Universidad de Oviedo

Universidá d'Uviéu

University of Oviedo

Programa de Doctorado de Investigación en Cirugía y Especialidades Médico-Quirúrgicas (RD 1393/2007)

El Efecto del Espesor Corneal en la Cirugía Foto-Refractiva

Trabajo de investigación realizado por

D. Jorge Eugenio Valdez García

para optar por el grado de Doctor.

Directores: Dr. Jesús Merayo Lloves

Tutor:

Oviedo, Febrero de 2017

Universidad de Oviedo
Universidá d'Uviéu
University of Oviedo

Programa de Doctorado de Investigación en Cirugía y Especialidades Médico-Quirúrgicas (RD 1393/2007)

El Efecto del Espesor Corneal en la Cirugía Foto-Refractiva

Trabajo de investigación realizado por

D. Jorge Eugenio Valdez García

para optar por el grado de Doctor.

Directores: Dr. Jesús Merayo Lloves

Tutor:

Oviedo, Febrero de 2017

RESUMEN DEL CONTENIDO DE TESIS DOCTORAL

1.- Título de la Tesis	
Español/Otro Idioma: **El Efecto del Espesor Corneal en la Cirugía Foto-refractiva**	Inglés: The Influence of Corneal Thickness in Photorefractive surgery

2.- Autor	
Nombre: Jorge Eugenio Valdez García	DNI/Pasaporte/NIE:
Programa de Doctorado: **Programa de Doctorado de Investigación en Cirugía y Especialidades Médico-Quirúrgicas (RD 1393/2007)**	
Órgano responsable: Universidad de Oviedo	

RESUMEN (en español)

El Efecto del Espesor Corneal en la Cirugía Foto-refractiva

Muchos factores determinan el espesor corneal y nuestro entendimiento del mismo no es suficiente. Esto es de gran interés teniendo en cuenta la relevancia de este parámetro oftalmológico en el manejo de varias condiciones clínicas como: la cirugía refractiva ola hipertensión ocular. Corneas delgadas se consideran débiles y no adecuadas para procedimientos quirúrgicos aunque varios estudios sugieren una ausencia de correlación entre el espesor y el posterior desarrollo de ectasia. Mecanismos moleculares subyacentes que influyen la biomecánica estromal, incluyendo estabilidad y resistencia, incluyen la disposición de las fibras de colágena el sulfato de queratan y los proteoglicanos. Estudios poblacionales genéticos demuestran el efecto de genes específicos (*COL5A1*, *FOXO1*, *AVGR8*, and *ZNF469*) y algunos otros genes SNPs sobe el espesor central. Factores adicionales como la radiación UV, edad, humedad, altitud y ciertas patologías afectan el espesor corneal central. El análisis de cada factor potencial que modifica el espesor corneal central nos arroja mas entendimiento sobre los mecanismos responsables de la biomecánica corneal en situaciones como la cirugía refractiva. Con el propósito de analizar estos factores en situaciones clinicas decidimos, `primero` describir la distribución de las mediciones del grosor central corneal (GCC) en una población sana de hispanos y analizar su correlación con la edad, queratometría simulada promedio (SimK) y el equivalente esférico refractivo (EE). Para lo cual realizamos un análisis retrospectivo, pacientes sanos del Instituto de Oftalmología y Ciencias Visuales, Tecnológico de Monterrey (enero de 2015 a agosto de 2015). Se obtuvo GCC, edad, género, SimK y EE. Se realizó análisis descriptivo de las variables y se utilizó el método de Spearman para correlaciones. La muestra se dividió en 3 subgrupos (<20 años, ≥20 y ≤40, y > 40 años) para analizar la correlación entre GCC y edad.
Resultados: Se incluyeron un total de 93 pacientes (186 ojos). Edad promedio: 32.54 ±

