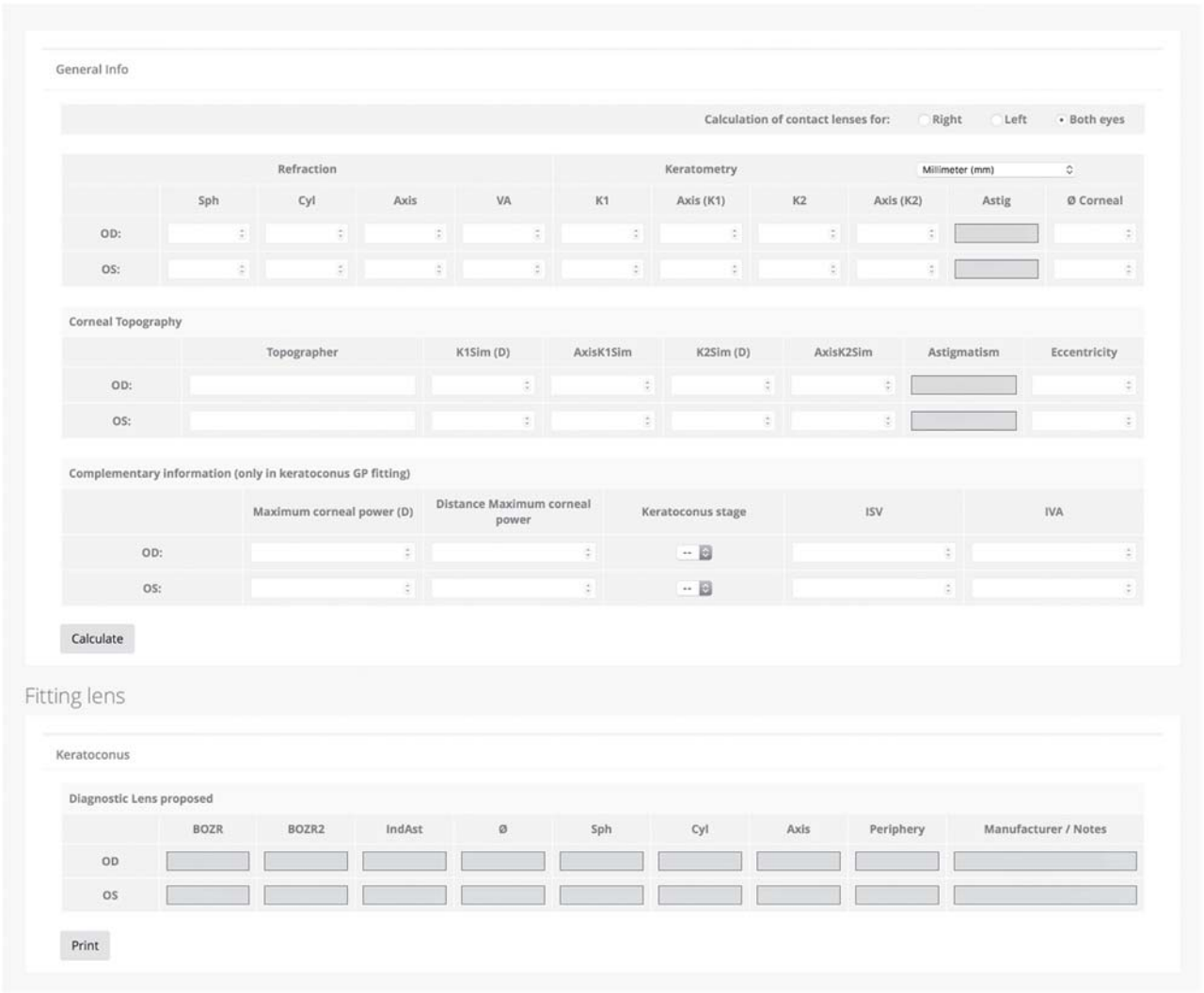

Fig. 2. Screenshot of Calculens.com. Refraction, keratometry and corneal diameter are essential to calculate GP CL in keratoconus eyes using Calculens.com. Other fields improve the GP calculation (i.e. periphery of the lens) but are not mandatory in BOZR calculation.

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wear, and the optimal physiology of corneal surface was obtained without CL-related complications. The fit was considered acceptable and finalized if all of these conditions occurred, and the number of visits was recorded. A new GP was reordered if the GP fit was inadequate, and a new follow-up visit was scheduled.

A control group formed of healthy eyes (non-keratoconus, without other eye pathology) was successfully fitted with GP spherical lenses (BIAS S GP, Conoptica-Hecht Contactlinsen, Germany) according to manufacturer guidelines to assess differences between the number of diagnostic lens, ordered lens and visits that were required to achieve optimal GP lens fit in healthy and keratoconus eyes.

2.5. Webpage design

In order to work at any place with this new algorithm to calculate GP CL in keratoconus, we utilized internet-based technology to facilitate Calculens.com use (www.calculens.com). HTML (Hypertext Markup Language) was applied to build the basic structure of web page beside Java Script. This system took the Apache Tomcat server running on the Java virtual machine (JVM) as web server. Calculens.com interacts with a MySQL database server, using Internet as means of transportation through the TCP/IP protocol. Calculens.com would allow multi-users parallel access at the same time and at different locations to calculate their GP CL parameters. Moreover, a Web-based interface allows for a fast and reliable data entry process (Fig. 2).

2.6. Data analysis

Statistical analysis was performed using the SPSS 15.0 (SPSS, Chicago, IL, USA) statistical package for Windows. A normal distribution of variables was assessed using the Kolmogorov–Smirnov test, and p-values > 0.05 indicated that the data were normally distributed in both phases of the study. Results were presented as means ± standard deviation (SD), maximum and minimum range and median and interquartile range (IQR) when data follows non-parametric distribution.

The new algorithm (retrospective study phase) was calculated using a multiple regression analysis (stepwise regression) of all registered biometric variables and the bidirectional elimination approach to choose the predictive variables to be included in the equation that provided the best adjusted R-squared value with the final fitted BOZR, CL diameter and periphery geometry.

To validate the use of our new algorithm we used patients' data in the prospective phase to calculate the BOZR of the first diagnostic lenses with three different methods: a) with our new algorithm (calculens.com), b) with the BOZR following current manufacturer's guidelines (BOZR = horizontal meridian – 0.1 mm) and c) with the BOZR showed by the APEX software CL fitting (APEX, version 1.1.0.6, developed by Hecht Contactlinsen in association with Oculus (Oculus Optikgeräte GmbH, Wetzlar, Germany), [displays a simulated fluorescein pattern of the specified GP design to aid the fitting procedure and includes the specific design for keratoconus KAKC lens]). These three values were compared with the final fitted BOZR in the prospective phase using a paired *t*-test (p-values < 0.05 were considered statistically significant). A linear regression quantified the r^2 correlation coefficient between the different calculated BOZRs (p-value < 0.05 was considered statistically significant).

The arithmetic and absolute mean differences between the final fitted BOZR with the BOZR calculated with the new algorithm, the BOZR calculated following the manufacturer's guideline, and showed by APEX were calculated. The absolute difference was calculated to avoid the effect of positive and negative differences that could affect the mean value. An absolute difference was clearly represented when the BOZR proposed by each method was closer to the final fitted BOZR.

Agreement between the BOZR of the final fitted GP lens with the BOZR of the first trial lens calculated by the new algorithm, manufacturer's guidelines and APEX software was evaluated using Bland-Altman analysis [14]. Differences between the BOZRs fitted and proposed by each method were plotted against the means of each BOZR. The 95% limits of agreement (LoA) were calculated (mean of the difference ± 1.96 × standard deviation).

The mean values of the diagnostic lenses, ordered lenses and visits were compared between the control group and keratoconus eyes using a non-parametric Mann-Whitney *U* test (p-values < 0.05 were considered significant).

3. Results

3.1. Retrospective phase: calculation of the new algorithm

Thirty-five keratoconus eyes of twenty-one patients (14 men and 7 women) with a mean age of 33.8 ± 12.8 years (range 18–56 years) were included in the retrospective phase. A new predicting algorithm was defined ($r^2 = 0.825$, $p < 0.001$) (Fig. 3). The mean spherical equivalent refractive error was −5.50 ± 3.60 D (range −0.75 D to −12.25 D), and the mean of simulated keratometry reading was 7.07 ± 0.48 mm. The BCVAs (decimal notation Snellen chart) with spectacles and CL were 0.60 ± 0.28 (median 0.60; IQR 0.40) and 0.90 ± 0.22 (median 1.00; IQR 0.23), respectively.

The mean of BOZR fitted was 7.12 ± 0.46 mm (range 5.80–7.75 mm), the total diameter of 9.20 mm was the most commonly fitted (in the 68.6% of the fittings) with a range between 8.80 to 9.40 mm; and the standard periphery geometry (N) was fitted in the 51.4% of the cases.

3.2. Prospective phase: validation of the new algorithm

Fifty new keratoconus eyes of twenty-eight patients (17 men and 11 women) with a mean age of 35.5 ± 10.1 years (range 19–55 years) were enrolled in the clinical validation of the new algorithm. Three of the initial patients included (6 eyes) were not included in statistical analyses because they did not achieve a comfortable wearing of the GP lens. The mean spherical equivalent refractive

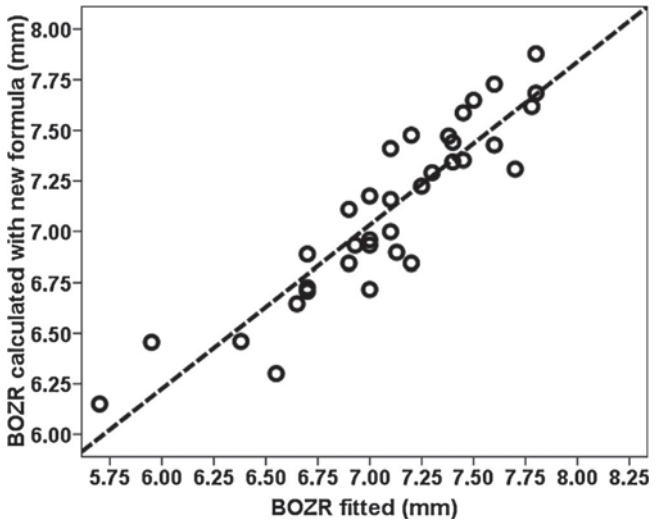

Fig. 3. Single linear regression analysis between the BOZR proposed by the new predicting algorithm and the final BOZR fitted in the retrospective phase. Regression equation: BOZR calculated with the new algorithm = 1.05 * BOZR fitted − 0.375.

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error was −3.91 ± 4.10 D (range 0.25 D to −13.25 D), and the mean simulated keratometry reading was 7.19 ± 0.47 mm. The BCVAs (decimal notation Snellen chart) with spectacles and CL were 0.72 ± 0.29 (median 0.80; IQR 0.58) and 0.94 ± 0.13 (median 1.00; IQR 0.20), respectively.

The control group included fifty healthy eyes of fifty patients (15 men and 35 women) with a mean age of 29.1 ± 12.3 years (range 18–49 years). The mean spherical equivalent refractive error was −4.01 ± 6.71 D (range +0.25 D to −14.50 D), and the mean simulated keratometry reading was 7.82 ± 0.27 mm. The BCVAs (decimal notation Snellen chart) with spectacles and CL were 0.95 ± 0.28 (median 1.00; IQR 0) and 1.04 ± 0.26 (median 1.00; IQR 0.20), respectively. The mean BOZR fitted was 7.87 ± 0.28 mm and the 76% of the cases were fitted with total diameter of 9.60 mm. Control group was younger than keratoconus group but not statistically significant ($p = 0.25$).

The mean BOZR fitted in keratoconus eyes was 7.21 ± 0.39 mm in prospective phase. The total diameter fitted was 9.20 mm in the 76% (range 8.80–9.40 mm) of the fittings and the periphery geometry N was fitted in the 54% of the cases. Table 1 shows the mean BOZR of the first diagnostic lens proposed by each method. A statistically significant difference was found in BOZRs between the first diagnostic lens suggested by Calculens.com, manufacturer's guidelines and APEX software ($p < 0.001$). The BOZR of the first diagnostic lens suggested by the manufacturer's guidelines and APEX software revealed a statistically significant difference compared with the definitive BOZR prescribed ($p < 0.001$). However, the BOZR proposed by Calculens.com was not significantly different ($p = 0.65$) than the BOZR of the final prescribed CL.

The BOZR of first diagnostic lens calculated by the three methods correlated with the fitted BOZR (Table 1), but the BOZR calculated with the new algorithm presented the smallest differences (arithmetic and absolute) with the final BOZR prescribed.

Fig. 4 shows the agreements between the BOZR calculated by each method with the final BOZR fitted. The LoA were higher using the manufacturer's guidelines (−0.31 to +0.55 mm) than the APEX software (−0.46 to +0.18 mm), and Calculens.com (−0.24 to +0.22 mm) exhibited the lower LoA.

The difference rate with the final BOZR prescribed was assessed to facilitate comparisons between the three BOZR calculation methods (Fig. 5) showed that the BOZR difference was ≤0.05 mm in 58% of the eyes using the new algorithm.

The number of diagnostic lenses, ordered lenses and visits necessaries to complete the GP fitting procedure in keratoconus and healthy subjects was compared to assess the clinical impact of the new algorithm to select the initial diagnostic lens. Statistically different ($p = 0.02$) (but with close values) number of diagnostic lenses were required in both groups. The new algorithm required between 1 and 4 diagnostic lenses (median 1, IQR 1, mean of 1.6 ± 0.8) before the ordering of the first GP lens [1 diagnostic lens (54%), 2 diagnostic lenses (34%), 3 diagnostic lenses (10%) and 4 diagnostic lenses (2%)]. The control group required between 1 and 3 diagnostic lenses (median 1, IQR 1, mean 1.3 ± 0.5) [1 diagnostic lens (74%), 2 diagnostic lenses (24%) and 3 diagnostic lenses (2%)].

Keratoconus patients required slightly more ordered lenses ($p < 0.001$) than the control group. Keratoconus eyes required order between 1 and 3 lenses (median 1, IQR 1, mean 1.4 ± 0.6) [1 ordered lens (64%), 2 ordered lenses (32%), 3 ordered lenses (4%)]. The reasons for lens reordering included changes in lens power to improve patients visual acuity and changes in BOZR (4 eyes), diameter (3 eyes) and peripheral edge lift (1 eye) to improve lens fitting. Healthy eyes required order between 1 and 2 lenses (median 1, IQR 0, mean 1.1 ± 0.3) [1 ordered lens (88%) and 2 ordered lenses (12%)]. Six eyes required the reordering of a second lens to adjust lens power to improve VA.

The mean of number of visits to achieve lens fitting was also similar between keratoconus and healthy subjects ($p = 0.08$). Keratoconus patients required between 3 and 6 visits (median 3, IQR 1, mean 3.4 ± 0.7) and healthy subjects required between 3 and 4 visits (median 3, IQR 0, mean 3.2 ± 0.4).

4. Discussion

GP contact lens fitting is the first non-surgical option in keratoconus management [1,2]. However, fitting is challenging because an increased number of trial lenses and longer practitioner and patient chair time are required to achieve a final acceptable fit compared with healthy eyes [7–12].

In this study we have developed a new predicting algorithm (Calculens.com) to select the BOZR, peripheral geometry and total diameter of the first diagnostic GP and reduce the complexity of CL fitting in keratoconus eyes using a specific keratoconus spherical tetra-curve GP design (KAKC GP, Conoptica-Hecht Contactlinsen). We included a prospective study fitting new keratoconus eyes using this new algorithm to provide sound evidence of the clinical advantages of its use. Statistical or mathematical comparisons with previous reports were performed to aid eye care practitioners in the keratoconus fitting procedure [12,15,16]. A comparison of GP fittings in a healthy group was included to compare the fitting procedure between keratoconus and healthy eyes. To the best of our knowledge, this is the first time that these fitting procedures were compared.

The number of diagnostic lenses that were required to establish the first ordered lens using the new algorithm in our sample of

Table 1
Summary of the means and standard deviation (SD) of the CL BOZR proposed by each method. The correlation, arithmetic and absolute means and SD of the BOZR differences between each method and final BOZR fitted are shown. *Paired *T*-Test ($p < 0.05$ statistically significant).

	New algorithm	Manufacturer's guidelines	APEX software CL fitting
Mean final BOZR fitted (mm)		7.21 ± 0.39 (6.2–7.9)	
Mean BOZR of first diagnostic lens proposed (mm) (Min–Max)	7.21 ± 0.42 (6.2–8.0)	7.09 ± 0.45 (6.0–7.7)	7.34 ± 0.42 (6.3–8.1)
Correlation between BOZR proposed and final BOZR fitted	$r^2 = 0.92$ $p < 0.001$	$r^2 = 0.76$ $p < 0.001$	$r^2 = 0.85$ $p < 0.001$
*P-Value between BOZR proposed and final BOZR fitted	$p = 0.65$	$p < 0.001$	$p < 0.001$
Arithmetic difference between BOZR proposed and final BOZR fitted (mm)	−0.01 ± 0.12 95%CI −0.03 to +0.04	+0.12 ± 0.22 95%CI −0.18 to −0.06	−0.14 ± 0.16 95%CI +0.09 to +0.18
Absolute difference between BOZR proposed and final BOZR fitted (mm)	0.09 ± 0.08	0.20 ± 0.14	0.16 ± 0.14

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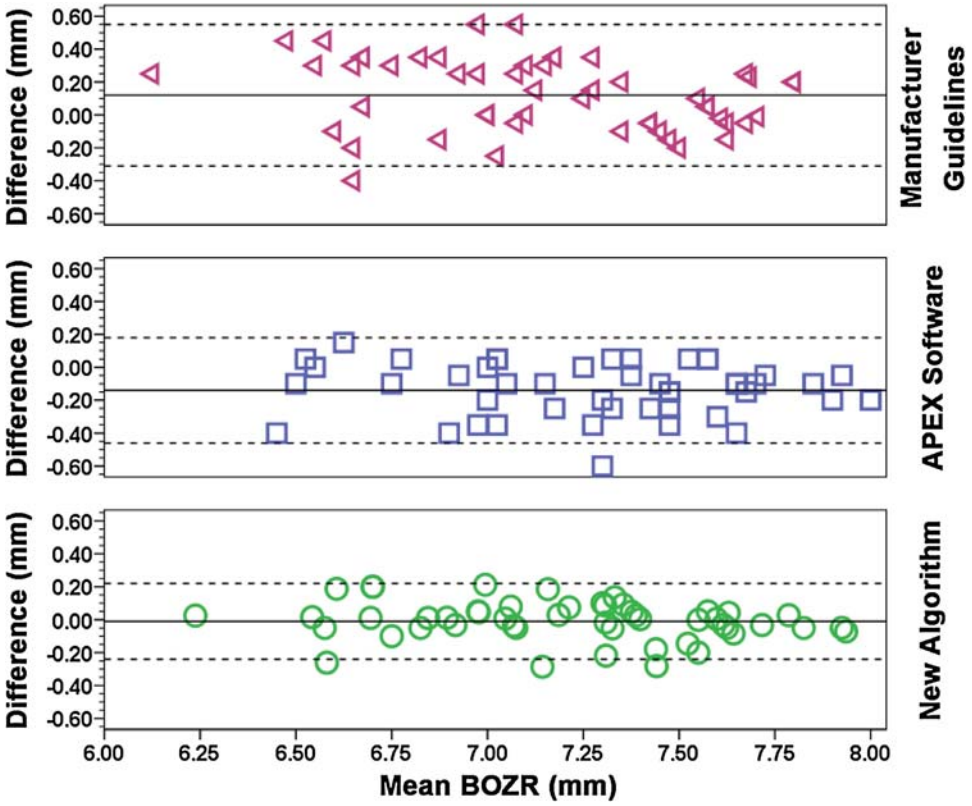

Fig. 4. Bland-Altman plot showing the agreement between the BOZR proposed by each method and the final BOZR fitted.

patients was small (median 1 lens and mean of 1.6 ± 0.8 lenses). Notably, only a 2% of keratoconus eyes required 4 diagnostic lenses, and no keratoconus required 5 or more diagnostic lenses. The number of diagnostic lenses found in our study was lower than previous reports that used traditional diagnostic lens method fitting [10,11]. Nosch et al. [7] analysed GP lens fits of the same manufacturer of our study (Hecht Contactlinsen) in 68 eyes with irregular corneal surfaces (75% keratoconus eyes) using a traditional empirical fitting procedure and diagnostic lenses and concluded that a mean of 3.25 ± 1.70 trial lens were required, however they used several toric and quadrant-specific back surface designs. These investigators achieved the fitting procedure using 3 diagnostic lenses or less in 70.7% of eyes [7]. Romero-Jiménez, et al. [11] proposed a standardized method to fit GP lens (Rose K2 design, Menicon Inc.) in 119 keratoconus eyes using the first definite apical clearance lens (FDACL) as a starting point to achieve an optimal lens and compared two different CL fitting techniques (three-point-touch versus apical touch) to reduce chair time. He find a mean of 2.3 ± 1.7 diagnostic lenses to obtain the FDACL, but another extra trial lens was necessary to obtain the three-point-touch (0.10 mm flatter than FDACL) or apical touch (0.30 mm flatter than FDACL) fittings. Therefore, the Romero-Jiménez et al. approach requires more diagnostic lenses (3.3 lenses) than our findings to achieve the three-point-touch fluorescein pattern. Zhou et al. [10] retrospectively identified keratoconus GP fits in 38 patients using several CL designs (Rose K, McGuire and standard spherical GP) and find a number of diagnostic lenses (1.8 ± 0.9) similar to our results. However, they did not describe the fitting method that they follow in these patients. In summary, our new algorithm reduces the number of diagnostic lenses that were necessary in our sample of keratoconus eyes to a number that is close to non-keratoconus GP fittings. A statistically significant difference between the number of diagnostic lenses was found between keratoconus (median 1, IQR 1) and healthy eyes (median 1, IQR 1), but this difference may be of limited clinical impact helping to reduce the complexity of GP fitting in keratoconus eyes.

A small number of ordered CLs were necessary to achieve an optimal fit (median 1, IQR 1, mean 1.4 ± 0.6), and a 64% optimal CL fit rate was found with the first ordered CL. The major reason (20%) for reordered CLs was a change in the power of the GP. However, perform the over-refraction is difficult in keratoconus eyes because of the initial discomfort of the GP CL and the irregular tear meniscus that forms between the back surface of the GP CL and the anterior corneal surface. The CL fit rate could increase from 64% to 84% with the first CL ordered if optimal over-refraction is obtained during the first visit. These results are relatively consistent with FDACL starting point method fitting [11], which permitted that 77% of the eyes achieves an optimal lens fit with the first ordered CL (83% with three- point-touch and 71% with apical touch fitting approaches). However, we found a lower mean number of ordered lenses than Zhou [10], who reported that 2.3 ± 1.4 CLs were required to finalize the fitting procedure in keratoconus eyes. In summary, our fitting approach may reduce the number of ordered CLs to a value that was close to healthy GP fitting (median 1, IQR 1, mean 1.1 ± 0.3). A statistically significant difference between healthy and keratoconus eyes was observed (with the same median value (1 lens) in both groups), but this difference was likely clinically acceptable.

The number of professional visits required to complete the fitting using the new algorithm (3.4 ± 0.7) was considerably lower than visits reported by Zhou (5.8 ± 1.6 visits) in a retrospective study [10]. Our results suggest a trend to simplify the fitting procedure using the new algorithm to calculate the first diagnostic lens because the number of required visits was similar (P = 0.08 and

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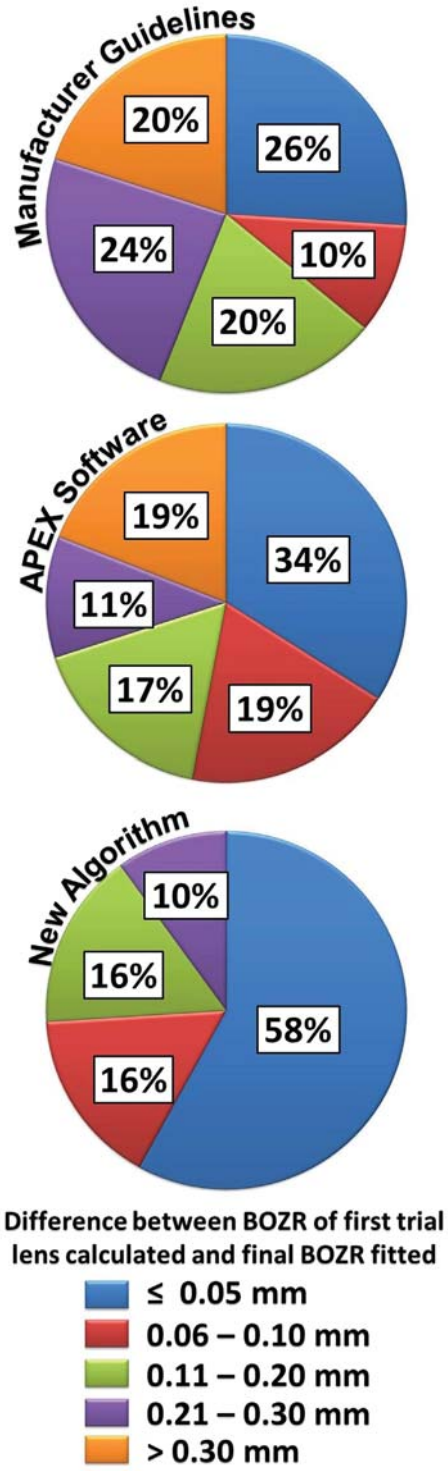

Fig. 5. Difference rates between the BOZR of the first diagnostic lens proposed by each method with the final BOZR prescribed.

same median value) to visits necessary to GP fitting in our sample of healthy subjects (3.2 ± 0.4, median 3).

The results of Calculens.com suggest a significant improvement compared to actual manufacturer's recommendations or APEX software CL fitting. Calculens.com produced lower differences with the definitive BOZR fitted in our sample of keratoconus patients. The lowest modification of GP BOZR is 0.05 mm, and the new predicting algorithm remained less than two BOZR steps (absolute difference) from the definitive BOZR fitted. However, the APEX software was three BOZR steps, and the manufacturer's guidelines was four BOZR steps from the definitive BOZR fitted in our study. Notably, the APEX software and manufacturer's guidelines produced differences between the proposed and fitted BOZR greater than 0.30 mm (approximately 20% of studied eyes), but the new algorithm never produced these values.

This study is not free of limitations. The inclusion of both eyes in the keratoconus group in both retrospective and prospective phases could be criticized. However, it is acceptable to include both eyes in this type of studies because keratoconus is an asymmetric disease [6–8,11,12] and the fluorescein pattern in one eye could be different of the fellow eye. Moreover the study design and data analysis follow the recommendations of Armstrong [17] to minimize the effect of both eyes inclusion. This study was also conducted in a single centre (IOBA Eye Institute) and the same CL practitioners assessed the fluorescein pattern in each patient (of the first diagnostic lens and of the final fitted lens) when other different practitioner calculated the first diagnostic lens parameters using the new algorithm. So, differences between CL practitioners could affect to final fluorescein pattern, but the research team has a wide experience working together, and most of the patients were co-managed; so they present a shared fitting philosophy that could minimize the impact of these differences in the study results. Further clinical research with blind and multicentre design is necessary to clarify the influence of practitioners' expertise in the usefulness of this new algorithm. A single and specific design of spherical GP lenses was used in each study group (BIAS in healthy corneas and KAKC in keratoconus patients), so a translation of these results to other GP CL designs or toric/quadrant specific designs, manufacturers or fitting philosophies must be interpreted with caution and requires future studies and research.

5. Conclusions

The selection of the BOZR, peripheral geometry and total diameter of the first diagnostic lens in keratoconus GP fittings using our new algorithm (included in Calculens.com) may improve the results provided by the actual manufacturer's guidelines and APEX software CLs fittings. This algorithm may decrease the number of trial CLs and may reduce practitioner and patient chair time that is required to achieve a final acceptable fit in keratoconus eyes using a comparable approach to standard GP fitting in healthy eyes.

Conflicts of interest

The authors report no conflicts of interest and have no proprietary interest in any of the materials mentioned in this article. Authors have not any financial or personal relationship with Conoptica-Hecht Contactlinsen Company including consultancy, participations, stocks, etc.

University of Valladolid has transferred the algorithm to Conoptica-Hecht Contactlinsen Company (Spain) with a license agreement contract that not includes any type of payment to authors at present or future (royalties, etc.).

Conoptica-Hecht Contactlinsen Company had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript and no direct and indirect funding have been received to conduct this project, except the provision of free of charge contact lenses to study participants.

Conoptica-Hecht Contactlinsen has not responsibility in design, maintenance or information provided in Calculens.com web site. Access to content of future users is not allowed as well (according

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to Spanish and European data protection legislation). This is a free access web site just managed by Optometry Research Group of the IOBA Eye Institute (University of Valladolid).

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References

[1] J.A. Gomes, D. Tan, C.J.C.J. Rapuano, R. Ambrósio Jr., Group of Panelists for the Global Delphi Panel of Keratoconus and Ectatic Diseases, Global consensus on keratoconus and ectatic diseases, Cornea 34 (2015) 359–369.
[2] M. Barnett, M.J. Mannis, Contact lenses in the management of keratoconus, Cornea 30 (2011) 1510–1516.
[3] Y.S. Rabinowitz, Keratoconus, Surv. Ophthalmol. 42 (1998) 297–319.
[4] M. Romero-Jiménez, J. Santodomingo-Rubido, J.S. Wolffsohn, Keratoconus: a review, Cont. Lens Anterior Eye. 33 (2010) 157–166.
[5] K.K. Leung, GP fitting philosophies for keratoconus, Clin. Exp. Optom. 82 (1999) 230–235.
[6] M. Nejabat, M.R. Khalili, C. Dehghani, Cone location and correction of keratoconus with rigid gas-permeable contact lenses, Cont. Lens Anterior Eye 35 (2012) 17–21.
[7] D.S. Nosch, G.L. Ong, I. Mavrikakis, J. Morris, The application of a computerised videokeratography (CVK) based contact lens fitting software programme on irregularly shaped corneal surfaces, Cont. Lens Anterior Eye 30 (2007) 239–248.
[8] P.S. Mandathara, M. Fatima, S. Taureen, S. Dumpati, M.H. Ali, V. Rathi, GP contact lens fitting in keratoconus using FITSCAN technology, Cont. Lens Anterior Eye 36 (2013) 126–129.
[9] K. Pullum, A keratoconus fitting system using the axial profile to establish optimum lens parameters, Cont. Lens Anterior Eye 26 (2003) 77–84.
[10] A.J. Zhou, K. Kitamura, B.A. Weissman, Contact lens care in keratoconus, Cont. Lens Anterior Eye 26 (2003) 171–174.
[11] M. Romero-Jiménez, J. Santodomingo-Rubido, J.M. González-Méijome, An assessment of the optimal lens fit rate in keratoconus subjects using three-point-touch and apical touch fitting approaches with the Rose K2 lens, Eye Cont. Lens 39 (2013) 269–272.
[12] P. Mandathara Sudharman, V. Rathi, S. Dumapati, Rose K lenses for keratoconus–an Indian experience, Eye Cont. Lens 36 (2010) 220–222.
[13] A. Gasson, J.A. Morris, Rigid lens selection and fitting, in: A. Gasson, J.A. Morris (Eds.), The Contact Lens Manual. A Practical Guide to Fitting, Ed Butterworth-Heinemann-Elsevier, Edinburgh, 2015, pp. 131–140.
[14] J.M. Bland, D.G. Altman, Statistical methods for assessing agreement between two methods of clinical measurement, Lancet 1 (1986) 307–310.
[15] M.T. Rajabi, Z. Mohajernezhad-Fard, S.K. Naseri, F. Jafari, A. Doostdar, P. Zarrinbakhsh, M.B. Rajabi, S. Kohansal, Rigid contact lens fitting based on keratometry readings in keratoconus patients: predicting algorithm, Int. J. Ophthalmol. 4 (2011) 525–528.
[16] S. Ortiz-Toquero, G. Rodriguez, V. de Juan, R. Martin, Rigid gas permeable contact lens fitting using new software in keratoconus eyes, Optom. Vis. Sci. 93 (2016) 286–292.
[17] R.A. Armstrong, Statistical guidelines for the analysis of data obtained from one or both eyes, Ophthalmic Physiol. Opt. 33 (2013) 7–14.

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6.2. Fiabilidad del proceso de cálculo de la primera lente de prueba a adaptar en queratocono

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Gas permeable contact lens fitting in keratoconus: comparison of different guidelines to BOZR calculation.

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Abstract

Purpose: Compare the agreement between the finally fitted back optic zone radius (BOZR) of spherical gas permeable (GP) contact lens (CL) with the BOZR proposed by different guidelines currently available to fit GP CL in keratoconus eyes. Methods: BOZR fitted in 81 keratoconus eyes were recorded and compared with the BOZR calculated with ten guidelines identified after a literature review; Guideline#1 APEX software CL fitting (Hecht-Contactlinsen); Guideline#2 BOZRAPEX*0.88)+0.77; Guideline#3 Horizontal K–0.10; Guideline#4 Centre of Contact Lens Research (University of Waterloo, Canada); Guideline#5 0.211*Kflat+5.904 (Kflat<7mm) or 0.465*Kflat+4.16 (Kflat>7mm); Guideline#6 Kmean–0.20; Guideline#7 Kflat– (1/3astigmatism); Guideline#8 Kmean; Guideline#9 Ksteep and Guideline#10 CALCULENS.com. Results: BOZR proposed by all guidelines correlated with the final BOZR fitted (R2>0.71; P<0.01). Statistically significant difference was found between the BOZR suggested by all guidelines with the BOZR prescribed (P<0.05), except with Guidelines #4, #8 and #10 (P≥0.11). Guidelines #10 presented the best agreement (mean difference of 0.00±0.12mm) and 50.6% of cases showed ≤0.05mm of difference with BOZR fitted. Guideline #5 showed the worst agreement (-0.38±0.22mm) and just 3.8% of cases with ≤0.05mm of difference with BOZR fitted. Conclusions: Several guidelines have been proposed to choose the BOZR of the first diagnostic lens to fit spherical GP in keratoconus with a lack in their clinical validation. The selection of the BOZR with CALCULENS.com provides better start point to spherical GP CL fitting in keratoconus than other methods or guidelines assessed. This study updates evidence-based information to CL practitioners who fit or prescribe GP lens in keratoconus patients.

Keywords	Gas permeable; contact lens; keratoconus; fitting guidelines; BOZR calculation

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Title Page

Title: Gas permeable contact lens fitting in keratoconus: comparison of different guidelines to BOZR calculation.

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Introduction

Rigid gas permeable (GP) contact lenses (CL) are the first option in keratoconus patient management [1-3] because of provide better visual rehabilitation and improve quality of life of these patients [1-5]. Fitting of GP lenses in keratoconus patients and achieving an acceptable fit can be considered challenging for eye care practitioners; owing to keratoconus is a progressive corneal disorder characterized by central and paracentral corneal steepening, corneal thinning, irregular corneal topography and irregular astigmatism provoking spectacle visual acuity impairment [1,5,6]. So, this procedure often requires a long practitioner and patient chair time in order to achieve optimal centration, minimum impact on ocular surface, best comfort and vision with final GP lens fit [7-10].

Classically, three GP corneal design fitting philosophies for keratoconus have been described in the literature [11]: steep or apical clearance (lens support or bearing on the peripheral cornea), flat or apical touch (lens support or bearing on the apex of the cornea), and three-point-touch or divided support (lens support or bearing is shared between the apex and the paracentral cornea) being this last philosophy the safest technique of GP fitting in keratoconus [11].

Nowadays, there are several methods or guidelines to select the parameters of the GP lens in keratoconus eyes to achieve three-point-touch fitting based on the corneal curvature values (K readings). Each CL manufacturer provides specific fitting-guideline according to lens geometry, besides different "CL fitting software programmes" have been proposed to simplify this procedure [2,12-18]. However, an analysis of the accuracy of most of these recommendations has not been reported previously to provide evidence based information that permit improve GP lens fitting in keratoconus eyes.

The aim of this study is to compare the agreement between the back optic zone radius (BOZR) proposed by different manufacturers' guidelines, nomograms or CL fitting software programmes designed to fit spherical GP CL in keratoconus eyes, with the BOZR final fitted in a sample of keratoconus eyes.

Materials and methods

Fitting Guidelines search

We performed an extensive electronic search of the Medline and PubMed databases, Google Scholar database, Science Direct database, Cochrane database, metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com) and ClinicalTrials.gov (www.clinicaltrials.gov) using individual and combinations of key words ("Keratoconus contact lenses", "Keratoconus fitting guideline", "Keratoconus GP fitting", "Keratoconus GP management") in May 2016 to identify the relevant publications in this field. We did not use any date or language restrictions in the electronic search. We also included additional references (from different sources, books, books chapters, manufactures websites, etc.) that were cited or included in these articles. In total, we identified 10 guidelines or general recommendations to select/calculate the BOZR of the spherical GP lens to fit in keratoconus eyes. We choose any reference only if they included a clear

description of the formula to choose or calculate the BOZR of the diagnostic lens to start with. Case reports were not assessed.

Study population

Clinical records of eighty-one keratoconus eyes of forty-six patients [(25 men and 21 women) with a mean age of 38.6 ± 11.7 years (range 19-66 years)] who were successfully fitted with spherical GP CLs specifically designed for keratoconus eyes (spherical tetra-curve; KAKC GP, Conoptica-Hecht Contactlinsen, Germany) were used. All patients were attended in the Optometry Group of the IOBA Eye Institute (University of Valladolid, Spain), which is a tertiary referral clinic that treats patients with irregular corneas and other eye disorders. Three different experienced CL practitioners conduct all GP CL fitting. The Human Sciences Ethics Committee of the University of Valladolid approved the study. Informed consent was obtained from each subject, and all subjects were treated in accordance with the Declaration of Helsinki.

Records of patients with any active ocular-surface disease (except keratoconus), medication use that could affect ocular physiology or with a history of acute corneal hydrops, any type of ocular surgery or any other ocular disease were excluded.

The following data were collected for all eyes included in the study: patients' age, refraction, best corrected visual acuity (BCVA) with spectacles and with CL, manual keratometry readings (OM-4 Topcon, Japan), corneal topography data (simulated keratometry, astigmatism power, axis of astigmatism; achieved with Placido-based topographer (Oculus Keratograph, Oculus Optikgeräte GmbH, Wetzlar, Germany), Amsler-Krumeich keratoconus severity stage, and definitive BOZR of GP lens fitted.

BOZR GP Fitting Guidelines comparison

Ten guidelines were identified after literature review (Table 1). BOZR following each spherical GP fitting guideline was calculated and compared with the final BOZR fitted in each patient's eye.

Data analysis

Statistical analysis was performed using the SPSS 15.0 (SPSS, Chicago, IL, USA) statistical package for Windows. A normal distribution of variables was assessed using the Kolmogorov–Smirnov test, and P-values>0.05 indicated that the data were normally distributed.

The difference between BOZR proposed by each guidelines and the BOZR final fitted was calculated using a paired t-test (P-values <0.05 were considered statistically significant). A linear regression quantified the R^2 correlation coefficient between the BOZR proposed and finally fitted (P-value <0.05 was considered statistically significant). The same lens diameter was maintained to allow comparisons between the BOZR of the fitted lens and the BOZRs calculated by each guideline.

The arithmetic and absolute mean difference between the BOZR calculated by each guideline and the BOZR finally fitted were calculated. The absolute difference was calculated to avoid the effect of positive and negative differences that could affect the mean value. An absolute difference was clearly represented when the BOZR proposed by each method was closer to the final fitted BOZR. We calculated a success rate of the GP

guideline fitting when the difference between the BOZR of the diagnostic lens proposed with the final BOZR prescribed was ≤0.05 mm. Also, we calculate this success rate of the GP guideline fitting in different keratoconus stage according to Amsler-Krumeich classification and were compared using a chi-square test (P-value of <0.05 were considered significant).

Agreement between the BOZR of the final fitted GP lens with the BOZR of the first diagnostic lens calculated by guidelines was evaluated using Bland-Altman analysis [19]. Differences between the BOZR fitted and proposed by each method were plotted against the means of each BOZR. The 95% limits of agreement (LoA) were calculated (mean of the difference ± 1.96 x standard deviation). The relationship between mean value (x) and the difference (y) was determined using linear regression analyses, R^2 correlation coefficient was calculated to test-retest reliability (P-values of < 0.05 were considered statistically significant).

Results

The mean spherical equivalent refractive error was -4.20 ± 3.82 D (range 0.25 D to -13.25 D), with a mean keratometry (Kmean) reading of 7.16 ± 0.47 mm. The flattest corneal curvature (Kf) was 7.43 ± 0.42 mm and the steepest corneal curvature (Ks) was 7.04 ± 0.44 mm. The BCVAs with spectacles and CL were 0.67 ± 0.29 and 0.96 ± 0.15 (Snellen chart), respectively. According to Amsler-Krumeich classification were included 18 eyes in stage 1; 35 eyes in stage 2 and 28 eyes in stage 3.

The mean BOZR fitted in keratoconus eyes was 7.19 ± 0.38 mm. Table 2 shows the mean BOZR of the diagnostic lens proposed by each guideline. The BOZR of diagnostic lens proposed by all guidelines well correlated with the final fitted BOZR (r^2>0.71; P<0.01). However, statistically significant difference was found between the BOZR suggested by all guidelines analysed with the BOZR prescribed (P<0.05), except in Guidelines #4, #8 and #10 (P≥0.11).

The arithmetic and absolute mean difference between the BOZR proposed by each guideline and BOZR finally fitted (Table 2) revealed the best agreement with Guideline #10 (0.00 ± 0.12 mm and 0.09 ± 0.08 mm, respectively) and the higher difference with Guideline #5 (-0.38 ± 0.22 mm and 0.39 ± 0.21 mm, respectively).

Figure 1 summarized the agreement between the BOZR proposed by each guideline with the final fitted BOZR being the Guideline #10 which exhibited the lower LoA.

Guideline #10 showed the best successful rate proposing a BOZR with a difference ≤0.05 mm in 50.6% of cases (Figure 2, Table 2) with lower difference with final BOZR fitted (no one case with a difference higher or 0.30 mm). Rest of guidelines (except Guideline #2 and Guideline #8 with a successful rate of 41.3% and 34.6% respectively) showed a successful rate lower than 30% and Guideline #5 presents a successful rate of 3.8% with a difference higher of 0.30 mm in more than 60% of cases. According to Amsler-Krumeich classification the successful rate of GP calculation was better with Guideline #10 in stage 1 (61.1%), Guideline #2 and #10 in stage 2 (40%) and Guideline #10 in stage 3 (57.1%) (Figure 3). In contrast, the worst results were presented by Guideline #6 (0%) in stage 1,

Guideline #3 and #5 in stage 2 (8.6%) and Guideline #5 in stage 3 (0%). No statistically significant difference was found between stages of keratoconus in successful rate with any guideline ($P \geq 0.10$), except in Guideline #3 ($P < 0.01$).

Discussion

Keratoconus is a bilateral and asymmetric ectatic condition affecting approximately 1/2000 people in the general population [1,5]. This disease commonly appears during the second decade of life and puberty and progresses until the fourth decade of life, when it generally stabilizes.

In the early stages of keratoconus, the refractive error can be managed with spectacles or soft CL, but when it progress the corneal irregularities induce higher-order aberrations that cannot be corrected with traditional ophthalmic lenses [1,5]. For this reason, GP CL are the first option in keratoconus patient management being that supply an adequate visual correction by providing a smooth optical surface to correct irregular astigmatism. However, fitting GP CL in keratoconus eyes is considered a challenge because development of irregular astigmatism increase the number of diagnostic lenses and practitioner time or patient chair time required to achieve a final acceptable fit compared with healthy eyes [6,8,9].
Manufacturers of GP lens or recently investigations published in the literature provide different guidelines to select the BOZR in keratoconus fittings, nevertheless, it is uncommon that these guidelines include an analysis of their accuracy or precision of the suggested BOZR. To the best of our knowledge, this is the first report those different fitting guidelines to select BOZR of GP lens in keratoconus eyes were compared in order to provide evidence based information of the accuracy of its recommendations.

Guideline #10 (CALCULENS.com) showed better agreement with BOZR final fitted compared with others guidelines. This open-access website allows the CL parameters calculation in a simple way with clinical data of keratoconus eyes (corneal keratometry or topography) and has been clinically validated with a sample of 50 keratoconus eyes, different of the patients used to its calculation [14]. The BOZR calculated on this website shows a difference with BOZR final fitted equal or less than 0.05 mm in 50.6% of the fittings with no one case with differences higher than 0.30 mm. Next, Guideline #2 [13] used the BOZR proposed by APEX software achieved a successful rate of 41.3% doubling the APEX software (Guideline #1) successful rate (26.3%). Nevertheless, both guidelines (#1 and #2) require the use of APEX software CL fitting (Oculus – Hecht Contactlinsen) and corneal topography achieved with Oculus topographers (Pentacam, Keratograph or Easygraph) that could be not easy to follow for all CL practitioners and have not been clinically validated with keratoconus eyes. In contrast Guideline #10 is an open access website easy to use for any CL practitioner and has been clinically validated [14].