Vicerrectorado de Organización
Académica

Universidad de Oviedo

ASTURIAS
CAMPUS DE EXCELENCIA
INTERNACIONAL
| AD FUTURUM |

12.04 años, 43% mujeres. GCC promedio: 545.69 ± 36.88 _m, SimK promedio: 43.56 ± 1.90 D y el EE promedio: -2.54 ± 3.15 D. No había correlación entre GCC y edad, género, SimK o EE con análisis Anderson-Darling (p = 0.006), Shapiro-Wilk (p = 0.043) y Kolmogorov-Smirnov (p = 0.01). GCC mostró distribución bimodal, pico principal en 540 _m. Los subgrupos <20 años y >40 años, mostraron diferencia significativa (p = 0.016) al comparar GCC. Se observó correlación positiva entre grupo <20 años y GCC (_ = 0.596, p = 0.001). Con los resultados anteriores en **segundo término** nos propusimos, evaluar el resultado y la seguridad del LASIK miópico realizado en pacientes con corneas centrales por debajo del promedio (<540µm) en el estudio anterior) y que tuviesen una topografía normal. Para lo cual se estudio una cohorte de pacientes que fueron sometidos a LASIK miópico entre enero 2014 y enero de 2015. Se analizo la información de pacientes mayores de 18 años con topografía normal, refracción estable, agudeza visual corregida de 20/20 (Snellen), espesor corneal central menor a 540 µm, con un seguimiento de al menos 12 meses posterior a cirugía. *Las variables de seguimiento :* Agudeza visual resultante estabilidad refractiva, análisis de tejido alterado. En este segundo estudio se incluyeron *un* total de 51 pacientes (102 ojos) , 56% (n=57) fueron mujeres. Edad promedio: 26.52 ± 8.06 (rango 18-55 años), seguimiento promedio: 13.9 ± 1.2 meses. Espesor corneal central preoperatorio de: 515.44 ± 17.87µm (rango 452-540µm), equivalente esférico promedio (SEQ): -4.08 ± 2.17 D (rango -0.75 to -9.75 D), cilindro refractivo promedio: -1.44 ± 1.29 D (rango 0.00 to -6.00 D). Predictividad promedio de esfera SEQ: -0.20 ± 0.40 D (rango -1.25 to +1.25). Equivalente esférico postopertorio: ±0.50 D en 71% y ±1.00 D en 93% de los ojos . Agudeza visual lejana postopertoria: ≥20/20 en 78% y ≥20/25 en 95%. Una linea de mejor agudeza visual corregida se perdio en 3% de los ojos, ningún ojo perdió ≥2 líneas de visión. No se observe ningún caso de ectasia durante el seguimiento. En primero lugar concluimos son muchos los factores que afecta el Grosor Corneal Central. En segundo termino, evidenciamos que la falta de normalidad en la distribución del GCC, la distribución bimodal (540 _m) y la tendencia a observar mayor GCC en jóvenes, llevan a redefinir los valores «normales» de GCC en nuestra población, esto con la finalidad de ajustar su uso para propósitos clínicos. Y por ultimo que la círugía de LASIK en pacientes con corneas consideradas mas delgadas de lo "normal" (<540 µm) es segura, eficiente y predecible a un año de seguimiento en tratamientos refractivos miópicos y sin evidencia de casos de ectasia en el mismo periodo de seguimiento. Pudiendo afirmar que el espesor corneal por si mismo no es un parámetro de riesgo.

RESUMEN (en Inglés)

The Influence of Corneal Thickness in Photorefractive surgery
Many factors determine the corneal thickness and our understanding of them is not sufficient. This is of main interest given the significance of this ophthalmological

parameter in the management of several clinical conditions like: refractive surgery and high intraocular pressure (IOP). Thin corneas are considered weak and not suitable for surgical procedures, though several studies demonstrate no correlation between thin CCT and development of post-surgical ectasia. Subjacent molecular mechanisms that influence stromal biomechanics, including strength and stability, comprise the role of collagen fibers disposition, keratan sulfate, and proteoglycans. Genetic population studies demonstrate the effect of four specific genes (*COL5A1*, *FOXO1*, *AVGR8*, and *ZNF469*) and several other gene SNPs over CCT. Additionally, factors such as UV radiation, age, humidity, altitude, and certain diseases affect CCT. The analysis of each potential factor that modifies CCT bring us closer to understanding the underlying mechanisms responsible for corneal biomechanics. This will provide a global vision of the way cornea behaves and the effect of surgical treatments or diseases. With the porpuse to describe the distribution of the central corneal thickness (CCT) measurements on a healthy Hispanic sample population and its correlation with age, mean simulated keratometry (SimK), and mean refractive spherical equivalent (MRSE). We realize a retrospective analysis on the records of healthy patients from the Ophthalmology and Visual Sciences Institute, Tecnológico de Monterrey, January 2015 to August 2015. CCT data, age, gender, corneal curvature, and spherical equivalent was obtained. A descriptive analysis and correlation by the Spearman method was performed. The sample was divided by age subgroups: <20 years old, ≥20 and ≤40 years, and >than 40 years old and correlation analysis with CCT values was determined. A total of 93 (186 eyes) patients were included. Mean age: 32.54 ± 12.04 years. 43% were women. Mean CCT: 545.69 ± 36.88 _m, mean SimK: 43.56 ± 1.90 D and MRSE: −2.54 ± 3.15 D. No correlation was registered between CCT and the variables when analyzed with the Anderson---Darling (p = 0.006), Shapiro---Wilk (p = 0.043), and Kolmogorov---Smirnov (p = 0.01). CCT showed a bimodal distribution with higher density at 540 _m. Age groups <20 and >40 years showed significant difference in CCT (p = 0.016), a positive correlation with CCT was observed in the group <20 (= 0.596, p = 0.001). With this evidence, we decided to assess the visual outcomes and safety of myopic LASIK performed in patients with corneas with *central* thickness below average <540μm and normal topography. We realized a retrospective cohort study. A group of Hispanic patients who underwent myopic LASIK between January 2014 and January 2015were enrolled. Analysis of records, patients >18 years-old with previous normal topography, stable refraction, corrected visual acuity ≥ 20/20 (Snellen), central corneal thickness (CCT) < 540μm and at least 12 months follow up after surgery.

Main outcome measures: Standard visual outcomes (efficacy, safety, refractive stability), percent tissue altered analysis. A total of 51 patients (102 eyes) were included, 56% (n=57) were female. Mean age: 26.52 ± 8.06 (range 18-55 years), mean follow up: 13.9 ± 1.2 months. Preoperative CCT: 515.44 ± 17.87μm (range 452-540μm), mean refractive spherical equivalent (SEQ): -4.08 ± 2.17 D (range -0.75 to -9.75 D), mean refractive cylinder: -1.44 ± 1.29 D (range 0.00 to -6.00 D). Mean predictability of postoperative SEQ: -0.20 ± 0.40 D (range -1.25 to +1.25). Postoperative SEQ: ±0.50 D in 71%, ±1.00 D in 93% of the eyes. Postoperative uncorrected distance visual acuity:

≥20/20 in 78% and ≥20/25 in 95%. One line of CDVA was lost in 3% of the eyes, no eyes lost ≥2 lines. No ectasia cases were observed during follow-up.

We may conclude that are many factors that have an effect over the central corneal thickness. Our findings regarding the lack of normality, the bimodal distribution (540 _m), and the correlation between age and CCT in younger patients, may lead us to redefine the ''normal'' CCT value in our population to be used properly for clinical purposes. Using the previous evidence we conclude that LASIK surgery in patients with thinner than "normal" corneas (<540 µm) is safe, efficient and predictable at 1 year follow up for myopic refractive corrections with no evidence of postoperative keratectasia. We can say that the corneal thickness as a "stand alone" parameter it´s not a risk factor.

SR. PRESIDENTE DE LA COMISIÓN ACADÉMICA DEL PROGRAMA DE DOCTORADO EN _____

A María Luisa, compañera de viaje.

A Jorge Aurelio, Andrés Miguel y Luis Mario motivos del viaje.

Agradecimientos

A mi director, Jesús Merayo LLoves, por plantearme el reto de realizar un doctorado que formalizara la labor de investigación que como docente y clínico venia efectuando. Su energía se contagia y lo motiva a uno.

A mi grupo de coinvestigadores, liderado por la Dra. Judith Zavala, Julio C. Hernández Camarena, Alejandro Tamez, José Nava, Denise Loya García, Paloma López, Eduardo Camacho con quienes en los últimos años he podido compartir ideas, pensamientos y reflexiones e ideas. Juntos hemos construido un grupo de lo más interesante y divertido.

A los compañeros del Instituto de Oftalmología y Ciencias Visuales, especialmente al Dr. Juan Homar Páez por su liderazgo transformador y su motivación a ser mejores, también a la Srta. Idalia Diaz por toda la cooperación que han mostrado para hacer compatible todas mis actividades y poder dedicar tiempo a esta empresa doctoral.

Y a todo el Personal de la Escuela de Medicina y Ciencias de la Salud del Tecnológico de Monterrey, en particular Isabel García, Mireya Guajardo, Javier Hernández y Adrián Flores, que en todo momento colaboraron de alguna manera ya sea en la obtención de los datos que fueron incluidos o generando espacios de tiempo para poder llevar a cabo esta empresa.

Al Dr. Guillermo Torre Rector de TecSalud que con su ejemplo y pasión por la investigación médica se convierte en una gran motivación y una aspiración a imitar.

Docmentos oficiales de la tesis

ÍNDICE

14. Anexos

14.1.   Publicación. Correlation of age, corneal curvature and spherical equivalent

with central corneal thickness.

14.2. Publicación. 3-Year follow-up after Lasik: assessing the risc factors for

retreatment.

14.3. Publicación.   Prevalence of keratoconus in a adolescent pouplation.

14.4. Publicación. Factors influencing Central Corneal Thickness.

14.5. Publicación. Safety and Efficacy of Myopic Lasik perfomed on thin Corneas

1. Motivación, Pregunta de investigación y estructura de la tesis.

1.1. Enunciado

La presente tesis doctoral se plantea como consecuencia de una pregunta inicial de investigación. ¿Cuál es el Efecto del Espesor Corneal en la Cirugía Foto-refractiva?