Based on the absolute difference with the final BOZR fitted, Guideline #8 showed a successful rate of 34.6% of the fittings. Guideline #8 is proposed to fit several GP lenses design for keratoconus that share the same recommendation to calculate the BOZR of the first diagnostic lens, with a BOZR halfway between Ks and Kf readings, or Kmean. Following this recommendation, better results are obtained than other manufacturer guidelines that propose a starting point with Ks (Guideline #9 with success rate of 28.7%), based on Km-0.20 (Guideline #6 with success rate of 12.3%), based on Kf-

($\frac{1}{3}$*Astigmatism) (Guidelines #7 with success rate of 23.7%) or horizontal K–0.10 (Guidelines #3 with success rate of 19.8%). Is important highlighted that no one of these guidelines provided by manufacturers of GP lens included information about its clinical validation with keratoconus patients to bring objective and evidence information of their usefulness.

Other methods to calculate the BOZR of the first diagnostic lens in GP keratoconus fitting have not been proposed by CL manufactures. The Centre of Contact Lens Research of University of Waterloo (Canada) published in 2010 the manual book "Correction of keratoconus with GP lenses" [15] which proposed a brief guideline to select the BOZR in keratoconus eyes (Guideline #4). This guideline presented low difference between BOZR suggested and BOZR final fitted (0.14 ± 0.11 mm) with a successful rate of 26.3%. On the other hand, Rajabi et al. [12] proposed in 2011 a new predicting formula to calculate the BOZR based on manual keratometry (Guideline #5). This predicting formula was calculated retrospectively after 400 GP CL fitting assessment, in keratoconus eyes. Although Guideline #5 was calculated with a great keratoconus sample, their BOZR proposed are very far to BOZR final fitted (0.39 ± 0.21 mm) and only 3.8% of the fittings achieve a successful rate. To the best of our knowledge, these formulas were not validated with a new sample of keratoconus eyes to double-check their precision.
Evaluation of fluorescein pattern in keratoconus GP fittings requires experience, practice and knowledge of CL design parameters by practitioners [20]. It is generally accepted that three-point-touch, provides acceptable vision and is the safest technique to fit in keratoconic eyes [11,21]. There is evidence that apical touch induced by too flat BOZR may cause staining or scarring [11]. On the other hand, excessive apical clearance (too steep BOZR) could be interfere with comfort and acuity due to bubbles may be trapped in the optic zone area [11].

The Collaborative Longitudinal Evaluation of Keratoconus (CLEK) study describe the concept of the First Definite Apical Clearance Lens (FDACL) as the flattest lens that shows an apical clearance fluorescein pattern in keratoconus developing an standardized protocol to fit GP lenses in keratoconus [22]. In CLEK study the initial BOZR matched the steeper keratometry reading (Guideline #9), and adjusted flatter or steeper until the FDACL was reached. The use of FDACL was a valid and reliable standardized method to GP CL and monitoring the disease progression [23]. However, requires practice and long practitioner time to archive FDACL due that the starting point (Guideline #9) shows wide limits of agreement range (0.87 mm) and provided a successful rate less than 30%.

Other guidelines or protocols to fit GP CL in keratoconus have been proposed and could not be analyzed due to the nature of our study. Romero-Jiménez, et al. [21] follow the CLEK study standardized method to fit GP lens (Rose K2 design, Menicon Inc.) in 119 keratoconus eyes using the FDACL as a starting point to achieve an optimal lens and compared two different CL fitting techniques (three-point-touch versus apical touch) with BOZR 0.10 mm and 0.40 mm flatter than FDACL. Following this protocol, 77% of the eyes achieved an optimal lens fit with the first lens ordered (83% with three- point-touch and 71% with apical touch fitting approaches). However, no comparison of the BOZR of the first diagnostic lens were conducted, but 2.3 ± 1.7 diagnostic lenses were necessaries to obtain the FDACL, with another extra trial lens to obtain the three-point-touch (0.10 mm flatter than FDACL) or apical touch (0.40 mm flatter than FDACL).

Mandathara et al. [24] proposed a formula to calculate the BOZR in keratoconus using the software FITSCAN (Orbscan II topography) [BOZR = (BOZR suggested by FITSCAN (mm) × 0.86563) + 0.78738]. Nevertheless, this study has not been clinically validated and it is conditioned to use specific corneal topographer (Orbscan) and software, so it is not possible included in our study.

Our study presents different limitations. Firstly, it is not a clinical study when different patients will be fitted using different guidelines in random and masked way. Because conduct this clinical research could be expensive and require a long sample of keratoconus we conduct a comparison of the BOZR calculated by different guidelines proposed to fit GP lens specifically designed to keratoconus eyes. This approach could provide relevant information to eye care and CL practitioners who fit GP lens in keratoconus patients to improve choosing of the BOZR of the first diagnostic lens. Moreover, the use of a single design of spherical keratoconus GP CL could influence in the fitted BOZR because different philosophies of fitting GP in keratoconus exist, making difficult found definitive end point of the GP fitted. So, small variation in final BOZR would be clinically accepted and practitioner practice and expertise should be necessary. However, this study demonstrated a lack of evidence to support some of the guidelines recommended by manufacturers or some research reports. In fact, just Guideline #10 has been clinically calculated and posteriorly validated with a new sample of keratoconus patients [14] and the comparison with final BOZR fitted shows better agreement and best successful rate that all compared guidelines. These results will be of great interest to help CL practitioners to reduce chair time and the number of trial lenses; providing best vision rehabilitation to keratoconus patients, improving their vision and quality of life [14].

Conclusions

Several guidelines have been proposed to choose the BOZR of the first diagnostic lens to fit in keratoconus eyes with a lack in clinical validation of their recommendations. The selection of the BOZR of the first diagnostic lens with CALCULENS.com provides better start point to GP CL fitting in keratoconus than other methods or guidelines assessed; showing a difference ≤0.05 mm with final BOZR in 50.6% of patients. This study provides evidence-based information to CL practitioners who fit or prescribe GP lens in keratoconus patients.

Figure Legends

Figure 1. Bland-Altman plot showing the agreement between the BOZR proposed by each guideline and the final BOZR fitted. Guideline #1 Limits of agreement (LoA) from -0.42 to 0.13 (R^2<0.01 P=0.50); Guideline #2 LoA from -0.3 to 0.24 (R^2=0.07 P=0.02); Guideline #3 LoA from -0.36 to 0.65 (R^2=0.17 P=<0.01); Guideline #4 LoA from -0.31 to 0.37 (R^2=0.03 P=0.12); Guideline #5 LoA from -0.82 to 0.05 (R^2=0.51 P<0.01); Guideline #6 LoA from -0.12 to 0.58 (R^2=0.25 P=<0.01); Guideline #7 LoA from -0.51 to 0.28 (R^2=0.03 P=0.15); Guideline #8 LoA from -0.32 to 0.38 (R^2=0.25 P<0.01); Guideline #9 LoA from -0.29 to 0.58 (R^2=0.07 P=0.02) and Guideline #10 LoA from -0.23 to 0.23 (R^2=0.03 P=0.12).

Figure 2. Cumulative percentage of differences between the BOZR proposed by each guideline and the final BOZR fitted.

Figure 3. Success rate of the GP guideline fitting (difference between the BOZR of the diagnostic lens proposed with the final BOZR prescribed was ≤0.05 mm) according to Amsler-Krumeich classification.

References

[1] M. Barnett, M.J. Mannis, Contact lenses in the management of keratoconus, Cornea. 30 (2011) 1510–6.

[2] L.E. Downie, R.G. Lindsay, Contact lens management of keratoconus, Clin. Exp. Optom. 98 (2015) 299–311.

[3] American Optometric Association. Optometric Clinical Practice Guideline: Care of the Contact Lens Patient. 2006. http:// http://www.aoa.org/documents/optometrists/CPG-19.pdf. [accessed 4.11.16].

[4] S. Ortiz-Toquero, S. Perez, G. Rodriguez, A. Mayo-Iscar, R. Martin, The influence of the refractive correction on the vision-related quality of life in keratoconus patients, Qual. Life Res. 25 (2016) 1043–51.

[5] M. Romero-Jiménez, J. Santodomingo-Rubido, J.S. Wolffsohn, Keratoconus: a review, Cont. Lens Anterior Eye. 33 (2010) 157–66.

[6] L. Sorbara, K. Mueller, Effect of lens diameter on lens performance and initial comfort of two types of GP lenses for keratoconus: a pilot study, J. Optom. 4 (2011) 22–9.

[7] A.J. Zhou, K. Kitamura, B.A. Weissman, Contact lens care in keratoconus, Cont. Lens Anterior Eye. 4 (2003) 171–4.

[8] D.S. Nosch, G.L. Ong, I. Mavrikakis, J. Morris, The application of a computerised videokeratography (CVK) based contact lens fitting software programme on irregularly shaped corneal surfaces, Cont. Lens Anterior Eye. 30 (2007) 239–48.

[9] M. Nejabat, M.R. Khalili, C. Dehghani, Cone location and correction of keratoconus with rigid gas-permeable contact lenses, Cont. Lens Anterior Eye. 35 (2012) 17–21.

[10] L. Sorbara, K. Dalton, The use of video-keratoscopy in predicting contact lens parameters for keratoconic fitting, Cont. Lens Anterior Eye. 33 (2010) 112–8.

[11] K.K Leung, GP fitting philosophies for keratoconus, Clin. Exp. Optom. 82 (1999) 230–5.

[12] M.T. Rajabi, Z. Mohajernezhad-Fard, S.K. Naseri, F. Jafari, A. Doostdar, P. Zarrinbakhsh, M.B. Rajabi, S. Kohansal, Rigid contact lens fitting based on keratometry readings in keratoconus patients: predicting algorithm, Int. J. Ophthalmol. 4 (2011) 525–8.13.

[13] S. Ortiz-Toquero, G. Rodriguez, V. de Juan, R Martin, Rigid gas permeable contact lens fitting using new software in keratoconus eyes, Optom. Vis. Sci. 93 (2016) 286–92.

[14] S. Ortiz-Toquero, G. Rodriguez, V. de Juan, R Martin, New web-based algorithm to improve rigid gas permeable contact lens fitting in keratoconus, Cont. Lens Anterior Eye. (2016) In press.

[15] L. Sorbara, C. Woods, A. Sivak A, Boshart B, Correction of keratoconus with GP lenses, first ed., Bausch and Lomb, Waterloo, 2010.

[16] L.B. Szczotka, D.M. Capretta, J.H. Lass, Clinical evaluation of a computerized topography software method for fitting rigid gas permeable contact lenses, CLAO J. 20 (1994) 231–6.

[17] N.S. Bhatoa, S. Hau, D.P. Ehrlich, A comparison of a topography-based rigid gas permeable contact lens design with a conventionally fitted lens in patients with keratoconus, Cont. Lens Anterior Eye. 33 (2010) 128–35.

[18] K. Zadnik, J.T. Barr, Contact lens practice, Butterworths Heinemann, London, 2002, pp. 301–12.

[19] J.M. Bland, D.G. Altman, Statistical methods for assessing agreement between two methods of clinical measurement, Lancet. 1 (1986) 3.

[20] B.A. Fink, J.T. Barr, T.B. Edrington, G.E. Pierce, K.B. Schechtman, M.J. Rah, R. Flom, K. Zadnik, CLEK Study Group, Collaborative Longitudinal Evaluation of Keratoconus, A comparison of two methods of evaluating cornea-to-contact lens base curve fluorescein patterns in keratoconus, Optom. Vis. Sci. 78 (2001) 589–98.

[21] M. Romero-Jiménez, J. Santodomingo-Rubido, J.M. González-Méijome, An assessment of the optimal lens fit rate in keratoconus subjects using three-point-touch and apical touch fitting approaches with the Rose K2 lens, Eye Contact. Lens. 39 (2013) 269–72.

[22] T.B. Edrington, J.T. Barr, K. Zadnik, L.J. Davis, R.E. Gundel, D.P. Libassi DP, T.T. McMahon, M.O. Gordon, Standardized rigid contact lens fitting protocol for keratoconus, Optom. Vis. Sci. 73 (1996) 369–75.

[23] T.B. Edrington, L.B. Szczotka, C.G. Begley, D.S. Burger, B.S. Wilson, J.T. Barr, K. Zadnik, M.O. Gordon, Repeatability and agreement of two corneal-curvature assessments in keratoconus: keratometry and the first definite apical clearance lens (FDACL). CLEK Study Group. Collaborative Longitudinal Evaluation of Keratoconus, Cornea. 17 (1998) 267–77.

[24] P.S. Mandathara, M. Fatima, S. Taureen, S. Dumpati, M.H. Ali, V. Rathi, GP contact lens fitting in keratoconus using FITSCAN technology, Cont. Lens Anterior Eye. 36 (2013) 126–9.

Table 1

Guideline	Description
Guideline #1	Suggested by the APEX software CL fitting (APEX, version 1.1.0.6, developed by Hecht Contactlinsen in association with Oculus, which displays a simulated fluorescein pattern of the specified GP design to aid the fitting procedure).
Guideline #2	BOZR = ($BOZR_{APEX}$*0.88)+0.77 Improvement of BOZR proposed by APEX software CL fitting.[13]
Guideline #3	BOZR = Horizontal K (mm) – 0.10 Recommended by Conoptica-Hecht Contactlinsen, (Germany) to fit KAKC lens.
Guideline #4	If corneal astigmatism < -3.75 D: BOZR = Kf (D) – 0.61 x Astigmatism If corneal astigmatism -4.00 to -7.50 D: BOZR = Kf (D) – 0.50 x Astigmatism If corneal astigmatism > -7.50 D: BOZR = Kf (D) – 0.35 x Astigmatism *Calculated to diameter of 9.40 mm Proposed by Centre of Contact Lens Research (University of Waterloo, Canada).[15]
Guideline #5	If Kf < 7.00 mm: BOZR = 0.211*Kf (mm) + 5.904 If Kf 7 to 8 mm: BOZR = 0.465*Kf (mm) + 4.16 Recommended by Rajabi MT et al.[12]
Guideline #6	BOZR = Km (mm) – 0.20 Recommended to fit RoseK2 GP lens (Menicon, Co., Ltd.)[21]
Guideline #7	BOZR = Kf (mm) – [$\frac{1}{3}$astigmatism (mm)] Proposed by Bausch & Lomb to fit their keratoconus lens design or OP8 GP lens (Soflex, Israel).
Guideline #8	BOZR = Kmean (mm) Recommended to fit ACL KERA lens (Australian Contact Lenses, Australia), FlexCone (SwissLens, Switzerland), Keracon (Gelflex, Australia), McGuire lens (Ultravision, United Kingdom) and Nissel K2 lens (Cantor+Nissel, United Kingdom).[18]
Guideline #9	BOZR = Ks (mm) Proposed to fit Comfort Kone lens (MetroOptics, USA) or iKone lens (Valley Contax, USA).
Guideline #10	Calculens.com Algorithm developed by our research group.[14]

Table 1. Description of guidelines used in the study. Kmean = Mean corneal curvature; Kf = Flattest corneal meridian; Ks = Steepest corneal meridian

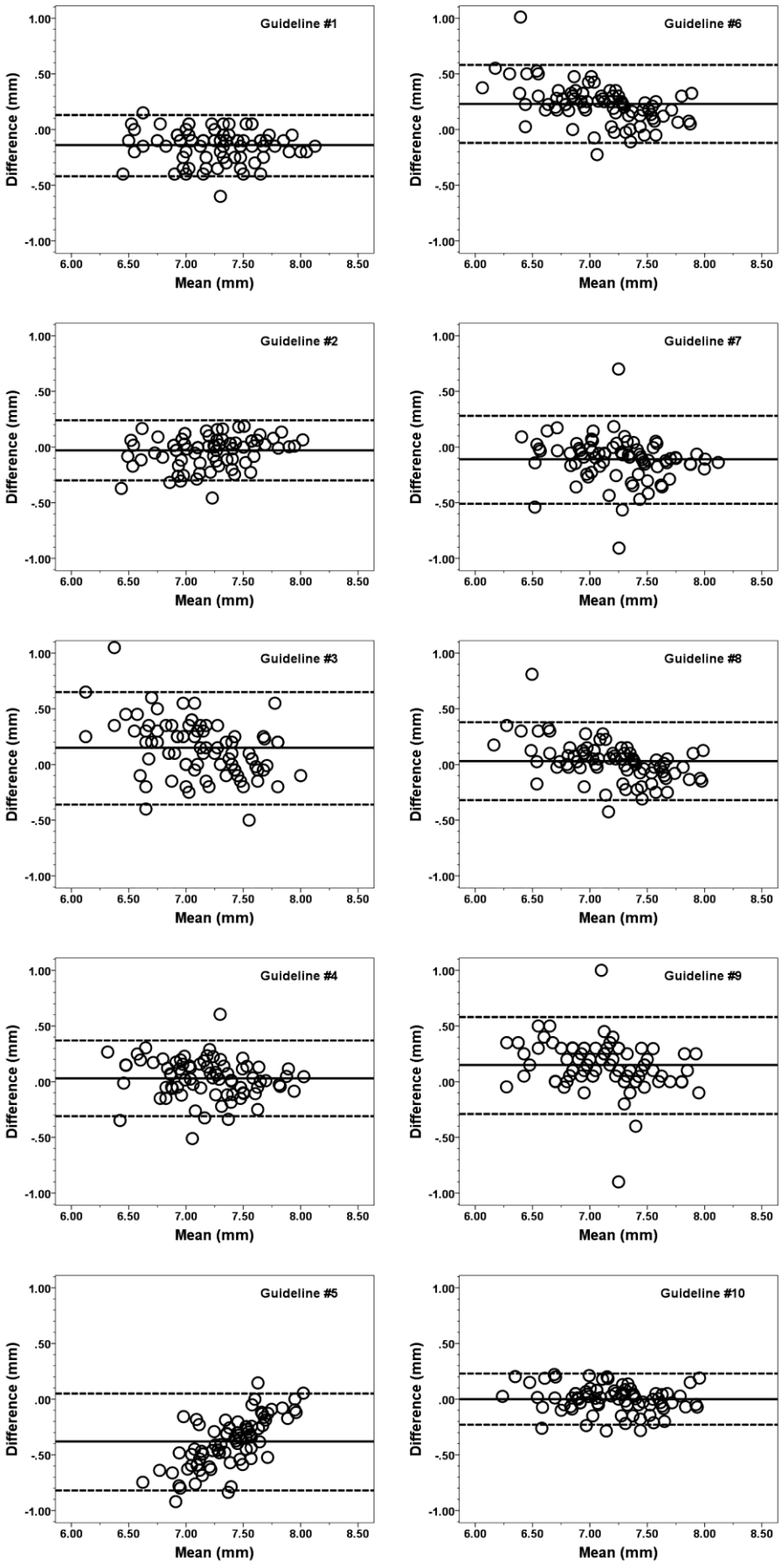
Table 2

N = 81	Guideline BOZR proposed	Correlation between BOZR proposed and BOZR fitted	Mean difference between proposed and fitted BOZR (mm)*	Absolute difference between proposed and fitted BOZR (mm)	Successful Rate** (95% CI)
Guideline #1	7.34 ± 0.39	R^2=0.869 (P<0.01)	-0.14 ± 0.14 (P<0.01)	0.16 ± 0.12	26.3% (16.5 to 36.0 %)
Guideline #2	7.23 ± 0.34	R^2=0.869 (P<0.01)	-0.03 ± 0.14 (P=0.04)	0.10 ± 0.10	41.3% (30.4 to 52.1 %)
Guideline #3	7.05 ± 0.48	R^2=0.719 (P<0.01)	+0.15 ± 0.26 (P<0.01)	0.23 ± 0.18	19.8% (11.0 to 28.5 %)
Guideline #4	7.16 ± 0.40	R^2=0.822 (P<0.01)	+0.03 ± 0.17 (P=0.11)	0.14 ± 0.11	26.3% (16.5 to 36.0%)
Guideline #5	7.58 ± 0.23	R^2=0.714 (P<0.01)	-0.38 ± 0.22 (P<0.01)	0.39 ± 0.21	3.8% (0.2 to 9.7%)
Guideline #6	6.96 ± 0.47	R^2=0.870 (P<0.01)	+0.23 ± 0.18 (P<0.01)	0.24 ± 0.16	12.3% (5.1 to 19.6%)
Guideline #7	7.31 ± 0.41	R^2=0.765 (P<0.01)	-0.11 ± 0.20 (P<0.01)	0.16 ± 0.16	23.4% (15.2 to 34.1%)
Guideline #8	7.16 ± 0.47	R^2=0.870 (P<0.01)	+0.03 ± 0.18 (P=0.15)	0.13 ± 0.12	34.6% (24.1 to 45.0%)
Guideline #9	7.04 ± 0.44	R^2=0.740 (P<0.01)	+0.15 ± 0.22 (P<0.01)	0.20 ± 0.18	29.6% (19.6 to 39.6%)
Guideline #10	7.19 ± 0.40	R^2=0.912 (P<0.01)	0.00 ± 0.12 (P=0.95)	0.09 ± 0.08	50.6% (39.7 to 61.6%)

Table 2. Summary of the means and standard deviation (SD) of the BOZR proposed by each guideline. The correlation, arithmetic and absolute means and SD of the BOZR differences between each guideline and BOZR fitted are shown.

*Paired T-Test (P<0.05 statistically significant). ** Percentage of cases with a difference ≤0.05 mm with definitive BOZR fitted.