1.2. Motivación

La Queratomileusis in Situ asistida por Laser (Laser *in situ* keratomileusis) LASIK ha sido el tratamiento de elección para la corrección de errores refractivos desde su aparición en 1990 [1,2]. Produciendo resultados visuales inmediatos con una gran eficacia, predictibilidad, estabilidad y seguridad. Por lo tanto, no resulta raro porque el LASIK es el procedimiento electivo más popular, comas de 28 millones de procedimientos realizados a nivel mundial [3,4]. Pero como ocurre con otros procedimientos a mayor numero realizado mayor prevalencia de complicaciones.

Aunque han aparecido métodos efectivos de tratar la mayoría de las complicaciones relativas al LASIK, [5,6] ya sea con medicamentos o correcciones quirúrgicas la ectasia posterior al mimo es una de las más temidas complicaciones e involucra una amplia gama de propuestas de solución que van desde el implante de segmentos intraestromales [7], el crosslinking [8] hasta la queratoplastia [9].

Se han identificado factores específicos para el desarrollo de ectasia corneal post-LASIK tales como: ablación profunda, lecho estromal residual menor a 300μm, topografía corneal anormal y un grosor/espesor corneal menor de 500μm [10–12]. Randleman et al. También consideran factores como la edad y el defecto refractivo a tratar en un sistema que han denominado *Ectasia Risk Score System* (ERSS) con el objetivo de valorar el riesgo preoperatorio de desarrollo de ectasia post-LASIK. [13]. En fechas recientes, el papel del porcentaje de tejido ablacionado (PTA) ha sido declarado por Santhiago et al. como un indicador muy robusto del desarrollo de ectasia en ojo con topografías normales. [14].

Ya sea directa o indirectamente, las corneas delgadas han sido consideradas anormales y por lo tanto como que representan un factor de riesgo mayor de desarrollo de ectasia corneal después de una cirugía fotorefractiva [13,14]. Sin embargo, evidencia reciente parece indicar que las corneas delgadas (<500μm) no solo no son un factor de riesgo, sino que pueden tener un resultado posterior a cirugía fotorefractiva similar a las corneas de un espesor mayo a 500μm [15,16].

1.3 Estructura de la Tesis.

En esta tesis hemos querido hacer una aproximación a este planteamiento dividiéndola en tres secciones, que se corresponden a la secuencia de las etapas en que se desarrolla la misma:

I.   Un estudio de los factores que determinan el espesor corneal a través de una

revisión de la literatura científica actual.

II. Determinar los parámetros de normalidad en nuestra población estableciendo un estudio de correlación del espesor corneal con la edad, la curvatura corneal y el defecto refractivo.

III. El comportamiento posterior a cirugía fotorefractiva (Queratomileusis In situ asistida por Laser) de corneas con un espesor corneal central por debajo del promedio establecido en esta misma tesis para nuestra población.

2. Introducción y Resumen

La introducción formal de la tesis se aborda en la sección I, hasta el punto 7.9. El espesor corneal es un parámetro de gran relevancia en oftalmología. Es utilizado en múltiples situaciones clínicas que van desde el glaucoma hasta la cirugía refractiva. Es en esta última en donde hemos centrado el foco de esta tesis. El espesor corneal se viene utilizando como un parámetro que define a la normalidad de la córnea. Sin embargo, nuestro entendimiento de que los factores que intervienen en su conformación son poco comprendidos y estudiados. Lo anterior ha provocado que un grupo de pacientes que buscan una solución definitiva a su problema refractivo sean excluidos de la cirugía fotorefractiva solo por el hecho de tener una cornea "delgada" al tener una pauimetria menor a un valor arbitrariamente definido.

Para abordar esta situación clínica, presente Tesis se ha conformado conformado en tres momentos de investigación que han dado lugar a las tres secciones en que estan divididos nuestros hallazgos y que se corresponden a las tres secciones de la misma.

En la primera sección se ha hecho una amplia revisión de la bibliografía científica existente sobre el tema del espesor corneal, sus determinantes genéticos, los factores posiblemente responsables de su expresión. También hemos revisado otros factores diversos. De ahí se ha extraído una de las conclusiones y es la que para definir una cornea como normal de acuerdo a su paquimetría (medición del espesor corneal) se ha de realizar en el contexto de una población definida. Esto da lugar al segundo estudio que conforma la sección dos

de la presente tesis, el cual se ha propuesto definir el parámetro de normalidad en nuestra población de estudio y su asociación con diversos factores como la edad, la curvatura corneal y el equivalente esférico. Con los resultados del mismo se ha podido concluir que los valores comúnmente utilizados para calificar una cornea como normal o anormal no necesariamente se aplican a nuestra población. Lo anterior entonces permitió permitió plantear el tercer estudio, que se corresponde a la tercera sección de la tesis, en el que se evalua el comportamiento de pacientes que fueron sometidos a una cirugía foto refractiva, pero que tenían como condicionante tener una cornea por debajo del promedio, de acuerdo a lo definido como valores normales en el segundo estudio.

La presente tesis debe ser vista como una unidad que integra en primer lugar el conocimiento del area en la actualidad. En segundo termino estaleciendo valores de normalidad para el factor a investigar, el espesor corneal. Para concluir con el efecto del mismo sobre la situación clinica a estudiar, la cirgía fotorefractiva.

3. Justificación

Hoy en dia, uno de los procedimietos quirurgicos mas frecuentes en oftalmología es a la cirugía fotorefractiva. Su aceptación y adopción es practicamente universal, lo anterior motivado por los convenietes resultados y las ventajas desde muchos puntos de vista que representa para el paciente. Sin embargo, existe un grupo de pacientes que a los que les hes negada esta opción terapeutica debido a la "anormalidad" de ciertos parametros corneales. El mas frecuente es la alteración en la paquimentria central de la cornea, que evalua el espesor de la misma.

Hasta nuestro conocimiento, no existe la suficiente información que establezca a ciencia cierta todos los factores que influyen en la determinción del espesor corneal. Tampoco pudimos encontrar un documento que de manera sistematica defina los posibles factores que intervienen, definidos hasta el momento. De ahí que consideramos que era de suma importancia aporar en este campo haciendo una revisón de toda la bibliografia existente hasta el momento y ordenandola de manera sistematica.

En segundo termino y teniendo en cuenta lo expresado antriormente, nos percatamos que en nuestra población no existia información suficiente sobre los parametros de normalidad en lo referente al espesor corneal y la relación o efecto de algunos otros factores sobre el mismo. Consideramos que era de vital importancia el poder realizar un estudio que definiera esto para nuestra población y que no se asumieran valores de otras poblaciones con una conformación etnica diferente.

Por lo anterior, también es entendible que exista poca evidencia sobre el comportamiento de cornea considerdas como "anormales" o limitrofes al ser sometidas a cirugía fotorefractiva, de ahí que consideramos que era imprtante el realizar un estudio que permitiera ver el comprtamiento de   este tipo de pacientes,   y que pudiera redefinir los   limites   de la cirugía fotorefractiva.

4. Hipotesis

Es posible estudiar el espesor corneal y los factores que en el influyen en una población determinada con la finalidad de asociarlo a la posibilidad de realizar cirugía refractiva corneal.

5. Objetivos

1. Definir los factores que influyen el espesor corneal.

2. Establecer los valores normales del espesor corneal en una población determinada y su correlación con la edad, la curvatura central y el equivalente esferico.

3. Establecer parametros de seguridad y eficacia de la queratomileusis in situ asistida por láser miopica (LASIK) en corneas delgadas.

6. Pacientes, Material y Método

Este apartado se describe con detalle en las secciones I, II y III. A continuación, se muestra un resumen de cada sección.

Metodo Seccion I. La revisión bibliografía se hizo a través de las bases de datos MEDLINE y PubMed utilizando los recursos de la Biblioteca Digital del Tecnológico de Monterrey, empleando las siguientes palabras clave en ingles: *corneal thickness, central corneal thickness* y *central corneal thickness* en combinación con: *genetics, genes, modifiers, factors influencing, normal values, and epidemiology.* La busqueda también incluyo articulos en otros idiomas. Se seleccionaron 145 publicados diez años previos a la fecha. Algunos publicados previamente fueron incluidos por su valor historico.

Método sección II: Análisis retrospectivo depacientes sanos del Instituto de Oftalmología y Ciencias Visuales, Tecnológico de Monterrey (enero de 2015 a agosto de 2015). Se obtuvo GCC, edad, género, SimK y EE. Se realizó análisis descriptivo de las variables y se utilizó el método deSpearman para correlaciones. La muestra se dividió en 3 subgrupos (<20 años, $\geq$20 y $\leq$40, y > 40 años) para analizar la correlación entre GCC y edad.

Metodo sección III: Estudio de cohorte retrsopectivo de pacientes del Instituto de Oftalmología y Ciencias Visuales, Tecnológico de Monterrey que fieron sometidos a LASIK miopico entre enero del 2014 y enero del 2015. Se analizaron los expedientes de pacientes mayores de 18 años con topografía normal, refracción estable, agudezavisual mayor de 20/20 (Snellen), espesor corneal central menor a 540 μ m y un segumiento de

al menos 12 meses postoperatorios. Se evaluaron las medidas estándares visuales (eficacia, seguridad y estabilidad refractiva) asi como el porcentaje de tejido corneal alterado.