Figure 1


Guideline #1
Guideline #6
Guideline #2
Guideline #7
Guideline #3
Guideline #8
Guideline #4
Guideline #9
Guideline #5
Guideline #10
Difference (mm)
Mean (mm)
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.00
-.50
-1.00
6.00
6.50
7.00
7.50
8.00
8.50

Figure 2

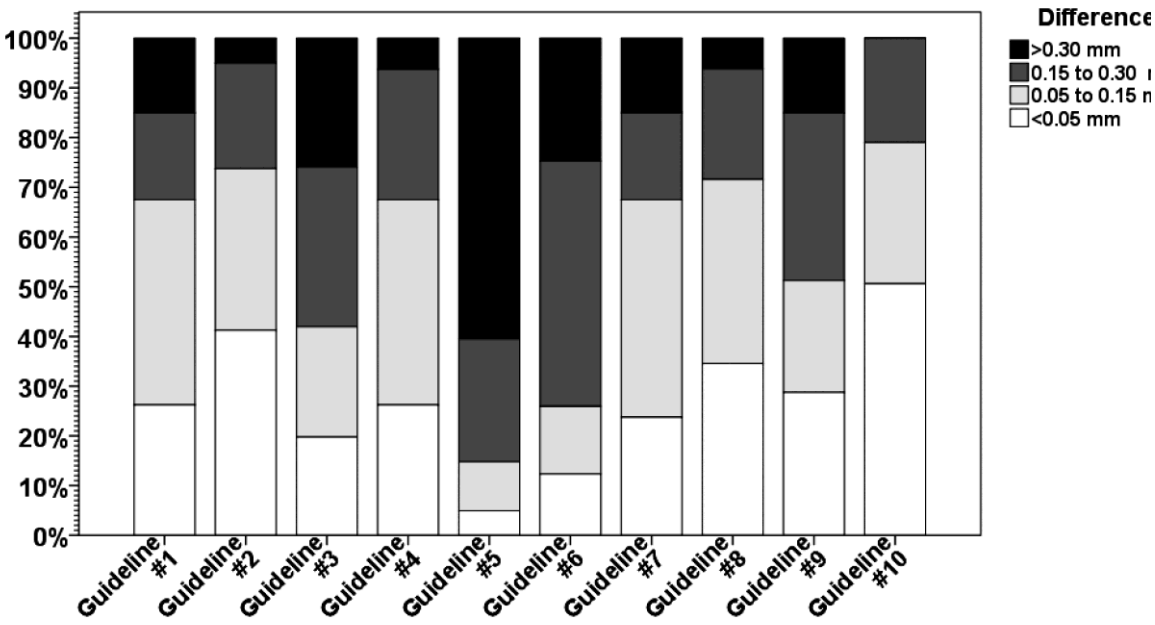
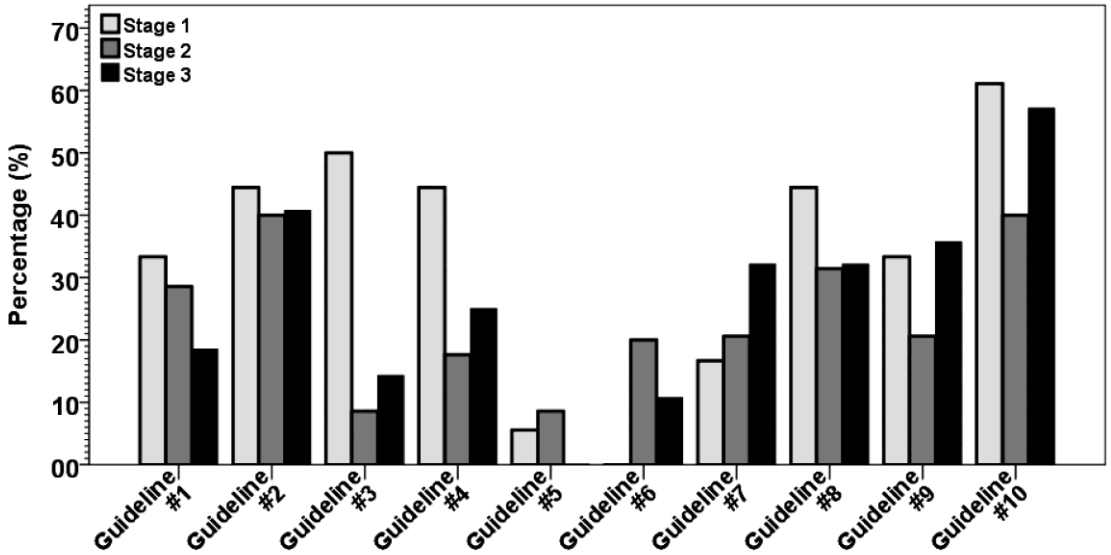


Figure 3



Capítulo 7

Guía clínica para la adaptación de LC RPG en queratocono

CHAPTER 7: Clinical practice guideline to fit corneal gas permeable contact lenses in keratoconus

7. Guía clínica para la adaptación de LC RPG en queratocono

Ortiz-Toquero S[1,2,3], Rodriguez G[1,2,3], De Juan V[1,2,3,4], Martin R[1,2,3,5]

Clinical Practice Guideline to fit corneal gas permeable contact lenses in keratoconus.

En fase de preparación (*in preparation*)

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7.1. Introduction

GP CLs are the first option in keratoconus management and present the best option for visual rehabilitation and improve quality of life of these patients.[1, 8, 18, 62, 65-69] However, GP CLs fitting in keratoconic patients and achieving an acceptable fitting are considered a challenge by eye care practitioners, requiring more trial lenses than standard GP fitting, due to central and paracentral corneal steepening, corneal thinning, and irregular astigmatism.[17, 18, 20, 21, 62, 65, 67] Thus, this procedure often requires longer chair time in order to achieve optimal centration, minimum impact on ocular surface, best comfort and vision with final GP CLs fitting.

Clinical Practice Guidelines (CPGs) are defined as systematically developed statements to assist practitioners and patient decisions about appropriate health care for specific circumstances.[116] In our knowledge, there are no previous evidence-based CPGs which contain recommendations for the choice and calculation of the parameters of the first diagnostic corneal GP CLs for keratoconic patients; for the assessment and management fitting procedures following a standardized schedule, defining the visits required to achieve an optimal GP fitting.

International recognized standards have been developed to assess the quality of CPGs and to guarantee the rigorous development of CPGs. For example, the AGREE II (The Appraisal of Guidelines for Research and Evaluation) instrument is a tool, specifically developed for quality assessment of guidelines.[105] It was also used for the appraisal of the World Health Organization guidelines, between others.[117]

The aim of this study was to develop and evaluate an evidence-based CPG, according to AGREE II instrument, to fit corneal GP CLs in keratoconic patients whilst reducing the patient and practitioner chair time and ensuring a safe fitting procedure that provides better visual rehabilitation of these patients.

7.2. Methods

An extensive search of the Medline and PubMed database, Google Scholar database, Science Direct database, Cochrane database, metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com) and ClinicalTrials.gov (www.clinicaltrials.gov) using individual and combinations of key words ("Keratoconus contact lenses", "Keratoconus fitting guideline", "Keratoconus gas permeable fitting", "Keratoconus gas permeable management") from 1990 to 2016 to identify the relevant publications in this field was performed to develop the CPG to fit corneal GP CLs in keratoconic eyes. It also included additional references (from different sources, books, books chapters, manufactures websites, etc.) that were cited or included in these articles with these inclusion and exclusion criteria:

- Inclusion criteria: These guidelines include recommendations to fit corneal gas permeable contact lens in keratoconus patients. English and Spanish results were collected.
- Exclusion criteria: Recommendations to fit soft CL, piggy-back, corneo-scleral, semi-scleral, mini-scleral, scleral or hybrid CL designs were excluded. Case reports were not assessed.

The quality of CPG was assessed by eight external appraisers with wide experience in GP CL fitting in keratoconus following the AGREE II instrument requirements.[105] It contains three items grouped into six quality domains followed by two overall assessment items: Domain 1 '*Scope and Purpose*'; Domain 2 '*Stakeholder Involvement*'; Domain 3 '*Rigour of Development*'; Domain 4 '*Clarity and Presentation*'; Domain 5 '*Applicability*' and Domain 6 '*Editorial Independence*' (Table 1).

A seven-point Likert scale (ranged between score 7 for strongly agree to score 1 for strongly disagree) is used to score each domain item. The overall assessment includes two items: the rating of the overall quality of the guideline (with a scale ranging from 7 for higher possible quality to 1 for lower possible quality) and a recommendation is made for the use of this guideline (yes; yes, with modifications; no).

Data analysis

Statistical analysis was performed using SPSS for Windows software (version 15.0, SPSS, Inc.) and Microsoft Excel (2010) spreadsheet. A quality score is calculated for each of the six AGREE II domains. The six domain scores are independent and should not be aggregated into a single quality score. Domain scores are calculated by summing up all the scores of the individual items in a domain and by scaling the total as a percentage of the maximum possible score for that domain according to the AGREE II manual [(Obtained score – Minimum possible score) / (Maximum possible score – Minimum possible score) * 100].[105]

Domain 1: Scope and purpose

1. The overall objective(s) of the guideline is (are) specifically described.
2. The health question(s) covered by the guideline is (are) specifically described.
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.

Domain 2: Stakeholder involvement

4. The guideline development group includes individuals from all relevant professional groups.
5. The views and preferences of the target population (patients, public, etc) have been sought.
6. The target users of the guideline are clearly defined.

Domain 3: Rigour of development

7. Systematic methods were used to search for evidence.
8. The criteria for selecting the evidence are clearly described.
9. The strengths and limitations of the body of evidence are clearly described.
10. The methods for formulating the recommendations are clearly described.
11. The health benefits, side effects and risks have been considered in formulating the recommendations.
12. There is an explicit link between the recommendations and the supporting evidence.
13. The guideline has been externally reviewed by experts prior to this publication.
14. A procedure for updating the guideline is provided.

Domain 4: Clarity of presentation

15. The recommendations are specific and unambiguous.
16. The different options for management of the condition or health issues are clearly presented.
17. Key recommendations are easily identifiable.

Domain 5: Applicability

18. The guideline describes facilitators and barriers to its application.
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.
20. The potential resource implications of applying the recommendations have been considered.
21. The guideline presents monitoring and/or auditing criteria.

Domain 6: Editorial independence

22. The views of the funding body have not influenced the content of the guideline.
23. Competing interests of guideline development group members have been recorded and addressed.

Overall assessment

- Judgement as to the quality of the guideline, taking into account the criteria considered in the assessment process.
- Provide a recommendation for use of the guideline.

Table 1. Appraisal of Guidelines for Research and Evaluation II domains and items.

7.3. Results

The developed CPG to fit corneal GP CLs in keratoconic eyes is presented in Appendix 1.

AGREE II domain scores across the eight appraisers are shown in Figure 1. This CPG has achieved satisfactory results in all domains evaluated with the Agree II Instrument: 89% in '*Scope and Purpose*' (88.88 ± 14.70% mean; 91.50% median and 100.00% mode); 74% in '*Stakeholder Involvement*' (73.63 ± 12.42% mean; 69.50% median and 61.00% mode); 84% in '*Rigour of Development*' (83.75 ± 11.49% mean; 86.50% median and 63.00% mode); 89% in '*Clarity and Presentation*' (88.75 ± 6.02% mean; 89.00% median and 83.00% mode); 72% in '*Applicability*' (72.38 ± 22.58% mean; 79.00% median and 58.00% mode) and 88% in '*Editorial Independence*' (87.50 ± 35.35% mean; 100.00% median and 100.00% mode). The overall guideline assessment obtained 85% of quality (85.42 ± 10.68% mean; 83.33% median and 83.00% mode). Finally, 100% of the experts would recommend this guideline for use (60% with modifications).

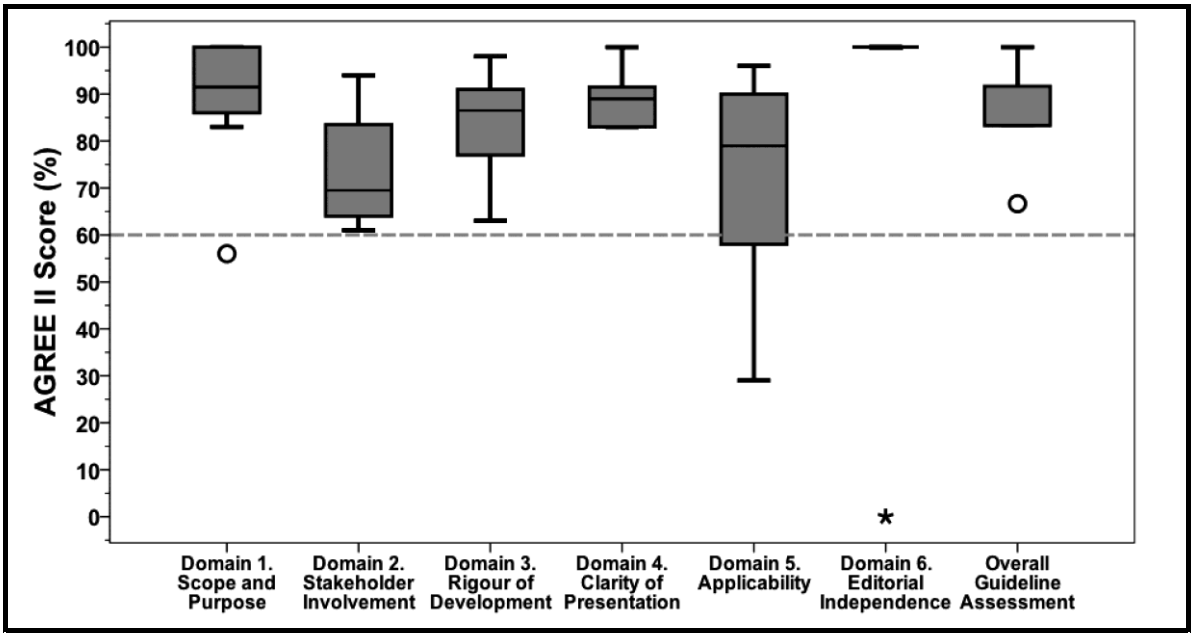


Figure 1. AGREE II domain scores across the eight appraisers.

7.4. Discussion

This is the first evidence-based CPG to fit GP CLs in keratoconic eyes including the appropriate eye-examination, fitting procedure and CL assessment procedures. Although the domain scores are useful for recommend the use of CPG in the clinical practice, the Consortium of AGREE II has not set minimum domain scores or cut-off values domains to differentiate between high quality and poor quality CPG.[105] Several authors 'recommend for immediate use' any CPG if more than half of the domains have an overall domain score of more than 60%. However, this recommendation change to 'recommended with modifications' if most domain scores are higher than 30%, and finally if most domain scores are below 30%, the guideline is 'not recommended for use'.[118]

These results obtained after eight experts appraised the developed CPG shows an overall domain score higher of 70%, so this CPG could be strongly recommended for the management of patients with keratoconus with corneal GP CLs. This CPG could reduce practitioner and patient chair time that is required to achieve a final acceptable fit in keratoconus eyes.

7.5. Conclusion

The CPG developed in this study describes the fitting process of corneal GP CLs in keratoconus eyes, including three different visits (diagnostic visit, dispensing visit and prescribing visit) supported by an online tool to calculate the first diagnostic GP CLs parameters (Calculens.com). Following this CPG, a minimum of three visits, one diagnostic and one ordered lens

should be all that is necessary to complete corneal GP fitting in keratoconus eyes.

7.6. Acknowledgments

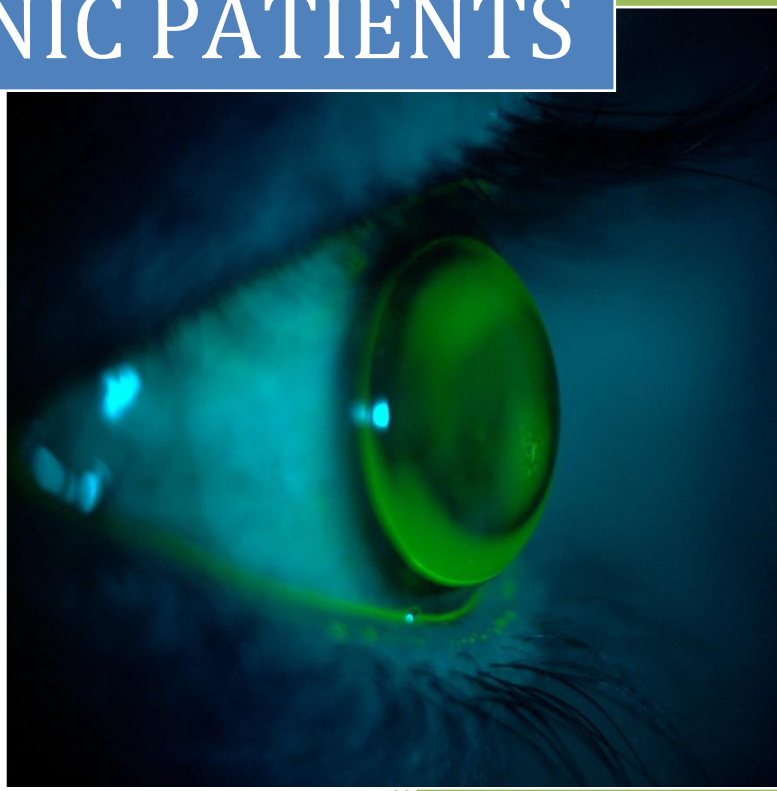
The authors would like to thank Dr. Luisa Simo (Plymouth University) for her help in the revision of the understandability of the guideline. Special thanks to the external appraisers: Dr. César Villa (Universidad Europea de Madrid, Spain); Dr. David Piñero (Universidad de Alicante, Spain); Dr. Gonzalo Carracedo (Universidad Complutense de Madrid, Spain); Dr. José Manuel González-Méijome (Universidade do Minho, Portugal); Dr. Lili Ho (University of New South Wales, Australia); Giancarlo Montani (Universitá del Salento, Italy); Henny Otten (Visser Contactlenzenpraktijk, The Netherlands) and Garry Orris (Orriss & Low Optometrists, UK) for accept the invitation to appraisal the CPG and for help to improve the guideline with their recommendations.

7.7. Appendix 1

CPG developed and assessed in this chapter.

APPENDIX 1

CLINICAL PRACTICE GUIDELINES: CORNEAL GAS PERMEABLE CONTACT LENSES IN KERATOCONIC PATIENTS



INDEX

Key to evidence statements and recommendations

Preferred practice patterns provide guidance for the pattern of practice, not for the care of a particular individual.[1] Different levels of evidence have been proposed [a scale based on the Scottish Intercollegiate Guideline Network (SIGN)][2] to allow for the recommendations, made throughout the guidelines, to be graded as defined by Grading of Recommendations Assessment, Development and Evaluation (GRADE).[3-7] Some recommendations can be made with more certainty than others. The wording used in the recommendations in these guidelines denotes the certainty with which the recommendation is made (the 'strength' of the recommendation). The 'strength' of a recommendation takes into account the quality (level) of the evidence. Although higher-quality evidence is more likely to be associated with strong recommendations than lower-quality evidence, a particular level of quality does not automatically lead to a particular strength of recommendation.

Levels of evidence

Level	Type of Evidence
I^{++}	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
I^{+}	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
I^{-}	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
II^{++}	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
II^{+}	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
II^{-}	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
III	Non-analytic studies (e.g., case reports, case series)
IV	Evidence obtained from expert committee reports or experts´ opinion and/or clinical experiences of respected authorities

Grades of Recommendations

Grade	Recommendation
Good Quality (GQ)	Further research is very unlikely to change our confidence in the estimate of the effect
Moderate Quality (MQ)	Further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate
Insufficient Quality (IQ)	Further research is very likely to have an important impact on our confidence in the estimate of the effect and is likely to change the estimate Any estimate of the effect is very uncertain

Key recommendations for care

Grade	Recommendation
Strong recommendation (SR)	For 'strong' recommendations on interventions that 'should' be used, the guidelines development group is confident that, for the vast majority of people, the intervention (or interventions) will do more good than harm.
Discretionary recommendation (DR)	For 'conditional' recommendations on interventions that should be 'considered', the guidelines development group is confident that the intervention will do more good than harm for most patients. The choice of intervention is therefore more likely to vary depending on a person's values and preferences, and so the healthcare professional should spend more time discussing the options with the patient.

Good-practice points (GPP)

Recommended best practice is based on the clinical experience of the guideline development group.

I. Introduction

A. Scope and purpose

The overall objective of these guidelines is to successfully achieve a GP CLs fit in keratoconic patients whilst reducing the patient and practitioner chair time and ensuring a safe fitting procedure that provides better visual rehabilitation of these patients. In these guidelines we describe the appropriate eye-examination, fitting and evaluation procedures to enable this

The guidelines contain recommendations for the choice and calculation of the parameters of the first diagnostic corneal GP CLs for keratoconic patients. For the assessment and management fitting procedures following a standardized schedule, defining the visits required to achieve an optimal GP fit.

To apply these guidelines correctly in clinical practice it is necessary to use a trial GP set, a manual keratometer and/or a corneal topographer and the use of the open-access website Calculens.com.

B. Statement of the problem

Keratoconus is a progressive corneal disorder that is characterized by thinning and steepening of the central and paracentral cornea.[8-11] This ectatic condition is bilateral and asymmetric, causes high myopia and irregular astigmatism and affects approximately 1/2000 people in the general population.[8-11] The etiology of this disease is uncertain but is likely to be multifactorial, involving a combination of genetic, biochemical and/or environmental factors.[8, 9] Keratoconus commonly appears during puberty, in the second decade of life, and it progresses until the fourth decade of life, at which point it generally stabilizes.[8-11]

There are several ocular symptoms and signs in keratoconus that are important in the diagnosis of this disease; such as significant loss of visual acuity which cannot be compensated with spectacles, increasing with-the-rule astigmatism, appearance of “scissor” shadows while performing retinoscopy, or presence of biomicroscopy findings (Fleischer’s ring, Vogt’s striae, corneal scarring and Munson’s sign). Corneal topography or tomography play a paramount role in keratoconus diagnosis.[8, 9]

In early stages of the disease, spectacles and soft CLs with toric design are adequate to correct myopia and regular astigmatism.[8, 11, 12] However, when keratoconus progresses, the corneal irregularities induce higher-order aberrations that cannot be corrected with traditional ophthalmic lenses.[8, 13] GP CLs are of paramount importance in keratoconus management to rehabilitate vision and improve patients' quality of life (QoL). GP lenses present the best option for visual rehabilitation in keratoconus.[8, 14, 15] This type of CLs generally improve the visual acuity because the tear layer between the CL and the anterior surface of the cornea reduces visual distortion providing a new regular optical surface.[11, 14] Fitting GP lenses in keratoconus patients and achieving an acceptable fit are considered a challenge by eye care practitioners,[16] requiring more trial lenses than standard GP fitting,[17] due to central and paracentral corneal steepening, corneal thinning, irregular corneal topography and irregular astigmatism.[12, 18-22] Thus, this procedure often requires longer chair time in order to achieve optimal centration, minimum impact on ocular surface, best comfort and vision with final GP CLs fit.[18, 21] However, the use of the open-access Calculens.com to calculate the parameters of the first diagnostic lens reduces the number of trials and visits improving the GP fitting procedure in keratoconic eyes.[23]

Alternative options for fitting patients with advanced stages of keratoconus or who have failed with standard GP lenses design for keratoconus have been documented: these include piggy-back, corneal-scleral, semi-scleral, mini-scleral, scleral or hybrid designs.[8, 9, 11] If patients develop CL intolerance or the disease progresses and/or corneal integrity is affected, ultraviolet crosslinking (UV-CXL) or intrastromal corneal ring segments (ICRS) may be indicated.[9] Descemetic deep anterior lamellar (dDALK), in patients without Descemet membrane compromise, or penetrating keratoplasty (PK) are the techniques of choice when a corneal transplant is needed in these patients.[9]

II. Key recommendations

The following recommendations were highlighted by the guidelines development group:

- GP CLs are the first choice for visual rehabilitation of a patient with keratoconus. **(SR; GQ, Level II^{++})**

- GP CL fitting in keratoconic patients should take places in three visits: initial or diagnostic visit, dispensing visit and prescribing visit. **(DR; MQ, Level II^{-})**

    - The use of Calculens.com to determine the first diagnostic GP lens allows a reduction in the number of trials and visits necessary to achieve a successful GP CL fitting in keratoconus. **(SR; GQ, Level II^{+})**

- The "three-point-touch" (divided support) pattern is the most widely-accepted and safest modality of GP CL fitting in keratoconus **(SR; GQ, Level I^{-})**

- Apply changes of back optic zone radius (BOZR) in steps of 0.10 mm to refine fluorescein pattern until achieve "three-point-touch" fluorescein pattern. **(DR; MQ, Level III)**

- Patient education in the correct maintenance and handling of GP CLs and hand hygiene is essential in reducing CL complications and adverse effects. **(SR; GQ, Level II^{-})**

- After dispensing the GP CLs, a wearing schedule starting with 1-2 hours per day and adding 1-2 hours each day until eight hours per day is achieved, during the 2-3 weeks before the prescribing visit. **(GPP, DR; IQ, Level IV)**

- During first year of GP CLs wear keratoconic patients should be checked every three months. After this six-monthly visits should be acceptable to check CL wear and disease evolution (with biomicroscopy, fluorescein pattern assessment and corneal topography). **(GPP, DR; MQ, Level IV)**

- Keratoconus patients should be advised to remove their GP CLs whenever redness, tearing, visual loss or pain occurs and to consult their eye-care professional at once. **(SR; GQ, Level IV)**

III. Care process

A.- Pre-fitting considerations

A.1. Detection of keratoconus

a) Symptoms and biomicroscopic signs

Clinical data provides a foundation for the diagnosis and contact lens (CL) management of keratoconus.[8, 12, 24] The characteristic symptoms and biomicroscopic signs indicators of keratoconus are well established (Table 1).[8, 9, 25, 26] Patients' history may identify major risk factors for keratoconus; such as: Down Syndrome, relatives of affected patients, ocular allergy, eye rubbing, floppy eyelid syndrome, atopy, connective tissue disorders (Marfan syndrome), and others.[8, 9, 26]

Table 1. Clinical signs in keratoconus detection

Refractive indicators:

- Myopia and irregular astigmatism (usually with-the-rule or oblique).
- Reduction of spectacle-corrected visual acuity at distance and near.
- Change in cylinder axis and power of astigmatic correction.
- Monocular diplopia and image ghosting.