7. Sección I.

Factors Influencing Central Corneal Thickness

7.1.   Centra Corneal Thickness

Central corneal thickness (CCT) is a parameter of high clinical relevance in ophthalmology. The measurement of corneal thickness, also called pachymetry, is not done just because it is something available at hand, but because of the relevance it can have in several fields of study. CCT can be used as an indirect method to evaluate functional status of the endothelial cell layer,(1) and it has been identified as an independent risk factor for developing glaucoma.(2) It also plays an important role in the management of ocular hypertension, since its measurement with some methods such as applanation tonometry can be altered by differences in CCT.(3) Corneal thickness is also of great relevance in the preoperative management of candidate patients for refractive surgery in order to determine which procedure is most suitable for each patient.(4,5) Conditions such as keratoconus and some corneal dystrophies have also been associated with decreased CCT.(6,7) Given the numerous areas in which corneal thickness plays a relevant role, there has been research done about each of these topics in particular. However, there is a gap in the literature when addressing the subject of corneal thickness, the majority of the articles published address very particular populations or specific problems in which corneal thickness play a part, but there is a lack of articles that give a general view of what is central corneal thickness, all the factors that can affect it and its clinical implications. The purpose of the present review is to fill in this gap by approaching the subject of CCT from a stand point that covers all aspects related to central corneal thickness form the anatomical and physiological basis behind it, to the field of

biomechanics and corneal topography, it's so called "normal" values, the genetic implications behind it and the factors influencing it. **Figure 1** illustrates some of the factors influencing CCT and the way they relate to thickness, these will be further analyzed throughout the article.

Figure 1. Factors influencing CCT

7.2   Cornea: physiology, structure, function

The cornea represents the most anterior part of the human eye. It is a highly specialized transparent tissue situated in front of the iris and the pupil, and inserts into the sclera at the limbus. In the adult, the average horizontal diameter is 11.3–12.1mm(8) and it is approximately 0.8 mm greater than the mean vertical diameter.(9) The cornea is flatter in the periphery and steeper centrally, giving it a shape that makes an aspheric optical system. The cornea is an avascular and

highly ordered tissue. Physiologically, the periphery depends more on the blood supply from the vessels that provide oxygen and some nutrients, while the central cornea depends mostly on surrounding fluids, aqueous humor and tear film.(10)

There are five layers distinguished in the cornea, from external to internal: the corneal epithelium, Bowman's membrane, the stroma, Descemet's membrane, and the endothelium. The epithelium acts as a barrier of the cornea; it has five or six layers of cells of non-keratinized, non-secretory, stratified squamous epithelium, which give it a thickness of 58μm. The epithelium is covered with a tear film of 5 μm.(11) Together, the tear-air border and the underlying cornea are responsible of two-thirds of the total refractive power of the eye. The corneal epithelium is constantly being regenerated and repaired, complete renewal of corneal epithelial cells is estimated to occur every 7–10 days.(12) The Bowman's membrane is one of the two acellular layers of the cornea. It is a modified portion of the stroma with a tightly intertwined meshwork of collagen fibrils that separates the epithelium from the stroma.(13) Underneath the Bowman's membrane is the corneal stroma, which accounts for about 90% of the corneal thickness (460-500 μm).(14,15) It is composed by extracellular matrix, keratocytes, and proteins.(16) It is responsible of corneal transparency and along with proteins as proteoglycans provide the strength and hydration needed for proper sight function.(17,18) The Descemet's membrane is a discrete layer composed of a fine strips mostly of type IV collagen, laminin, and fibronectin secreted by the corneal endothelium.(19) It is known to have regenerative potential,(20) but its function is not entirely known. The endothelium is the posterior corneal monolayer of hexagonal cells that functions as a system through which nutrients pass in and waste is removed trough simple and facilitated diffusion and active transport. Its main function is to regulate corneal hydration through active ATP bicarbonate-dependent pump, which allows the eye to perform its visual function.(21,22)

The existence of a sixth corneal layer has been proposed in recent years. This new corneal layer

was discovered thanks to the big bubble technique of deep anterior lamellar keratoplasty (DALK), and is called Dua's layer. It has been defined as an acellular, strong layer in the pre-Descemet's cornea of 10.15 ± 3.6 microns composed of 5 to 8 lamellae of predominantly type-1 collagen bundles arranged in transverse, longitudinal, and oblique directions.(23) The discovery of this layer has raised controversy, with some surgeons stating this discovery brings further insight on the field of DALK surgery,(24) while others question the existence of the Dua's layer stating it is stroma and not a new corneal layer.(25) Further research on this subject is needed in order to reach a consensus on the existence of this corneal layer.