Ophthalmoscopy and retinoscopy signs:

- Irregular or scissoring retinoscopic reflex.
- Visualization of the shadow of the cone in the red reflex within the pupil area during ophthalmoscopy (Charleaux's oil droplet sign).

Biomicroscopy signs:

- Prominent corneal nerves.
- Vogt's striae, which disappear transiently on digital pressure.
- Fleischer's ring (iron ring).
- Corneal scarring.
- Focal thinning.
- Munson's sign, inferior displacement of the lower lid on down gaze.
- Corneal hydrops (late stages), a breakdown in endothelial function causing acute epithelial corneal edema followed by scarring.
- Rizzuti's sign, a bright reflection on the nasal area of the limbus when light is directed to the limbus temporal area.

b) Corneal topography and keratoconus classification

One of the most important tools in detecting and managing keratoconus is videokeratography (Placido-based topographers), especially in primary care.[27] These devices are one of the most extensively used in clinical practice.[18, 19, 24, 28-30] Scheimpflug imaging is also potentially useful for corneal assessment in keratoconus. Imaging systems that do not rely upon the quality of the surface image, such as optical coherence tomography (OCT) can also be.[9, 24, 31] Diagnosis of forme fruste keratoconus, early forms of keratoconus or subclinical keratoconus is a challenge and a lack of consensus exists in the exact diagnosis criteria but anterior and posterior corneal topography analysis and patient follow up is mandatory.[9, 32, 33]

Corneal topography can help to identify the type or shape and the severity of the keratoconic cornea. The location or shape of the cone has been classified into: nipple or central type (cone diameter <5mm), oval or inferior-temporal (cone diameter >5mm), and globus or generalized type (cone comprises 75% of the cornea).[8, 29, 34] There is no clinically adequate classification system for the severity of keratoconus.[9, 31] The Amsler-Krumeich classification[35, 36] and the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) classifications[34] are the most commonly used to classify the keratoconus severity.[9] However, both classifications fail to consider current information and technological advances and new classification criterion are necessary.[9]

Clinical progression requires changes in at least 2 of these 3 parameters; anterior and/or posterior corneal steepening and progressive corneal thinning.[9] The assessment of disease progression is directly dependent on the accuracy and reliability of the corneal device used in patient assessment.[9]

A.2. Contact lens management

Non-surgical procedures are the primary method of clinical management in keratoconic patients.[9] Spectacles or soft CLs can be useful to correct the visual distortion in early stages, but corneal GP CLs are the first choice in a keratoconic patients´ management and their visual rehabilitation.[9, 14, 15, 37, 38] There are numerous commercial corneal GP CLs designs available for keratoconus, including multicurve (spherical) and aspheric designs (Table 2).

Clinical recommendation (SR; GQ, Level II^{++})
Gas permeable contact lenses are the first choice for visual rehabilitation of a patient with keratoconus

In a patient with keratoconus who has failed a trial of conventional corneal GP CLs, the alternative CL options available would be: piggy-back (soft CL is used in conjunction with GP CL), hybrid CL (GP centre, soft skirt) or large diameter GP CLs designs such as corneal-scleral or semi-scleral (between 3.0 to 6.0 mm larger than horizontal visible iris diameter or 12.9-14.9 mm), mini-scleral (up to 6 mm larger than horizontal visible iris diameter or 15-18 mm) or scleral (more than 6 mm larger than horizontal visible iris diameter or 18.1-25 mm).[8, 14, 39]

Table 2. Several GP CLs designs and manufacturers for keratoconus*

Proprietary name	Manufacturer	Back Optic Zone Radius (BOZR) (mm)	Total Diameter (mm)	Power (D)
KAKC	Hecht Contactlinsen (Germany)	4.80-8.90	8.40-12.20	±30.00
ROSE K2	Menicon (Japan)	4.30-8.60	7.90-10.40	Any Power
Queratokon	Lenticon (Spain)	5.30-8.00	9.00-9.80	+10 to -30
KeraKone	No7 (UK)	4.50-7.50	8.70-9.30	±25.00
iKone	Valley Contax (USA)	Any BOZR	8.80-10.40	±30.00
Comfort Kone	Metro Optics (USA)	4.50-8.00	7.50-9.50	Any Power
McGuire	UltraVision (UK)	5.00-8.60	8.50-11.00	±30.00
FlexCone	SwissLens (Switzerland)	5.70-9.00	7.50-12.00	±40.00
OP8	Soflex (Israel)	5.80-7.60	8.50-10.20	Any Power

* Non-extensive table.

A.3. Pre-fitting eye examination

The initial steps to determine a GP CL prescription for keratoconus include a full history, symptoms and a comprehensive eye examination. The patient will be asked structured questions relating to the reason for the visit, the nature of the presenting problem, their visual and ocular history. General health, medication and allergies, their family eye and medical histories and vocational visual requirements will also be covered.[40]

A complete eye examination should be conducted to determine whether the patient is a good candidate for CL wear.[41] This examination should include: visual acuity and vision for distance and near measured monocularly and binocularly, retinoscopy, subjective refraction, baseline quantification of corneal curvature (manual keratometry and/or corneal topography) and careful assessment of the anterior segment and tear film with slit-lamp biomicroscopy and documentation of all pre-fitting abnormalities which must be considered and managed when appropriate.[42, 43] Posterior eye exam is also recommended.[42, 43]

B.- Schedule and GP fitting clinical procedure

GP CL fitting in keratoconus patients takes place in three different visits: initial or diagnostic visit, dispensing visit and prescribing visit (Figure 1). The practitioner's aim is to prescribe a GP CL in a physiologically adequate material that will induce minimal mechanical impact on the corneal surface while providing the required optical correction to improve the patient´s quality of vision and QoL.[15, 44]

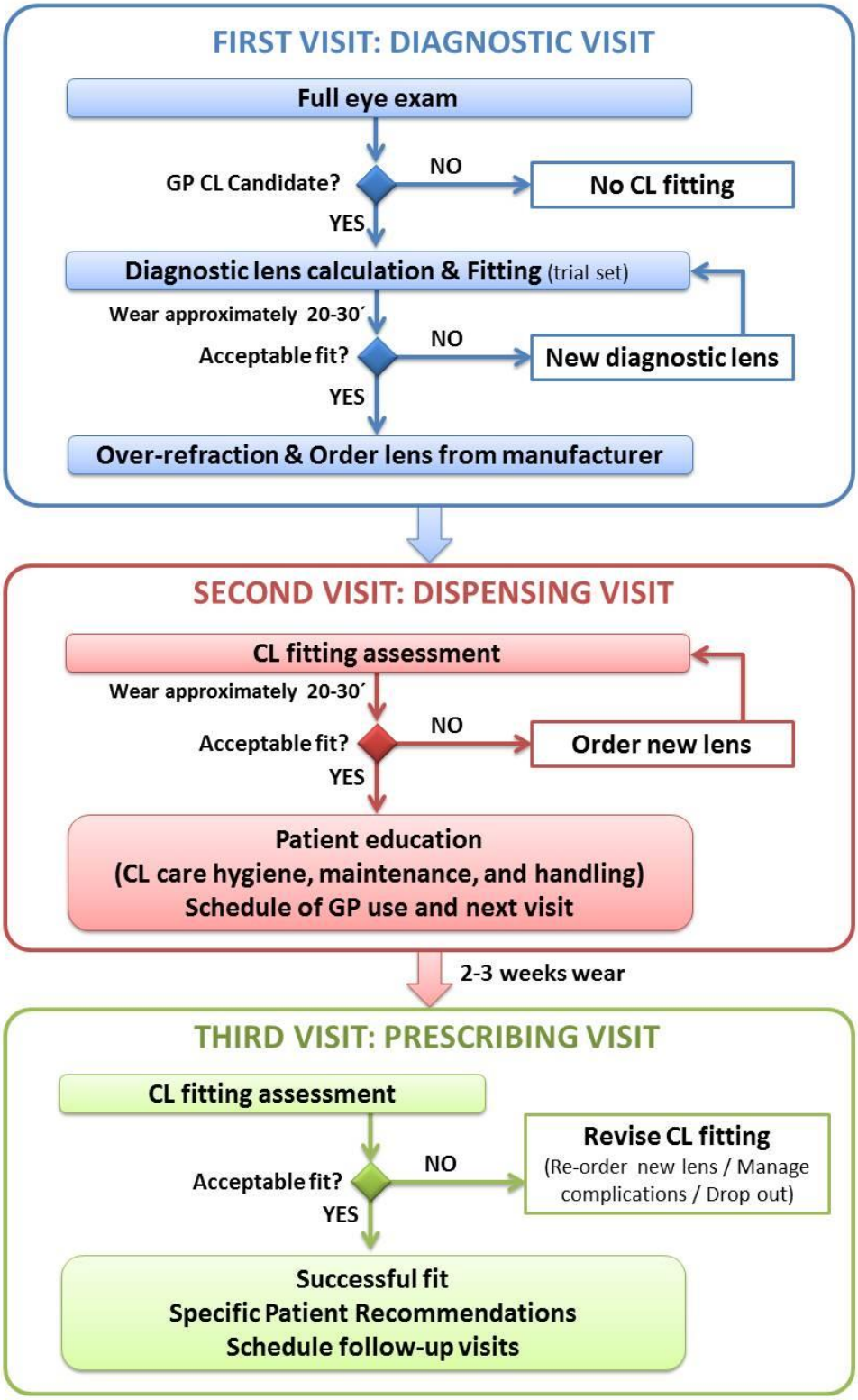
Clinical recommendation (DR; MQ, Level II^{-})
The GP CL fitting in keratoconic patients should take place in three visits: initial or diagnostic visit, dispensing visit and prescribing visit

B.1. Initial or diagnostic visit

The purpose of the initial visit is to determine whether a patient is a good candidate for GP CLs, to calculate the first diagnostic GP CL and to determine the parameters of the first GP CL.

A complete patient history and symptoms and an exhaustive eye examination should be performed. The eye care practitioner will provide full information on GP CLs including the wearing schedules and replacement frequency suggesting the best lens design and/or material to meet the needs of the patient. If the patient passes the initial examination and accepts GP CL wear, the first diagnostic GP CL will be calculated (see Section C) and evaluated (see Section D). Once the parameters for the GP CL are determined (BOZR, periphery, total diameter and power) the GP lens is ordered from the manufacturer.

Figure 1. Flow chart of GP CL standardised fitting protocol from the initial eye examination to the successful fitting of the GP in keratoconus. Modified from Ortiz-Toquero et all, 2016.[41]



The patients who are not good candidate for CL wear drop out of the CL fitting process. However, for patients who are good candidates for CL wear but are not happy with GP CL fitting, the eye care practitioner can suggest other options regarding CLs (soft, scleral or hybrid lenses following manufacturer or other fitting guidelines) or other non-CLs related options.

B.2. Dispensing Visit

The purpose of the dispensing visit is to assess the ordered GP CL and double check that this lens shows correct movement, centration, fluorescein pattern and vision (See Section D). If all is correct, the patient should be trained in correct lens handling and care systems of the GP CLs (See Section E). The eye care practitioner must schedule the patient for a follow-up visit after 2 or 3 weeks of lens wear.

If the GP CL fit is not adequate, the CL specifications (BOZR, periphery, total diameter or power) must be modified, and a new GP CL reordered. This new GP CL should be re-evaluated in a new dispensing visit following the same procedure as above.

B.3. Prescribing Visit

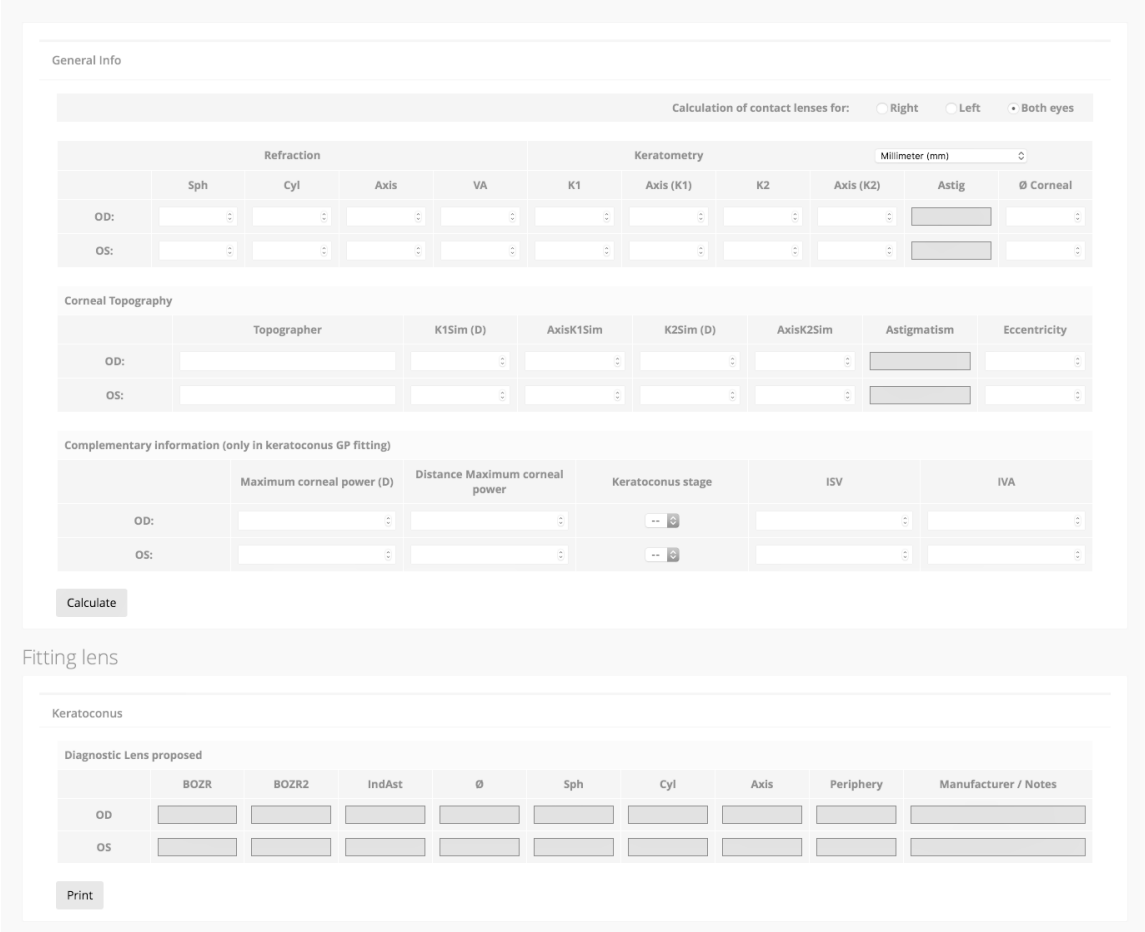
The purpose of the prescribing visit is to guarantee that the dispensed GP CL is correct and safe. So, after 2-3 weeks of wear the GP CL fit should be assessed considering lens movement, centration, and fluorescein pattern, vision and ocular surface health. The GP CL fit is considered to be good if all these conditions are acceptable: the GP CL provides good vision that cannot be improved with over-refraction, enough comfortable daily wear (6-8 hours per day or more), and optimal physiology of corneal surface without CL-related complications. The eye care practitioner must provide follow up recommendations and a schedule of aftercare visits (see Section F).

If any parameter of the GP fit is found to be inadequate, a new GP CL should be reordered and a new dispensing visit should be scheduled. Finally, if an optimal GP CL fit is not achieved, the eye care practitioner should suggest other CL options such as scleral lens, hybrid lens or piggy back system or not CL related options (surgical management).

C.- Calculation of first diagnostic lens parameters

To calculate the first diagnostic GP CL for keratoconic eyes with Calculens.com[23] (www.calculens.com) (Figure 2) only the corneal curvature obtained with a manual keratometer or corneal topography is necessary. Total diameter and peripheral geometry of the lens is also provided by the robust algorithm of Calculens.com, Additional corneal parameters could be used to improve the Calculens.com suggestion; for example, maximum corneal power or back vertex distance among others.

Figure 2. Screenshot of Calculens.com. Corneal curvature is essential to calculate GP CL in keratoconic eyes using Calculens.com and set trial GP CL. Other fields improve the GP calculation (i.e. to gain a suggestion for peripheral geometry or diameter of the lens) but are not mandatory in BOZR calculation.



This guideline encourages the use of a trial lens set. The minimum parameters necessary to define the first diagnostic lens is the BOZR. Calculens.com allows BOZR calculation with keratometry or simulated keratometry (achieved after corneal topography) and provides a diameter value and peripheral geometry. The practitioner may choose the closest lens to the Calculens´ suggestion from the trial lens set. Using this recommendation more than one diagnostic lenses can be fitted in the same session. Using Calculens.com no more than 2 trial are expected to achieve final BOZR and diameter (median of 1 trial lens).[23] An alternative could be to order the first diagnostic lens from the manufacturer but this option delays the fitting procedure.

Clinical recommendation (SR; GQ, Level II^{+})
The use of Calculens.com to determine the first diagnostic GP lens allows a reduction in the number of trials and visits necessary to achieve a successful GP CL fitting in keratoconus.

D.- First diagnostic lens assessment.

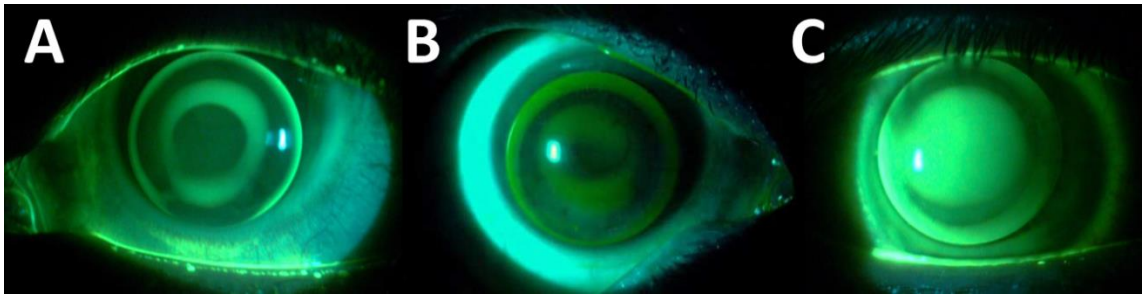
The first diagnostic GP lenses is selected from a trial set, based on the suggested parameters. Usually, the GP trial set has lenses with the same power and a standard diameter but different BOZR. The first GP diagnostic CL calculated (see Section C) is inserted into the patient's eye and the eye care practitioner must allow the GP diagnostic CL to settle on the eyes for approximately 20-30 minutes.[21, 41, 45] The use of topical anaesthetic may improve the patient's comfort in the first trials and visits.[46]

After 20-30 minutes of wear, the GP diagnostic CLs are evaluated.[41, 45] Optimal static and dynamic fit will be achieved with good centration of the lens and correct movement to allow tear exchange under the lens during the blink. GP lenses usually centre at the apex of the cone (usually displaced inferior and nasal relative to pupil in nipple cone and inferior-temporal in oval cones).[42,47]

The total diameter should be evaluated to determine if it is adequate (covering pupil diameter, correct lens centration, etc.) and is dependent on any lid interaction (lid attachment or interpalpebral fitting) in providing correct lens positioning, stability and centration.[45]

The fluorescein pattern is assessed in three different areas; central, mid-periphery and edge. A standard fluorescein strip should be wetted with saline solution or multi-purpose solution and applied to the eye by applying the tip of the fluorescein strip onto the temporal superior bulbar conjunctiva to maximise longevity on the ocular surface. The fluorescein pattern should be assessed with a slit-lamp using a cobalt filter and a Wratten 12 or Tiffen 2 yellow filter[48] 1 to 3 minutes after fluorescein instillation.[49] Alternatively a Burton lamp can be used.[50] The eye care practitioner may use the patient's eyelids to position the CL over the corneal apex and to prevent the patient from blinking. The fit is judged to be one of the following fluorescein patterns: flat or "apical touch", optimal or "three-point-touch" and steep or "apical clearance".[51] This guideline encourages the three-point touch fitting philosophy as the optimal fluorescein pattern.[51, 52] (Figure 3)

Figure 3. Fluorescein patterns of the three fitting philosophies. A: Apical touch; B: Three-point-touch; C: Apical clearance



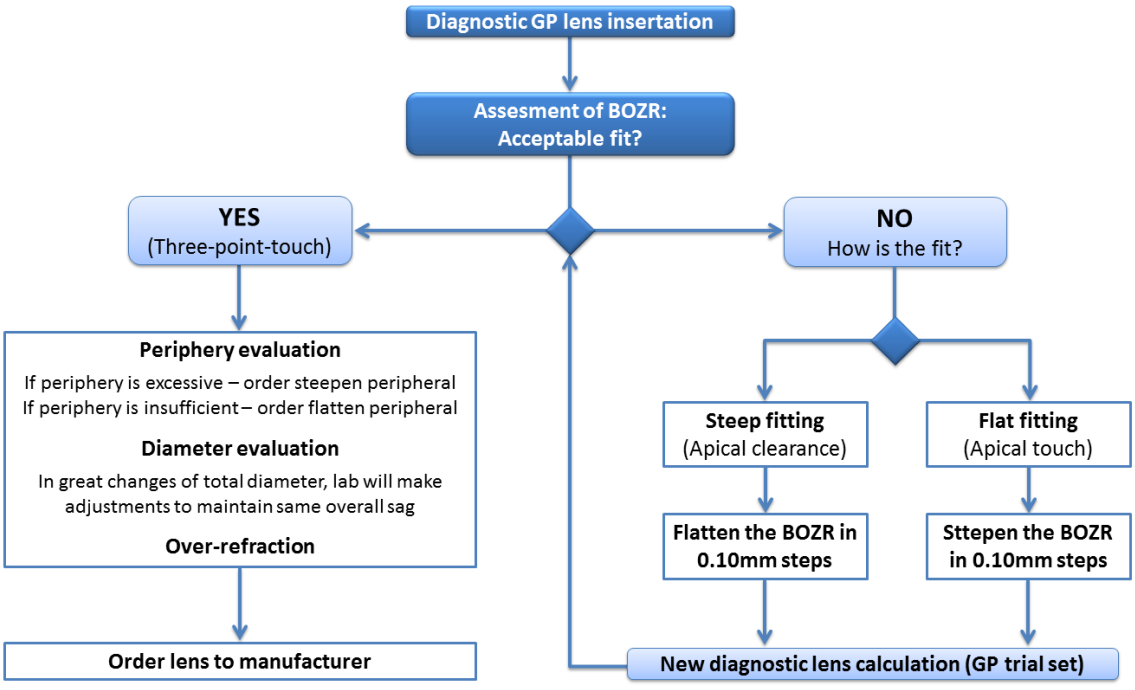
"Three-point-touch" (divided support) pattern is the most widely-accepted and safest modality of GP CL fitting in keratoconus.[51, 52] In this fitting philosophy the GP CL has light touch on the apex with peripheral alignment. Lens support and bearing is shared between the apex and the paracentral cornea. The location of this touch is dependent on the location of the apex of the cone. "Apical touch" is induced by excessive flat BOZR and the GP CL supports or bears on the apex of the cornea. This flat fit may increase corneal staining or abrasion, apical scarring and distortion of vision. When the BOZR is too steep ("apical clearance") the GP CL is supported by or bears on the peripheral cornea and may lead to poor visual acuity, flare, poor or non-existent tear exchange, trapped bubbles and dimple veiling.

Clinical recommendation (SR; GQ, Level I⁻)
The "three-point-touch" (divided support) pattern is the most widely-accepted and safest modality of GP CL fitting in keratoconus.

Central flat ("apical touch") or steep ("apical clearance") fluorescein patterns indicate that the BOZR must be changed. If any parameter of the diagnostic lens is inadequate, the GP CL must be changed, and a second diagnostic lens selected. It is advised adjustments of at least 0.10mm are made to modify the BOZR; for example the next diagnostic lens is decreased by 0.10mm steps if the BOZR of the lens was too flat.[53] In contrast, the BOZR of the next diagnostic lens will be increased 0.10mm steps if the BOZR was too steep.[53] Fitting assessments should be repeated until a correct lens fit is achieved (Figure 4). Special attention should be paid to the mid-peripheral fluorescein pattern because mid-peripheral alignment is necessary to avoid a flat or tight lens fit. Finally correct peripheral alignment with a narrow band of edge clearance at the periphery is recommended to enable adequate tears exchange and comfort, avoiding an excess or reduced edge clearance.

Once the BOZR and peripheral design are determined, over-refraction should be performed to determine the power of the GP lens and the BCVA and the GP lens will be ordered from the manufacturer.

Figure 4. Flow chart of diagnostic lens selection and BOZR evaluation at the first visit.



Clinical recommendation (DR; MQ, Level III)
Apply changes of BOZR in steps of 0.10 mm to refine fluorescein pattern until achieve "three-point-touch" fluorescein pattern.

E.- Dispensing and patient education.

The eye care practitioner must verify the accuracy of the ordered GP CLs which should be free from defects and all parameters of the GP CLs must be within accepted tolerances. Before dispensing the GP CL, the eye care practitioner must check the fit of the ordered GP CL on the patient's eyes.[41] Following the recommendations of this Guideline 64% of keratoconus patients will be fitted with the first ordered lens and just a small number of patients (32% of cases) may require a second ordered lens (mainly related to lens power refinement).[23]

The patient should be trained in the care, maintenance, and handling of GP CLs.[44, 54] The eye care practitioners must highlight the importance of proper hygiene (washing hands, the cleaning, storing and disinfecting of GP CLs with appropriate solutions), compliance with CL care techniques, and warnings, precautions, and directions for use of CLs to avoid patients developing risky behaviour.[55]

Clinical recommendation (SR; GQ, Level II$^-$)
Patient education in the correct maintenance and handling of GP CLs and hand hygiene is essential in reducing CL complications and adverse effects.

The eye care practitioner prescribes wearing schedule starting with 1 - 2 hours the first day and then adding 1-2 hours each day until a minimum of eight hours of wear each day (with a maximum of 12 hours per day) is achieved in new GP CLs wearers. It is suggested that the 8-hour wearing period is not exceeded until the eye care practitioner has checked the fit in the prescribing visit and provides the information about normal adaptive symptoms and signs.

Clinical recommendation (GPP, DR; IQ, Level IV)
After dispensing the GP CLs, a wearing schedule starting with 1-2 hours per day and adding 1-2 hours each day until eight hours per day is achieved, during the 2-3 weeks before the prescribing visit.

Finally, the eye care practitioner should provide each patient with all the information necessary for GP CL wear, follow up, possible complications and warnings encourage patient education.

F.- Follow up visits.

Follow-up visits are important for the proper management of the keratoconus patient with GP CLs. After the prescribing visit, consider a three-month visit, followed by six-month visits for follow-up except if the patient requires shorter follow up care intervals (high risk of progression or anterior eye complication). Visit frequency may decrease in subsequent years depending on the severity of the disease and case evolution. At all follow-up visits, the eye care practitioner must check the visual acuity with GP lens, comfort, over-refraction, corneal topography (if is available), GP lens surface (e.g. polishing, scratches, chips, fogging) and fit assessment with fluorescein (attention should be paid to the apical touch and changes in the fluorescein pattern, which can be indicate keratoconus progression, and the GP CL should be refitted)[48] and biomicroscopy with and without GP CLs. The eye care practitioner should recommend additional visits whenever the GP CL keratoconus patient experiences an unexpected problem in vision or ocular condition. The manufacturers of GP CLs usually recommended replacing the lens yearly however lens replacement frequency should be adapted to each patient.

Clinical recommendation (GPP, DR; MQ, Level IV)
During first year of GP CLs wear keratoconic patients should be checked every three months. After this six-monthly visits should be acceptable to check CL wear and disease evolution (with biomicroscopy, fluorescein pattern assessment and corneal topography).

The most effective way to address the complications of CL wear is to prevent them from occurring.[56] Lid diseases such as blepharitis, Meibomian gland dysfunction, and dry eye, are many of the complications of CL wear. Lid hygiene or the use of artificial tear drops is helpful in these cases.[57]

GP CL wear can lead to warpage of the corneal surface, which results in a reversible loss of good visual acuity.[57] There are a number of different causes of corneal staining that may be observed by the eye care practitioner. The most common complication of GP CL wear is 3 and 9 staining, resulting from inadequate lid closure and leading to localized corneal desiccation.[58] Keratoconus patient may have dry eye associated with atopic disease, which contributes to

peripheral staining. To optimize the position of the CL, the eye care practitioner should increase the diameter of the lens to decrease the distance between the cornea and the lens.[57]

Eye care practitioners may also observe apical staining if the GP CL is too flat with apical touch and excessive lens movement. The constant irritation of the flat GP CL may lead to scarring. To manage this problem it is necessary to decrease the pressure of the GP lens on the apex of the cone (refit the GP CL with a steeper BOZR).[57] When bubbles of air are trapped between GP CLs and the ocular surface, it produces "dimple veiling" in epithelial depressions with associated symptoms of discomfort. If the bubbles are located in the centre, is recommended to decrease apical clearance (refit GP CL with flatter BOZR). However if bubbles are located in the periphery, reducing the axial edge clearance is recommended.[57]

The eye care practitioner must inform the keratoconus patient that any episodes of severe pain, tearing, visual loss or redness need to be reported and extra visits may be required. Conditions with differing severity require different management; for example infiltrates, infectious keratitis[59] or corneal hydrops secondary to GP CL wear[57] could occur in keratoconus patients wearing GP CLs.

Clinical recommendation (SR; GQ, Level IV)
Keratoconus patients should be advised to remove their GP CLs whenever redness, tearing, visual loss or pain occurs and to consult their eye-care professional at once.

IV. Conclusions

GP CLs are the primary method for clinical management of the keratoconic patient. This Clinical Practice Guideline describes the fitting process of GP CLs in keratoconus eyes. It includes three different visits (diagnostic, dispensing and prescribing visit) supported by an online tool to calculate the first diagnostic GP lens' parameters (Calculens.com). Following this guideline, a minimum of three visits, one diagnostic and one ordered lens should be all that is necessary to complete corneal GP fitting in keratoconus eyes.

V. References

1. American Academy of Ophthalmology. Preferred Practice Pattern Guidelines. Available at: http://one.aao.org/CE/PracticeGuidelines/PPP.aspx. Accessed Dec 28, 2016.

2. Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. BMJ. 2001;323:334-6.

3. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336:924-6.

4. Guyatt GH, Oxman AD, Kunz R, et al. What is "quality of evidence" and why is it important to clinicians? BMJ. 2008; 336:995-8.

5. Guyatt GH, Oxman AD, Kunz R, et al. Going from evidence to recommendations. BMJ. 2008;336:1049-51.

6. Schünemann HJ, Schünemann AH, Oxman AD, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. BMJ. 2008;336:1106-10.

7. Guyatt GH, Oxman AD, Kunz R, et al. Incorporating considerations of resources use into grading recommendations. BMJ. 2008;336:1170-3.

8. Romero-Jiménez M, Santodomingo Rubido J, Wolffsohn JS. Keratoconus: a review. Cont Lens Anterior Eye. 2010;33: 157-66.

9. Gomes JA, Tan D, Rapuano CJ, et al. Global consensus on keratoconus and ectatic diseases. Cornea. 2015;34:359-69.

10. Rabinowitz YS. Keratoconus. Surv Ophthalmol. 1998;42:297-319.

11. Barnett M, Mannis MJ. Contact lenses in the management of keratoconus. Cornea. 2011;30:1510-6.

12. Zhou AJ KK, Weissman BA. Contact lens care in keratoconus. Cont Lens Anterior Eye. 2003;4:4.

13. Ortiz-Toquero S, Rodriguez G, de Juan V, Martin R. Repeatability of Wavefront Aberration Measurements With a Placido-Based Topographer in Normal and Keratoconic Eyes. J Refract Surg. 2016;32:338-44.

14. Downie LE, Lindsay RG. Contact lens management of keratoconus. Clin Exp Optom. 2015;98:299-311.

15. Ortiz-Toquero S, Perez S, Rodriguez G, et al. The influence of the refractive correction on the vision-related quality of life in keratoconus patients. Qual Life Res. 2016;25:1043-51

16. Ortiz-Toquero S, Martin R. Fitting gas permeable contact lens in keratoconus, still a challenge? Ophthalmol Open J. 2016;1: e9-e12. doi:10.17140/OOJ-1-e004

17. Ortiz-Toquero S, Martin R. Current optometric practices and attitudes in keratoconus patient management. Contact Lens and Anterior Eye. 2016. In press

18. Nosch DS, Ong GL, Mavrikakis I, Morris J. The application of a computerised videokeratography (CVK) based contact lens fitting software programme on irregularly shaped corneal surfaces. Cont Lens Anterior Eye. 2007;30:239-48.

19. Mandathara PS, Fatima M, Taureen S, et al. RGP contact lens fitting in keratoconus using FITSCAN technology. Cont Lens Anterior Eye. 2013;36(3):126-9.

20. Pullum K. A keratoconus fitting system using the axial profile to establish optimum lens parameters. Cont Lens Anterior Eye. 2003;26:77-84.

21. Romero-Jiménez M, Santodomingo Rubido J, González-Méijome JM. An assessment of the optimal lens fit rate in keratoconus subjects using three-point-touch and apical touch fitting approaches with the rose K2 lens. Eye Contact Lens. 2013;39:269-72.

22. Mandathara Sudharman P, Rathi V, Dumapati S. Rose K lenses for keratoconus--an Indian experience. Eye Contact Lens. 2010;36:220-2.

23. Ortiz-Toquero S, Rodriguez G, De Juan V, Martin R. New web-based algorithm to improve rigid gas permeable contact lens fitting in keratoconus. Contact Lens Anterior Eye. 2016; In Press

24. Piñero DP, Nieto JC, Lopez-Miguel A. Characterization of corneal structure in keratoconus. J Cataract Refract Surg. 2012; 38:2167-83.

25. Gore DM, Shortt AJ, Allan BD. New clinical pathways for keratoconus. Eye (Lond). 2013;27:329-39.

26. Kok YO, Tan GF, Loon SC. Review: keratoconus in Asia. Cornea. 2012;31:581-93.

27. Ortiz-Toquero S, Martin R. Keratoconus screening in primary eye care: A general overview. European Ophthalmic Review. 2016. In press

28. Hashemi H, Yekta A, Khabazkhoob M. Effect of keratoconus grades on repeatability of keratometry readings: Comparison of 5 devices. J Cataract Refract Surg. 2015;41:1065-72.

29. Nejabat M, Khalili MR, Dehghani C. Cone location and correction of keratoconus with rigid gas-permeable contact lenses. Cont Lens Anterior Eye. 2012;35:17-21.

30. Sorbara L, Dalton K. The use of video-keratoscopy in predicting contact lens parameters for keratoconic fitting. Cont Lens Anterior Eye. 2010;33:112-8.

31. Cavas-Martínez F, De la Cruz Sánchez E, Nieto Martínez J, et al. Corneal topography in keratoconus: state of the art. Eye Vis (Lond). 2016;3:5.

32. Bühren J, Kühne C, Kohnen T. Defining subclinical keratoconus using corneal first-surface higher-order aberrations. Am J Ophthalmol. 2007;143: 381-9.

33. Bühren J, Kook D, Yoon G, Kohnen T. Detection of subclinical keratoconus by using corneal anterior and posterior surface aberrations and thickness spatial profiles. Invest Ophthalmol Vis Sci. 2010;51:3424-32.

34. McMahon TT, Szczotka-Flynn L, Barr JT, et al. A new method for grading the severity of keratoconus: the Keratoconus Severity Score (KSS). Cornea. 2006;25: 794-800.

35. Amsler M. Kératocõne classique et kératocône fruste; arguments unitaires. Ophthalmologica. 1946;111:96-101.

36. Krumeich JH, Daniel J, Knülle A. Live-epikeratophakia for keratoconus. J Cataract Refract Surg. 1998;24:456-63.

37. Ortiz-Toquero S, Rodriguez G, de Juan V, Martin R. Rigid Gas Permeable Contact Lens Fitting Using New Software in Keratoconic Eyes. Optom Vis Sci. 2016; 93:286-92.

38. Martin R. Keratoconus management: Role of GP contact lenses. J Clin Exp Ophthalmol. 2016;7:e118. doi: 10.4172/ 2155-9570.1000e118

39. Van der Worp E, Bornman D, Ferreira DL, et al. Modern scleral contact lenses: A review. Cont Lens Anterior Eye. 2014;37:240-50.

40. Harvey W, Franklin A. Routine Eye Examination: Elsevier; 1st ed. 2005.

41. Ortiz-Toquero S, Martin M, Rodriguez G, et al. Success of Rigid Gas Permeable Contact Lens Fitting. Eye Contact Lens. 2016. DOI: 10.1097/ ICL.0000000000000254

42. Sorbara L FD, Woods C, Sivak A, Boshart B. Correction of keratoconus with GP lenses. Waterloo. Baush and Lomb, 1st ed. 2010.

43. Wang M. Keratoconus and Keratoectasia. Slack, 1st ed. 2009.

44. American Optometric Association. Optometric Clinical Practice Guideline: Care of the Contact Lens Patient. 2006.

http://www.aoa.org/documents/optometrists/CPG-19.pdf. Accesed Dec 4, 2016.

45. Wolffsohn JS, van der Worp E, de Brabander J. Consensus on recording of gas permeable contact lens fit. Cont Lens Anterior Eye. 2013;36:299-303.

46. Bennett ES, Smythe J, Henry VA, et al. Effect of topical anesthetic use on initial patient satisfaction and overall success with rigid gas permeable contact lenses. Optom Vis Sci. 1998;75:800-5.

47. Gasson A, Morris JA. The contact lens manual. A practical guide to fitting. Butterworth-Heinemann-Elsevier. 4th ed. 2010.

48. Zadnik K, Barr JT, Steger-May K, et al. Comparison of flat and steep rigid contact lens fitting methods in keratoconus. Optom Vis Sci. 2005;82:1014-21.

49. Wolffsohn JS, Tharoo A, Lakhlani N. Optimal time following fluorescein instillation to evaluate rigid gas permeable contact lens fit. Cont Lens Anterior Eye. 2015;38:110-4.

50. Fink BA, Barr JT, Edrington TB, et al. A comparison of two methods of evaluating cornea-to-contact lens base curve fluorescein patterns in keratoconus. Optom Vis Sci. 2001;78:589-98.

51. Leung KK. RGP fitting philosophies for keratoconus. Clin Exp Optom. 1999;82:230-5.

52. Zadnik K, Barr JT, Edrington TB, et al. Baseline findings in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study. Invest Ophthalmol Vis Sci. 1998;39:2537-46.

53. Orsborn GN, Zantos SG, Godio LB, Jones WF, Barr JT. Aspheric rigid gas permeable contact lenses: practitioner discrimination of base curve increments using fluorescein pattern evaluation. Optom Vis Sci. 1989;66:209-13.

54. Contact Lens Care. Clinical practice guidelines. Singapur. Ministry of Health-National Medical Research Council-Nacional Commitee of Ophthalmology; 2001.

55. Cope JR, Collier SA, Rao MM, , et al. Contact Lens Wearer Demographics and Risk Behaviors for Contact Lens-Related Eye Infections-United States, 2014. MMWR Morb Mortal Wkly Rep. 2015;64:865-70.

56. Weissman B. Assessing and Treating Complications. Contact Lens Spectrum, 2006 (6).

57. Efron N. Contact lens complications. Oxford: Butterworth-Heinemann. 2nd ed, 2004.

58. Van der Worp E, De Brabander J, Swarbrick H, Nuijts R, Hendrikse F. Corneal desiccation in rigid contact lens wear: 3- and 9-o'clock staining. Optom Vis Sci. 2003;80:280-90.

59. Cope JR, Collier SA, Srinivasan K, et al. Contact Lens-Related Corneal Infections - United States, 2005-2015. MMWR Morb Mortal Wkly Rep. 2016;65:817-20.

APPENDIX: GUIDELINE DEVELOPMENT PROCESS

I. Implementing the guideline

A. Guidelines audience and stakeholder involvement

These guidelines are aimed at CL practitioners who fit or prescribe gas permeable contact lens for keratoconic patients.

These guidelines help to focus the GP CL fitting procedure, the selection of the parameters of the GP CLs, and provide a detailed procedure to help choose/calculate the first diagnostic lens. The guidelines also describe a schedule required to achieve an optimal gas permeable CL fitting as eye-care practitioners find GP CL fitting in keratoconus more challenging and time-consuming than in healthy corneas.

B. Implementation strategy

These guidelines are easy to implement in clinical practice by eye-care practitioners who fit or prescribe gas permeable CLs in keratoconic patients, because it recommends standardised patient care and visits with a simple, efficient and economical way to the calculate first trial lens parameters using an open-access web tool (www.calculens.com). However, because gas permeable contact lens fitting on irregular corneas could require small changes of the first suggested trial lens, it is highly recommended that eye-care practitioners use a trial set of gas permeable designed to fit keratoconic corneas. This will facilitate the fitting procedure reducing the number of visits necessary to achieve an ideal gas permeable contact lens fit.

C. Auditing current practice

Due the characteristics of these guidelines it is not necessary to have an audit or monitoring process.

II. Development of the guideline

A. Systematic literature review

The development group have performed an extensive search of the Medline and PubMed database, Google Scholar database, Science Direct database, Cochrane database, metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com) and ClinicalTrials.gov (www.clinicaltrials.gov) using individual and combinations of key words ("Keratoconus contact lenses", "Keratoconus fitting guideline", "Keratoconus gas permeable fitting", "Keratoconus gas permeable management") from 1990 to 2016 to identify the relevant publications in this field. It also included additional references (from different sources, books, books chapters, manufactures websites, etc.) that were cited or included in these articles.

Inclusion criteria: These guidelines include recommendations for fitting corneal gas permeable contact lens in keratoconus patients. English and Spanish results were collected.

Exclusion criteria: Recommendations for fitting soft CL, piggy-back, corneo-scleral, semi-scleral, mini-scleral, scleral or hybrid CL designs were excluded. Case reports were not assessed.

When the search was complete, the development team summarised the results found using a focus group and conducted different discussion rounds. Consensus among the development team was reached.

B. Review and updating

These guidelines will be updated every 5 years to include results of high quality research and well-designed studies that provide evidence based results that improve the Guidelines recommendations.

C. Guideline development group

These guidelines have been developed by the Optometry Research Group of the IOBA Eye Institute of the University of Valladolid (Spain). The development team was supported by:

- Raul Martin: Head of Optometry Research Group, IOBA Eye Institute University of Valladolid (Spain). PhD in Visual Science from the University of Valladolid (2010). He has over 20 years of clinical experience, teaching and research. He is responsible for more than 75 publications, 5 books, >100 presentations in national and international meetings etc.