As stated above, the stroma is the corneal layer that accounts for most of the corneal thickness. Its extracellular matrix is composed mainly of collagen fibrils. Corneal collagen is synthesized by keratocytes in the form of procollagen with two additional peptides, one at each end. Procollagen proteinases located in the extracellular space remove the extension peptides from the precursor molecule and transform it to collagen. The enzyme lysyl oxidase deaminates the lysine or hydroxylisine of the end chains, allowing collagen to form cross-links between fibrils, which then convert during maturation to trivalent cross-links.(26–29) Corneal fibrils are composed mostly of type I collagen that co-assemble into a complex with heterotypic fibrils of type V collagen. The ratio of type V to type I collagen seems to regulate the fibril diameter and the thickness of the corneal stroma.(30,31) Type V collagen co-aggregates with type I collagen and the protruding NH_2 terminal domains of this aggregate cause steric hindrance to prevent accretion of more molecules onto the fibril surface. This limits the diameter of the fibrils in the cornea, from 31 to 34 nm.(32) Corneal collagen fibrils are packed in parallel bundles extending from limbus to limbus.(30) These bundles arrange in layers known as lamellae, which assemble in the middle and posterior regions of the stroma at approximate right angles, and those in the anterior stroma at less than right angles. The small diameter of the collagen fibrils and their close, regular packing are responsible

for the ability of the cornea to scatter 98% of incoming light. The lamellar organization of the stroma also allows the cornea to maintain intraocular pressure and the appropriate curvature.(30) The difference in the organization of the collagen bundles in the anterior stroma may contribute to a tighter cohesive strength in this area, and may explain why anterior curvature resists change to stromal hydration more than posterior stroma.(1) Another mechanism of cross-linking that influences the strength of the stromal tissue is nonenzymatic glycation, in which prolonged exposure to monosaccharides results in bonding between the reducing sugar and the amino group of a protein.(26,28,33,34)

Keratan sulfate proteoglycans are the predominant proteoglycans within the corneal stroma. Lumican and keratocan are the core proteins of keratan sulfate proteoglycans, lumican being a regulatory protein for keratocan expression. These molecules are regulators of collagen matrix organization an assembly in the corneal stroma.(35) Lumican, keratocan and mimecam are believed to play a significant role in corneal transparency due to their specific collagen binding sites.(36) Proteoglycans bind to the exterior surfaces of collagen fibrils, and their glycosaminoglycan side chains attract cations and water molecules, which may cause swelling pressure on collagen fibrils that is balanced by interactions between collagen types I and XII.(30) Keratocytes are the principal cell type of the stroma. They produce the collagen and ground substance and are arranged parallel to the corneal surface and located between the collagen lamellae. There have been differences identified between the anterior and posterior stromal keratocytes, such as fenestrations that indicate heterogeneous functions including facilitating of diffusion and mechanical attachment of collagen fibers. The organization of keratocytes forming closed sheets of communication create equal chances for all light rays to pass and minimize variation in light scattering over the entire cornea (37).

As mentioned, part of the corneal endothelium function is to regulate corneal hydration and as a

direct consequence of this, corneal transparency (21). This pump function of the corneal endothelium is mainly in charge of the transport protein Na^+/K^+- ATPase. A healthy cornea has a density of 4.4 trillion ATPase sites/mm^2, and the cornea has compensatory mechanisms to prevent corneal edema such as increasing the activity or density of the pump sites. Its function can even be clinically assessed by measuring changes in corneal thickness (pachymetry). The point at which the compensatory mechanisms of the corneal endothelium fail, and corneal edema results, is when the central endothelial cell density reaches around 700-400 cells/mm2 (38,39).

The cornea is one of the most innervated and sensitive tissues of the human body.(40–42) Epithelial nerve density of the cornea is 300-600 times that of the skin, with corneal sensitivity being most acute in the central cornea and along the horizontal meridian and least sensitive in the vertical meridian.(43,44) Most of the corneal nerves are sensory in origin and are derived from the nasociliary branch of the ophthalmic division of the trigeminal nerve.(40,42). Corneal nerves respond to mechanical, thermal, and chemical stimulation of the cornea, hence protecting the cornea form external threats and stimuli by initiating nerve reflex mechanisms.(37,41). In addition to their sensitive function, corneal nerves have a role in the maintaining of the functional integrity of the ocular surface by releasing trophic substances, such as neuropeptides and growth factors, that promote epithelial homeostasis and by activating brainstem circuits that stimulate tear production and blinking.(41,43) Central corneal nerves do not have a myelin sheath in order to maintain corneal transparency. Also, thick stromal nerve trunks move radially from the periphery towards the center below the anterior third of the stroma in order to preserve the organization of the collagen lamellae (42).