Role: Guideline coordinator. Research supervisor, selecting and reviewing/rating the evidence, formulating the final recommendations, guideline writer and authorization.

- Sara Ortiz-Toquero: IOBA Eye Institute University of Valladolid (Spain). Master in Research Vision Sciences (2012); Master in Optometry (2011) and Degree in Optometry from the University of Valladolid (2010). She is a specialist in gas permeable contact lens fitting and is conducting her PhD in contact lens fitting in keratoconus.

  Role: Research and bibliography revision, selecting and reviewing/rating the evidence, formulating the final recommendations, guideline writer.

- Guadalupe Rodríguez: IOBA Eye Institute University of Valladolid (Spain). Master in Education Research (2010); Master in Research Vision Sciences (2007) and Master in Optometry (2006); Degree in Optometry from the University of Valladolid (1999). She is a contact lens expert with extensive experience in specialist contact lens fitting (irregular cornea, cosmetic, paediatric, etc.)

  Role: Bibliography revision, selecting and reviewing/rating the evidence, formulating the final recommendations, guideline writer.

- Victoria de Juan: Department of Ophthalmology, Ramón y Cajal University Hospital, Madrid (Spain). PhD in Vision Science from the University of Valladolid (2013); Master in Research Vision Sciences and Master in Optometry (2008); Degree in Optometry from the University of Valladolid (2003). She is an expert in contact lens and the ocular surface.

  Role: Bibliography revision, selecting and reviewing/rating the evidence, formulating the final recommendations, guideline writer.

D. Consultation and peer review

This guideline has been externally revised by Dr. Luisa Simo (Plymouth University) who revised the understandability of the guideline, the coherence between its steps and procedures, etc. after receiving a draft of the guideline and an open-questionnaire to detail her assessment.

E. Funding source and conflicts of interest

None of the authors has a financial or proprietary interest in any material or method mentioned.

Capítulo 8

Limitaciones y perspectivas de futuro

8. Limitaciones y perspectivas de futuro

8.1. Limitaciones de la tesis

Ningún proyecto de investigación está exento de limitaciones y a continuación se va a discutir el efecto sobre los resultados y conclusiones de esta tesis de las principales limitaciones identificadas.

Efecto del diseño de la LC RPG

Se ha utilizado un único diseño específico de LC RPG corneal (KAKC, Conóptica-Hecht Contactlinsen) para queratocono con la intención de reducir el número de variables en el estudio y garantizar una metodología de investigación cuidadosa. Sin embargo, esto hace que los resultados encontrados deban ser interpretados con cautela cuando se utilicen diseños de otros fabricantes, ya que cada casa comercial tiene su diseño propio de LC RPG para queratocono, pudiendo diferir en menor o mayor medida unos de otros, ya que esta información es confidencial y no es compartida o publicitada por los fabricantes. Por ello, el uso de Calculens.com en el cálculo de LC RPG corneal para queratocono de otros fabricantes podría presentar resultados distintos a los reportados en esta tesis doctoral, requiriéndose futuros estudios que analicen la correlación

entre diferentes diseños y que puedan permitir optimizar Calculens.com para cada diseño.

Así mismo, la elección de una técnica o filosofía de adaptación diferente a la de "*toque en tres puntos*" o de "*apoyo dividido*" como podrían ser las adaptaciones con "*toque apical*" o con "*levantamiento apical*", condicionará la elección del radio y demás parámetros de la LC RPG corneal lo que lógicamente afectará al valor del radio base adaptado.

Finalmente, con la intención de garantizar una muestra homogénea y comparable, en esta tesis doctoral se han incluido solamente LC RPG corneales para queratocono de diseño esférico, excluyéndose adaptaciones que precisaran diseños tóricos internos, bitóricos o LC RPG no corneales. Sin embargo, dado que sólo en 2 casos (3,3%) analizados en esta tesis no pudo completarse la adaptación con LC RPG esféricas, el impacto de esta limitación puede considerarse poco relevante desde un punto de vista clínico.

Centros de investigación/adaptación implicados

Otra limitación relevante es que el algoritmo incluido en Calculens.com se ha validado en un único centro (Grupo de Optometría del IOBA), por el mismo equipo de adaptadores implicado en el proyecto que, aunque acaparen una amplia experiencia en la adaptación de LC en general, y en córneas irregulares en particular, puede suponer un sesgo en la evaluación del fluorograma de la lente final y por ende en la elección de los parámetros de las lentes adaptadas. Este hecho puede sugerir que los resultados encontrados no sean fácilmente extrapolables a otros profesionales con diferente grado de experiencia en la adaptación de LC RPG y evaluación del fluorograma en casos de queratocono, si bien

muestran un protocolo de adaptación que puede ayudar a los profesionales nóveles a identificar el proceso para mejorar y adquirir experiencia.

En resumen, la tasa de éxito en la adaptación de LC RPG corneales se ha realizado en base a la experiencia de un único centro que ha empleado un protocolo de adaptación estandarizado (estructurado en 3 tipos de visitas), por lo que la tasa de éxito en otros centros que empleen otros protocolos o maneras de trabajar diferentes pueden concluir con resultados distintos a los encontrados en esta tesis (mayor o menor tasa de éxito o frecuencia de abandonos de la adaptación).

Características de los pacientes con queratocono adaptados con LC RPG corneales

En esta tesis se han incluido pacientes con queratocono leve y moderado, excluyendo los queratoconos avanzados puesto que el uso de LC RPG está indicado en la rehabilitación visual del paciente con queratocono, recomendándose su uso en estadios iniciales sin esperar a que el queratocono avance y muestre mayor irregularidad corneal que pueda dificultar la adaptación (tolerancia) del paciente al uso de cualquier tipo de LC (tanto RPG corneal como escleral). De esta manera se pretende proporcionar una herramienta que se adecue a la realidad clínica de esta patología, que mejorará la calidad de vida de estos pacientes, facilitando su adaptación (tolerancia) al uso de LC que en el caso de que el queratocono progresara y requiriera el uso de un diseño diferente al RPG corneal, facilitará (a priori) la adaptación (tolerancia) a esta nueva adaptación.

Además, en los casos avanzados es frecuente obtener una topografía poco repetible o con mayores errores y/o artefactos (presencia de cicatrices por ejemplo) lo que sin duda afectaría a los trabajos de análisis de la topografía incluidos en esta tesis (**Capítulos 4.2, 5.1, 5.2, 5.3, 5.4 y 6.2**).

Se han excluido también pacientes con queratocono sometidos a cualquier tipo de intervención quirúrgica ocular, puesto que se apuesta por un manejo del paciente con queratocono desde su detección o diagnóstico (en estadios incipientes) que permita reducir o minimizar el número de casos que requieran una opción quirúrgica ya que está ampliamente aceptado que el uso de LC RPG reduce el número de casos que recurren a cirugía.

Además, pacientes sometidos a cirugía como implante de anillos intraestromales o queratoplastia pueden presentar una irregularidad corneal diferente a la inicial y requerir un diseño de LC distinto, por lo que los resultados usando el algoritmo de Calculens.com en estos casos pueden discrepar de los resultados encontrados en este proyecto.

Finalmente, la inclusión de ambos ojos de los pacientes con queratocono en los **Capítulos 4.2, 5.3, 5.4, 6.1 y 6.2** puede ser criticable, aunque está ampliamente aceptado en la literatura la inclusión de ambos ojos debido a que el queratocono es una enfermedad bilateral pero asimétrica de manera que la topografía de un ojo muestra diferencias significativas (clínica y estadísticamente) con la del ojo contralateral lo que permita analizar de forma independiente el proceso del cálculo de los parámetros de la LC RPG corneal a adaptar en cada ojo. Concretamente, en el **Capítulo 6.1**, el número de visitas necesarias para completar la adaptación, se contabilizó por ojo y no por paciente, ya que un paciente podría finalizar la

adaptación con éxito en uno de los ojos, pero continuar el proceso de adaptación con el otro ojo, porque presentase mayor irregularidad y fuera más complicado estabilizar la LC. Por ello se quiso evaluar de forma independiente cada ojo por separado para no sobreestimar el número de visitas total.

Tecnología (topografía/tomografía) empleada

En esta tesis se han empleado diferentes topógrafos que incorporan diferente tecnología para el análisis de la topografía corneal como son los discos de Plácido (Allegro Topolyzer – Oculus Keratograph), el Plácido-Barrido de hendidura (Orbscan II, Bausch & Lomb Surgical) y Plácido-Scheimpflug (Galilei G4, Ziemer), por lo que obviamente los resultados encontrados en esta tesis no pueden extrapolarse a otros equipos o a diferentes tecnologías para el análisis de la topografía corneal (por ejemplo, OCT o interferometría de coherencia óptica).

Países incluidos

En esta tesis se ha encuestado a optometristas de Reino Unido y de España sobre su práctica optométrica en el manejo del paciente con queratocono al considerarse de gran interés la comparación con uno de los países de referencia en los que se practica una Optometría más avanzada. Sin embargo, se desconoce la práctica profesional en otros países europeos de referencia como puede ser Holanda con gran desarrollo en la adaptación de LC RPG por ejemplo o del mundo como pueden ser países con mayor prevalencia de queratocono (por ejemplo, India) (**Capítulo 4.3**). Además, la realización de este tipo de estudios con encuestas presenta grandes limitaciones a la hora de establecer con detalle el control sobre las personas que deciden responder, al haberse difundido vía internet,

incluidas redes sociales de manera que pueden haber respondido profesionales muy motivados por la adaptación de LC RPG o por el manejo de pacientes con queratocono lo que podría afectar a los resultados e interpretaciones extraídas de esta encuesta. Sin embargo, estos sesgos podrían considerarse similares en ambas poblaciones (Reino Unido y España) de manera que las principales conclusiones extraídas de este estudio pueden ser razonablemente válidas.

Expertos evaluadores de la guía

La selección de los expertos para la evaluación de la guía clínica propuesta siguiendo las recomendaciones del instrumento AGREE II puede ser criticable puesto que los expertos fueron contactados por internet y decidieron participar en la evaluación, lo que podría suponer una cierta proximidad con el equipo investigador que hiciera que su valoración fuera más favorable que la que puede hacer un evaluador independiente (tipo peer-review en las revistas de impacto). Para minimizar este efecto, aunque las recomendaciones de AGREE II proponen un mínimo de 2 expertos, se optó por invitar a participar a un mayor equipo de profesionales (8 expertos) de los cuales 3 no tenían ningún tipo de relación personal o profesional con el equipo investigador, ejerciendo su actividad en diferentes países y centros públicos o privados. La selección de un mayor grupo de expertos que incluyó profesionales ajenos al equipo desarrollador de la guía ayuda a minimizar cualquier posible sesgo e impacto en la evaluación y recomendación de la guía.

8.2. Perspectivas de futuro

Un proyecto de tesis doctoral lejos de cerrar o concluir una línea de investigación suele servir para abrir nuevas líneas o aspectos que precisan ser aclarados en el futuro, y esta tesis no es una excepción. Por tanto, las líneas futuras de este proyecto de tesis doctoral son varias.

La primera de ellas, sería validar clínicamente Calculens.com con otros diseños de LC RPG corneales de otras casas comerciales en nuevos pacientes con queratocono, para comprobar si los resultados encontrados en este estudio son extrapolables a otros diseños o fabricantes. La realización de este trabajo se considera de gran interés para mejorar el manejo de los pacientes con queratocono con la mayor parte de los diseños disponibles, si bien su realización dependerá del interés de los diferentes fabricantes para colaborar en esta validación.

También es necesario verificar el impacto de la pericia profesional en la adaptación de LC, que podría requerir un estudio multicéntrico en el que distintos profesionales de diferentes centros, con distintos grados de experiencia usaran Calculens.com para adaptar LC RPG a sus pacientes con queratocono, evaluando el número de pruebas y de visitas requeridas para finalizar la adaptación, así como la diferencia entre los parámetros propuestos y los finalmente adaptados, de manera que se clarificara el impacto del adaptador en los resultados de este proyecto.

Además, parece interesante que dado el necesario abordaje multidisciplinar que requiere el paciente con queratocono se pudieran desarrollar guías clínicas que identificaran el manejo global de esta enfermedad, facilitando criterios inequívocos para el diagnóstico y

clasificación de la enfermedad que ayuden a cuantificar u objetivizar su progresión; proponiendo la estrategia de selección de la técnica más adecuada para la rehabilitación visual del paciente (selección del tipo de LC en cada caso), clarificando la indicación de las técnicas quirúrgicas (CXL, ICRS y queratoplastia) de manera que los diferentes profesionales de la salud implicados en el manejo del paciente con queratocono puedan ofrecer el mejor tratamiento para minimizar el impacto de la enfermedad en su calidad de vida.

Por último, esta tesis doctoral abre la puerta a otras áreas de la contactología en la que se podría aplicar una metodología de análisis similar para intentar estandarizar el proceso de adaptación de otros diseños de LC en otras tipologías de pacientes. De esta manera se podrían desarrollar guías basadas en la evidencia para la adaptación de LC esclerales, ortoqueratología o LC multifocales para controlar la progresión de la miopía, que ayuden al profesional en la toma de decisiones clínicas, simplificando la adaptación, de manera que un mayor número de pacientes puedan ser adaptados con garantías de seguridad y de éxito.

Capítulo 9

Conclusiones

9. Conclusiones

Las conclusiones que se pueden extraer de esta tesis doctoral son las siguientes:

1. Los pacientes con queratocono tienen mejor calidad de vida (cuestionario estandarizado NEI-VFQ-25) cuando usan LC RPG corneales que cuando usan gafas.

2. El proceso de adaptación de LC RPG corneales siguiendo un protocolo estandarizado y basado en la evidencia, permite obtener una alta tasa de éxito en la adaptación al uso o porte de LC RPG tanto en sujetos sanos (7 de cada 10) como con queratocono (9 de cada 10).

3. Las recomendaciones actuales que ofrecen los fabricantes y algunos autores para adaptar LC RPG corneales en queratocono presentan diferencias clínicamente relevantes entre el radio de la LC RPG propuesto y el radio finalmente adaptado que obligan a realizar varios cambios de lente de prueba hasta identificar el radio adecuado.

4. La práctica clínica optométrica entre profesionales de Reino Unido y España es similar en el manejo del paciente con queratocono, siendo la adaptación en estos pacientes más complicada que en ojos sanos.

5. La topografía corneal basada en discos de Plácido proporciona medidas repetibles en ojos con queratocono, pero existe una falta de acuerdo entre la topografía de Placido y la de Placido-Scheimpflug que impide que las medidas topográficas sean intercambiables en pacientes con queratocono.

6. El uso de indicadores de aberraciones corneales, concretamente del coma con un valor de corte de 0,377 µm permite discriminar entre ojos sanos y ojos con queratocono lo que podría ser de gran utilidad en la detección y clasificación de los ojos con queratocono.

7. El nuevo nomograma para la selección de los parámetros de las LC RPG en ojos con queratocono (Calculens.com) permite simplificar el proceso de adaptación, reduciendo la diferencia entre los parámetros de la lente probada y los de la lente finalmente adaptada.

8. La guía de adaptación de LC RPG corneales en queratocono, desarrollada bajo los estándares del consorcio AGREE-II, permite estandarizar y simplificar el proceso de adaptación, reduciendo el número de LC, ya sean de prueba o pedidas al fabricante, necesarias para completar la adaptación de la LC RPG corneal adecuada en cada caso.

Capítulo 10

Referencias

References

10. Referencias

1. Gomes JA, Tan D, Rapuano CJ, et al. Global consensus on keratoconus and ectatic diseases. *Cornea* 2015; 34:359-369.
2. Vazirani J, Basu S. Keratoconus: current perspectives. *Clin Ophthalmol* 2013; 7:2019-2030.
3. Romero-Jiménez M, Santodomingo Rubido J, Wolffsohn JS. Keratoconus: a review. *Cont Lens Anterior Eye* 2010; 33:157-166.
4. Rabinowitz YS. Keratoconus. *Surv Ophthalmol* 1998; 42:297-319.
5. Kok YO, Tan GF, Loon SC. Review: keratoconus in Asia. *Cornea* 2012; 31:581-593.
6. Gore DM, Shortt AJ, Allan BD. New clinical pathways for keratoconus. *Eye (Lond)* 2013; 27:329-339.
7. Gokul A, Patel DV, Watters GA, McGhee CN. The natural history of corneal topographic progression of keratoconus after age 30 years in non-contact lens wearers. *Br J Ophthalmol* 2016. In press
8. Mandathara PS, Stapleton FJ, Willcox MD. Outcome of Keratoconus Management: Review of the Past 20 Years' Contemporary Treatment Modalities. *Eye Contact Lens* 2016. In press
9. Godefrooij DA, de Wit GA, Uiterwaal CS, Imhof SM, Wisse RP. Age-specific incidence and prevalence of keratoconus: a nationwide registration study. *Am J Ophthalmol* 2016. In Press
10. Piñero DP, Nieto JC, Lopez-Miguel A. Characterization of corneal structure in keratoconus. *J Cataract Refract Surg* 2012; 38:2167-2183.
11. Rabinowitz YS. Videokeratographic indices to aid in screening for keratoconus. *J Refract Surg* 1995; 11:371-379.
12. de Sanctis U, Loiacono C, Richiardi L, et al. Sensitivity and specificity of posterior corneal elevation measured by Pentacam in discriminating keratoconus/subclinical keratoconus. *Ophthalmology* 2008;115:1534-1539.
13. Prakash G, Srivastava D, Choudhuri S, Thirumalai SM, Bacero R. Differences in central and non-central keratoconus, and their effect on the objective screening thresholds for keratoconus. *Acta Ophthalmol* 2016; 94:e118-129.
14. Henriquez MA, Izquierdo L, Mannis MJ. Intereye asymmetry detected by Scheimpflug imaging in subjects with normal corneas and keratoconus. *Cornea* 2013; 32:779-782.
15. Dienes L, Kránitz K, Juhász E, et al. Evaluation of intereye corneal asymmetry in patients with keratoconus. A scheimpflug imaging study. *PLoS One* 2014; 9:e108882.

16. Cavas-Martínez F, De la Cruz Sánchez E, Nieto Martínez J, et al. Corneal topography in keratoconus: state of the art. *Eye Vis (Lond)* 2016; 3:5.

17. Nosch DS, Ong GL, Mavrikakis I, Morris J. The application of a computerised videokeratography (CVK) based contact lens fitting software programme on irregularly shaped corneal surfaces. *Cont Lens Anterior Eye* 2007; 30:239-248.

18. Mandathara PS, Fatima M, Taureen S, et al. RGP contact lens fitting in keratoconus using FITSCAN technology. *Cont Lens Anterior Eye* 2013; 36: 126-129.

19. Hashemi H, Yekta A, Khabazkhoob M. Effect of keratoconus grades on repeatability of keratometry readings: Comparison of 5 devices. *J Cataract Refract Surg* 2015; 41:1065-1072.

20. Nejabat M, Khalili MR, Dehghani C. Cone location and correction of keratoconus with rigid gas-permeable contact lenses. *Cont Lens Anterior Eye* 2012; 35:17-21.

21. Sorbara L, Dalton K. The use of video-keratoscopy in predicting contact lens parameters for keratoconic fitting. *Cont Lens Anterior Eye* 2010; 33:112-118.

22. Chastang PJ, Borderie VM, Carvajal-Gonzalez S, Rostène W, Laroche L. Automated keratoconus detection using the EyeSys videokeratoscope. *J Cataract Refract Surg* 2000; 26:675-683.

23. McMahon TT, Anderson RJ, Roberts C, et al. Repeatability of corneal topography measurement in keratoconus with the TMS-1. *Optom Vis Sci* 2005; 82:405-415.

24. Saad A, Gatinel D. Topographic and tomographic properties of forme fruste keratoconus corneas. *Invest Ophthalmol Vis Sci* 2010; 51:5546-5555.

25. Jafarinasab MR, Shirzadeh E, Feizi S, et al. Sensitivity and specificity of posterior and anterior corneal elevation measured by orbscan in diagnosis of clinical and subclinical keratoconus. *J Ophthalmic Vis Res* 2015; 10:10-15.

26. Quisling S, Sjoberg S, Zimmerman B, Goins K, Sutphin J. Comparison of Pentacam and Orbscan IIz on posterior curvature topography measurements in keratoconus eyes. *Ophthalmology* 2006;113:1629-1632.

27. Feizi S, Yaseri M, Kheiri B. Predictive Ability of Galilei to Distinguish Subclinical Keratoconus and Keratoconus from Normal Corneas. *J Ophthalmic Vis Res* 2016; 11:8-16.

28. Reddy JC, Rapuano CJ, Cater JR, et al. Comparative evaluation of dual Scheimpflug imaging parameters in keratoconus, early keratoconus, and normal eyes. *J Cataract Refract Surg* 2014; 40:582-592.

29. Piñero DP, Alió JL, Alesón A, Escaf Vergara M, Miranda M. Corneal volume, pachymetry, and correlation of anterior and posterior corneal shape in subclinical and different stages of clinical keratoconus. *J Cataract Refract Surg* 2010; 36:814-825.

30. Meyer JJ, Gokul A, Vellara HR, Prime Z, McGhee CN. Repeatability and agreement of Orbscan II, Pentacam HR and Galilei tomography systems in corneas with keratoconus. *Am J Ophthalmol* 2016. In press

31. Pahuja N, Shroff R, Pahanpate P, et al. Application of high resolution OCT to evaluate irregularity of Bowman's layer in asymmetric keratoconus. *J Biophotonics* 2016. In press

32. Xu Z, Jiang J, Yang C, et al. Value of corneal epithelial and Bowman's

layer vertical thickness profiles generated by UHR-OCT for subclinical keratoconus diagnosis. *Sci Rep* 2016; 6:31550.

33. Steinberg J, Katz T, Lücke K, et al. Screening for Keratoconus With New Dynamic Biomechanical In Vivo Scheimpflug Analyses. *Cornea* 2015; 34:1404-1412.

34. Roy AS, Shetty R, Kummelil MK. Keratoconus: a biomechanical perspective on loss of corneal stiffness. *Indian J Ophthalmol* 2013; 61:392-393.

35. Simo Mannion L, Tromans C, O'Donnell C. An evaluation of corneal nerve morphology and function in moderate keratoconus. *Cont Lens Anterior Eye* 2005; 28:185-192.

36. Vinciguerra R, Ambrósio R, Elsheikh A, et al. Detection of Keratoconus With a New Biomechanical Index. *J Refract Surg* 2016; 32:803-810.

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

38. Alió JL, Shabayek MH. Corneal higher order aberrations: a method to grade keratoconus. *J Refract Surg* 2006; 22: 539-545.

39. Alió JL, Piñero DP, Alesón A, et al. Keratoconus-integrated characterization considering anterior corneal aberrations, internal astigmatism, and corneal biomechanics. *J Cataract Refract Surg* 2011; 37:552-568.

40. Piñero DP, Alio JL, Barraquer RI, Michael R, Jiménez R. Corneal biomechanics, refraction, and corneal aberrometry in keratoconus: an integrated study. *Invest Ophthalmol Vis Sci* 2010; 51:1948-1955.

41. Piñero DP, Alió JL, Alesón A, Escaf M, Miranda M. Pentacam posterior and anterior corneal aberrations in normal and keratoconic eyes. *Clin Exp Optom* 2009; 92:297-303.

42. Barbero S, Marcos S, Merayo-Lloves J, Moreno-Barriuso E. Validation of the estimation of corneal aberrations from videokeratography in keratoconus. *J Refract Surg* 2002; 18:263-270.

43. Bühren J, Kühne C, Kohnen T. Defining subclinical keratoconus using corneal first-surface higher-order aberrations. *Am J Ophthalmol* 2007; 143:381-389.

44. Rabinowitz YS, Rasheed K. KISA% index: a quantitative videokeratography algorithm embodying minimal topographic criteria for diagnosing keratoconus. *J Cataract Refract Surg* 1999; 25:1327-1335.

45. Mahmoud AM, Roberts CJ, Lembach RG, et al. CLMI: the cone location and magnitude index. *Cornea* 2008; 27: 480-487.

46. Smolek MK, Klyce SD. Current keratoconus detection methods compared with a neural network approach. *Invest Ophthalmol Vis Sci* 1997; 38:2290-2299.

47. Maeda N, Klyce SD, Smolek MK, Thompson HW. Automated keratoconus screening with corneal topography analysis. *Invest Ophthalmol Vis Sci* 1994; 35:2749-2757.

48. Rabinowitz YS, McDonnell PJ. Computer-assisted corneal topography in keratoconus. *Refract Corneal Surg* 1989; 5:400-408.

49. Kilin A, Roberts C. *Corneal Topography: From Theory to Practice*. Amsterdam. The Netherlands: Kugler Publications; 2013.

50. Dingeldein SA, Klyce SD, Wilson SE. Quantitative descriptors of corneal shape derived from computer-assisted analysis of photokerato-

graphs. *Refract Corneal Surg* 1989; 5: 372-378.

51. Wilson SE, Lin DT, Klyce SD. Corneal topography of keratoconus. *Cornea* 1991; 10:2-8.

52. Toprak I, Yaylalı V, Yildirim C. A combination of topographic and pachymetric parameters in keratoconus diagnosis. *Cont Lens Anterior Eye* 2015; 38:357-362.

53. Holladay JT. Corneal topography using the Holladay Diagnostic Summary. *J Cataract Refract Surg* 1997; 23:209-221.

54. Abad JC, Rubinfeld RS, Del Valle M, Belin MW, Kurstin JM. Vertical D: a novel topographic pattern in some keratoconus suspects. *Ophthalmology* 2007; 114:1020-1026.

55. Belin MW, Ambrósio R. Scheimpflug imaging for keratoconus and ectatic disease. *Indian J Ophthalmol* 2013; 61:401-406.

56. McMahon TT, Szczotka-Flynn L, Barr JT, et al. A new method for grading the severity of keratoconus: the Keratoconus Severity Score (KSS). *Cornea* 2006; 25:794-800.

57. M A. Kératocône classique et kératocône fruste; arguments unitaires. *Ophthalmologica* 1946; 111:96-101.

58. Krumeich JH, Daniel J, Knülle A. Live-epikeratophakia for keratoconus. *J Cataract Refract Surg* 1998; 24:456-463.

59. Zadnik K, Barr JT, Gordon MO, Edrington TB. Biomicroscopic signs and disease severity in keratoconus. Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study Group. *Cornea* 1996; 15:139-146.

60. Belin M, Duncan J, Ambrósio R, Gomes JA. A new tomographic method of staging/classifying keratoconus: The ABCD Grading System. *Int J Kerat Ect Cor Dis* 2015; 4:85-93.

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

62. Downie LE, Lindsay RG. Contact lens management of keratoconus. *Clin Exp Optom* 2015; 98:299-311.

63. Bilgin LK, Yilmaz S, Araz B, Yüksel SB, Sezen T. 30 years of contact lens prescribing for keratoconic patients in Turkey. *Cont Lens Anterior Eye* 2009; 32:16-21.

64. Barnett M, Mannis MJ. Contact lenses in the management of keratoconus. *Cornea* 2011; 30:1510-1516.

65. Romero-Jiménez M, Santodomingo Rubido J, González-Méijome JM. An assessment of the optimal lens fit rate in keratoconus subjects using three-point-touch and apical touch fitting approaches with the Rose K2 lens. *Eye Contact Lens* 2013; 39:269-272.

66. Hodge C, Chan C, Zantos S, et al. Therapeutic treatment of keratoconus: a survey of local optometric practice criteria. *Clin Exp Optom* 2015; 98:312-318.

67. Rajabi MT, Mohajernezhad-Fard Z, Naseri SK, et al. Rigid contact lens fitting based on keratometry readings in keratoconus patients: predicting formula. *Int J Ophthalmol* 2011; 4:525-528.

68. Mandathara Sudharman P, Rathi V, Dumapati S. Rose K lenses for keratoconus - an Indian experience. *Eye Contact Lens* 2010; 36:220-222.

69. Zhou AJ KK, Weissman BA. Contact lens care in keratoconus. *Cont Lens Anterior Eye* 2003; 26:171-174.

70. Dorronsoro C, Barbero S, Llorente L, Marcos S. On-eye measurement of optical performance of rigid gas

permeable contact lenses based on ocular and corneal aberrometry. *Optom Vis Sci* 2003; 80:115-125.

71. Choi J, Wee WR, Lee JH, Kim MK. Changes of ocular higher order aberration in on- and off-eye of rigid gas permeable contact lenses. *Optom Vis Sci* 2007; 84:42-51.

72. Negishi K, Kumanomido T, Utsumi Y, Tsubota K. Effect of higher-order aberrations on visual function in keratoconic eyes with a rigid gas permeable contact lens. *Am J Ophthalmol* 2007; 144:924-929.

73. Romero-Jiménez M, Santodomingo Rubido J, Flores-Rodríguez P, González-Méijome JM. Which soft contact lens power is better for piggyback fitting in keratoconus? *Cont Lens Anterior Eye* 2013; 36:45-48.

74. Carracedo G, González-Méijome JM, Lopes-Ferreira D, Carballo J, Batres L. Clinical performance of a new hybrid contact lens for keratoconus. *Eye Contact Lens* 2014; 40:2-6.

75. Abdalla YF, Elsahn AF, Hammersmith KM, Cohen EJ. SynergEyes lenses for keratoconus. *Cornea* 2010; 29:5-8.

76. Van der Worp E, Bornman D, Ferreira DL, et al. Modern scleral contact lenses: A review. *Cont Lens Anterior Eye* 2014; 37:240-250.

77. Schornack MM, Patel SV. Scleral lenses in the management of keratoconus. *Eye Contact Lens* 2010; 36:39-44.

78. Scleral Lens Education Society. https://www.sclerallens.org/sites/default/files/files/SLS_Nomenclature_LtrHead06_26_2013.pdf (Consultada el 24/02/2017)

79. Mastropasqua L. Collagen cross-linking: when and how? A review of the state of the art of the technique and new perspectives. *Eye Vis (Lond)* 2015;2:19.

80. Meek KM, Hayes S. Corneal cross-linking-a review. *Ophthalmic Physiol Opt* 2013; 33:78-93.

81. Sykakis E, Karim R, Evans JR, et al. Corneal collagen cross-linking for treating keratoconus. *Cochrane Database Syst Rev* 2015; 3:CD010621.

82. Giacomin NT, Mello GR, Medeiros CS, et al. Intracorneal Ring Segments Implantation for Corneal Ectasia. *J Refract Surg* 2016; 32:829-839.

83. Vega-Estrada A, Alio JL. The use of intracorneal ring segments in keratoconus. *Eye Vis (Lond)* 2016; 3:8.

84. Ertan A, Colin J. Intracorneal rings for keratoconus and keratectasia. *J Cataract Refract Surg* 2007; 33:1303-1314.

85. Coskunseven E, Kymionis GD, Tsiklis NS, et al. One-year results of intrastromal corneal ring segment implantation (KeraRing) using femtosecond laser in patients with keratoconus. *Am J Ophthalmol* 2008; 145: 775 -779.

86. Chan TC, Ng AL, Chan KK, Cheng GP, Wong IY, Jhanji V. Combined application of prophylactic corneal cross-linking and laser in-situ keratomileusis - a review of literature. *Acta Ophthalmol* 2016. In press

87. Krueger RR, Kanellopoulos AJ. Stability of simultaneous topography guided photorefractive keratectomy and riboflavin/UVA cross-linking for progressive keratoconus: case reports. *J Refract Surg* 2010; 26:S827-832.

88. Kymionis GD, Kontadakis GA, Kounis GA, et al. Simultaneous topography-guided PRK followed by corneal collagen cross-linking for keratoconus. *J Refract Surg* 2009; 25:S807-811.

89. Ayres BD, Rapuano CJ. Excimer laser phototherapeutic keratectomy. *Ocul Surf* 2006; 4:196-206.

90. Elsahn AF, Rapuano CJ, Antunes VA, Abdalla YF, Cohen EJ. Excimer laser phototherapeutic keratectomy for keratoconus nodules. *Cornea* 2009; 28:144-147.

91. Leccisotti A, Fields SV. Angle-supported phakic intraocular lenses in eyes with keratoconus and myopia. *J Cataract Refract Surg* 2003; 29:1530-1536.

92. Antonios R, Dirani A, Fadlallah A, et al. Safety and Visual Outcome of Visian Toric ICL Implantation after Corneal Collagen Cross-Linking in Keratoconus: Up to 2 Years of Follow-Up. *J Ophthalmol* 2015; 2015:514834.

93. Arnalich-Montiel F, Alió Del Barrio JL, Alió JL. Corneal surgery in keratoconus: which type, which technique, which outcomes? *Eye Vis (Lond)* 2016; 3:2.

94. Villarrubia A, Mendicute J. Queratoplastia lamelar: técnicas quirúrgicas. Comunicación Solicitada 81 Congreso de la Sociedad Española de Oftalmología; 2005.

95. Gordon MO, Steger-May K, Szczotka-Flynn L, et al. Baseline factors predictive of incident penetrating keratoplasty in keratoconus. *Am J Ophthalmol* 2006; 142:923-930.

96. Leung KK. RGP fitting philosophies for keratoconus. *Clin Exp Optom* 1999; 82:230-235.

97. Zadnik K, Barr JT, Steger-May K, et al. Comparison of flat and steep rigid contact lens fitting methods in keratoconus. *Optom Vis Sci* 2005; 82:1014-1021.

98. Sorbara L FD, Woods C, Sivak A, Boshart B. Correction of keratoconus with GP lenses. Waterloo. Baush and Lomb, 1st ed. 2010.

99. Pullum K. A keratoconus fitting system using the axial profile to establish optimum lens parameters. *Cont Lens Anterior Eye* 2003; 26:77-84.

100. Aydin Kurna S, Altun A, Gencaga T, Akkaya S, Sengor T. Vision related quality of life in patients with keratoconus. *J Ophthalmol* 2014; 2014:694542.

101. Kymes SM, Walline JJ, Zadnik K, Gordon MO, group CLEoKs. Quality of life in keratoconus. *Am J Ophthalmol* 2004; 138:527-535.

102. Smiddy WE, Hamburg TR, Kracher GP, Stark WJ. Keratoconus. Contact lens or keratoplasty? *Ophthalmology* 1988; 95:487-492.

103. Martin R. Keratoconus management: Role of GP contact lenses. *J Clin Exp Ophthalmol* 2016; 7:e118.

104. Rebenitsch RL, Kymes SM, Walline JJ, Gordon MO. The lifetime economic burden of keratoconus: a decision analysis using a markov model. *Am J Ophthalmol* 2011; 151:768-773.e762.

105. AGREE Enterprise website http://www.agreetrust.org/agree-ii/ (Consultada el 12/01/2017)

106. Mangione CM, Lee PP, Gutierrez PR, et al. Development of the 25-item National Eye Institute Visual Function Questionnaire. *Arch Ophthalmol* 2001; 119:1050-1058.

107. Massof RW. An interval-scaled scoring algorithm for visual function questionnaires. *Optom Vis Sci* 2007; 84:E690-705.

108. Sahebjada S, Fenwick EK, Xie J, Snibson GR, Daniell MD, Baird PN. Impact of keratoconus in the better eye and the worse eye on vision-related quality of life. *Invest Ophthalmol Vis Sci* 2014; 55:412-416.

109. Jones-Jordan LA, Walline JJ, Sinnott LT, Kymes SM, Zadnik K. Asymmetry

in keratoconus and vision-related quality of life. *Cornea* 2013; 32:267-272.

110. Tatematsu-Ogawa Y, Yamada M, Kawashima M, Yamazaki Y, Bryce T, Tsubota K. The disease burden of keratoconus in patients' lives: comparisons to a Japanese normative sample. *Eye Contact Lens* 2008; 34:13-16.

111. Gothwal VK, Reddy SP, Fathima A, et al. Assessment of the impact of keratoconus on vision-related quality of life. *Invest Ophthalmol Vis Sci* 2013; 54:2902-2910.

112. Labiris G, Giarmoukakis A, Sideroudi H, Kozobolis V. Impact of keratoconus, cross-linking and cross-linking combined with topography-guided photorefractive keratectomy on self-reported quality of life: a 3-year update. *Cornea* 2013; 32:e186-188.

113. Labiris G, Sideroudi H, Angelonias D, Georgantzoglou K, Kozobolis VP. Impact of corneal cross-linking combined with photorefractive keratectomy on blurring strength. *Clin Ophthalmol* 2016; 10:571-576.

114. Ramos-López D, Martínez-Finkelshtein A, Castro-Luna GM, Piñero D, Alió JL. Placido-based indices of corneal irregularity. *Optom Vis Sci* 2011; 88:1220-1231.

115. Gonen T, Cosar CB, Sener B, Keskinbora KH. Comparison of keratometric data obtained by automated keratometer, Dicon CT 200, Allegro Topolyzer, and Pentacam. *J Refract Surg* 2012; 28: 557-561.

116. IOM Committee to advise the Public Health Service on clinical practice, guidelines. In: Field MJ, Lohr KN, editors. (eds). Clinical practice guidelines: directions for a new program, Washington, DC: National Academies Press, 1990.

117. Burda BU, Chambers AR, Johnson JC. Appraisal of guidelines developed by the World Health Organization. *Public Health* 2014; 128:444-74.

118. Ou Y, Goldberg I, Migdal C et al. A critical appraisal and comparison of the quality and recommendations of glaucoma clinical practice guidelines. *Ophthalmology*. 2011; 118:1017–23.

Anexos

Certificado de la estancia en institución extranjera

Aprobación del Comité Ético de Investigación Clínica

Hoja de información y consentimiento informado del paciente

CERTIFICADO DE ESTANCIA EN UNA INSTITUCIÓN EXTRANJERA
CERTIFICATE OF STAY IN A FOREIGN INSTITUTION

1. Becario/ *Applicant:*

Nombre y apellidos/ *Name:* Sara Ortiz Toquero

D.N.I./ *National identity Card:* 71.156.853-M

Centro de aplicación de la beca/ *Home Institución:* Universidad de Valladolid

2. Centro en el que se ha realizado la estancia/ *Host institution:*

Nombre/ *Name:* School of Health Professions (Peninsula Allied Health Centre), Plymouth University.

Dirección/ *Adress:* Derriford Road PL6 8BH, Plymouth.

Localidad/ *Country:* Plymouth, Reino Unido.

3. Investigador responsable en el centro de la estancia/ *Responsable person in the Host*

Institución/ *Institution:* School of Health Professions, Plymouth University.

Nombre/ *Name:* Dr. Phillip Buckhurst

Cargo/ *Post:* Associate Professor in Optometry

CERTIFICO:
que el becario arriba mencionado ha realizado una estancia en este centro en las siguientes fechas:
desde 07 / 01 / 2016 hasta 07 / 04 / 2016

THIS IS TO CERTIFY:
that the above mentioned person has performed a stay in this Institution in the following dates:
From: 07 /01 /2016 *To:* 07 /04 /2016

Lugar y fecha: Plymouth (U.K.), April 7th, 2016
City and date:

Firma y Sello/ *Signature & Stamp*

Dr Phillip Buckhurst

SCHOOL OF HEALTH PROFESSIONS
PLYMOUTH UNIVERSITY
PENINSULA ALLIED HEALTH CENTRE
DERRIFORD ROAD
PLYMOUTH
PL6 8BH

Universidad de Valladolid FACULTAD DE MEDICINA C/ RAMÓN Y CAJAL,7 47005 VALLADOLID.	Reunión De 18 de abril de 2012	COMITÉ ÉTICO DE INVESTIGACIÓN CLÍNICA DE LA UNIVERSIDAD DE VALLADOLID

INFORME DEL COMITÉ ÉTICO DE INVESTIGACIÓN CLÍNICA

Evaluados y Ponderados los Aspectos Éticos y Legales aplicables, según la legislación vigente, en territorio nacional, europeo y de organismos internacionales para la Evaluación de Ensayos Clínicos y Proyectos de Investigación, realizada por el Comité Ética de Investigación Clínicas de la Universidad de Valladolid, contemplada en la directiva Europea 2001/20/EC y cumple plenamente con los Procedimientos Operativos Estándar para Comités de Ética de la Investigación en España. (Real Decreto 223/2004, de 6 de febrero)

DATOS DEL PROTOCOLO EVALUADO:

Valladolid .18./.Abril./2012. Código CEIC: Protocolo 2012/ 25
Versión: 27 de enero de 2012.
Protocolo: M01/12-27/01/2012. trabajo fin de Máster de la alumna Sara Ortiz
Título: Determinar un nomograma para la adaptación de lentes de contacto de geometría diseñada para córneas con queratocono (KAKC, Conóptica, España) a partir de los datos biométricos obtenidos con el queratómetro y/o el topógrafo corneal.
Con los objetivos de: Determinar un nomograma para la adaptación de lentes de contacto de geometría diseñada para córneas con queratocono (KAKC, Conóptica, España) a partir de los datos biométricos obtenidos con el queratómetro y/o el topógrafo corneal.
Para ser realizado en la Universidad de Valladolid. , en el Instituto Universitario de Oftalmobiología Aplicada (IOBA).
Investigador Principal: Dº Raúl Martín Herranz
Investigadores colaboradores: Sara Ortiz, Victoria de Juan y Guadalupe Rodríguez.

Dictamen del CEIC Los miembros del Comité presentes en la reunión celebrada el **18 de febrero de 2012** han evaluado la solicitud referida y emitieron un dictamen favorable. Por lo que se ha resuelto **INFORMAR FAVORABLEMENTE**, la realización del estudio.

Valladolid a 18 de abril de 2012

COMITÉ ÉTICO DE INVESTIGACIÓN CLÍNICA
Universidad de Valladolid
Facultad de Medicina
C/. Ramón y Cajal, 7
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Fdo: Dr. José Luís García Roldán
Profesor Titular de Farmacología. Facultad de Medicina. Universidad de Valladolid.
Secretario Técnico del CEIC de la Universidad de Valladolid.

Hoja de información

Estudio : "Cálculo de un nomograma de adaptación de lentes de contacto con geometría especial para queratocono"

El queratocono es una patología progresiva de la córnea que se caracteriza por presentar un adelgazamiento corneal central con un aumento de curvatura. La curvatura excesiva y anormal de la córnea, afecta a la visión por miopía progresiva y astigmatismo, que se va haciendo cada vez más irregular.

En estadíos precoces de queratocono, se puede corregir el defecto refractivo (miopía y astigmatismo) con gafas y lentes de contacto blandas. Sin embargo, cuando progresa suele provocar distorsión en la visión incluso corregida con gafas por lo que es necesario el uso de lentes de contacto permeables al gas para mejorar la visión (agudeza visual).

El objetivo del presente estudio es calcular un nomograma de adaptación, esto es una regla de cálculo de los parámetros (medidas) de las lentes de contacto que facilite la adaptación reduzca el número de pruebas y de visitas al adaptador.

Para cumplir el objetivo del estudio, se le realizará a Ud. una **adaptación completamente gratuita de lentes de contacto** semirrígidas con geometría especial para queratocono, llevando a cabo las pruebas necesarias para completar la adaptación.

Las posibles complicaciones de este estudio son las mismas que se derivan del uso de lentes de contacto como queratitis, conjuntivitis, úlceras y más grave y excepcionalmente el caso de infección corneal, si bien es muy improbable que estas puedan aparecer en grado significativo. Pero, en el caso hipotético de que Ud. presentara alguna complicación ésta será tratada en el IOBA según los protocolos clínicos adecuados.

Si quiere consultarnos alguna duda o pregunta no dude en consultar con cualquier miembro del equipo.

Muchas gracias por su colaboración.

Dr. Raúl Martín Herranz

Consentimiento informado para el estudio *"Cálculo de un nomograma de adaptación de lentes de contacto con geometría especial para queratocono".*

D/Dña _____ con DNI _____ y _____ años de edad residente en _____ provincia de _____ manifiesto que he sido informado/a por _____ sobre los siguientes aspectos en cuanto a mi participación en el estudio arriba mencionado.

1. He leído la hoja de información que se me ha entregado.
2. Mi participación en este estudio es de forma voluntaria.
3. Acepto que se me realicen las exploraciones oftalmológicas y optométricas necesarias para el desarrollo del estudio (adaptación de lentes de contacto).
4. Conozco y asumo los efectos secundarios que se puedan derivar de este estudio y que me han explicado los investigadores.
5. He podido hacer preguntas sobre el estudio y he recibido suficiente información sobre el estudio.
6. He hablado con el equipo investigador abajo firmante.

Por lo que declaro que todas mis dudas y preguntas han sido aclaradas, que he comprendido que mi participación es voluntaria y que comprendo que puedo retirarme del estudio cuando quiera, sin tener que dar explicaciones y sin que esto repercuta en mis cuidados médicos. Por ello doy mi consentimiento para participar en el estudio.

En Valladolid, a _____ de _____ de 201_

Firma del sujeto Firma del Testigo Firma del Investigador

Estoy de acuerdo en que mis datos personales relativos a este trabajo sean almacenados, procesados electrónicamente y transmitidos, con propósitos de análisis de los datos derivados de este estudio. Doy mi consentimiento para que el personal autorizado del IOBA o las autoridades sanitarias revisen que el estudio se está llevando a cabo de manera correcta e inspeccionen mi historial referente a mi colaboración en el mismo.

Así mismo autorizo a mi investigador a que revele la información necesaria recogida en el estudio para que pueda ser procesada, sin que se revele mi identidad.

Fecha