7.3   Corneal Topography

The cornea has a complex geometric structure. There are basic anatomic components of the cornea: thickness, radius of curvature and surface irregularity (45). The measurement and quantification of these components are essential to know the physiologic functions, the diagnosis of corneal diseases and as a screening tool for corrective surgery. Some technologies like corneal tomography, very high frequency ultrasound (VHF), slit scanning, and high-speed anterior segment optical coherence tomography (OCT) are used to measure these components. The ultrasound pachymetry, used to measure the thickness of the cornea, has been considered the gold standard for years (46).

Typically, the shape of the cornea is not spherical; instead, it is considered to have a toroidal shape. Topographically, the anterior cornea is divided in three zones: the apical, peripheral, and limbal zone (45). The apical zone is also named as the central region of the cornea with a constant radius of curvature, which shows a gradual flattening resulting in an aspheric surface called peripheral zone, and the limbal zone is defined as the junction of the cornea with the sclera.

The cornea is characterized by its complex nonlinear anisotropic elastic and viscoelastic properties(47) and the maintenance of the corneal shape and curvature are governed by the intrinsic biomechanical structure and extrinsic environment in a dynamic equilibrium. The intraocular pressure that exerts a force on the inside face of the cornea is the most important extra-corneal factor; less important factors are the external atmospheric pressure, the lids, extraocular and ciliary muscles during accommodation that induce a change in its curvature during accommodation (48–50). The stroma is responsible for the majority of the cornea's tensile strength and its mechanical properties. It has been established that the most anterior part (120μm) is responsible for the stability and maintenance of its curvature (51). It has also been

discussed if the Bowman's layer has a real function for the maintenance of the corneal curvature, suggesting that it constitutes only a visible indicator of ongoing stromal-epithelial interactions (52).

Corneal topography is the measurement of the corneal shape. There are two different ways of studying topography, one method is called videokeratoscopy and the other is elevation based topography. Videokeratoscopy, also known as Placido-based topography, studies corneal shape by analyzing rings reflected off the corneal surface.(53) Even though this method is better than its precursor keratometry it has some disadvantages.(54) Videokeratoscopy evaluates only about 60% of the total corneal area, which can leave out relevant data of peripheral or para-central pathologies such as keratoconus.(53,55) Another disadvantage of videokeratoscopy is that it doesn't provide information about the posterior corneal surface, which can give information on ectatic disorders before they present on the anterior corneal surface and is key in the development of pachymetric maps, as well as in reconstruction of corneal surface.(53,56) The other method used for the study of corneal topography is called elevation-based topography, and it uses a stereo-triangulation technique to make direct measurements of the corneal surface. Elevation-based topography uses optical cross sectioning to triangulate both the anterior and posterior corneal surfaces, which offers important advances over Placido-based devices, such as the ability to produce pachymetric maps, as well as being more accurate in determining morphology as well as identifying keratoconus (57–61). This method of topography allows clinicians to view elevation data compared with a best fit sphere, which gives the most useful qualitative map (53).

7.4 Corneal Biomechanics.

Biomechanics is the development, extension and application of mechanics for the better understanding of the physiology and physiopathology, as well as the diagnosis and treatment of disease and injury. The aim of biomechanical modelling of human tissues is to predict the results or effects of different surgical treatments or therapies. (62) Corneal biomechanics includes the measurement of central pachymetry, but it also englobes other parameters such as viscosity, elasticity, hydration, regional pachymetry and other factors (63). As exposed in the corneal physiology section, pachymetry is given mainly by the corneal stroma and its components. Corneal elasticity, curvature and transparency are related to the way collagen fibrils are arranged. Proteoglycans and its relationship with collagen types I and XII are related with corneal hydration (35) as are endothelial integrity and function (64). Recalling the anatomical structure of the cornea is important since alteration of the components can affect corneal biomechanics, as can be seen with collagen tension disruption in refractive surgery (65,66). **Figure 2** summarizes the factors that influence corneal biomechanics.

To date, there are only 2 devices available for providing corneal biomechanical data in a clinical setting, the Ocular Response Analyzer (ORA) (Reichert Technologies, Buffalo, New York, USA), a dynamic bidirectional applanation device, and the Corvis ST (Oculus Optikgeräte GmbH, Wetzlar, Germany), a dynamic Scheimpflug analyzer device.(62) Both of these devices report a dynamic assessment of corneal biomechanical properties such as corneal hysteresis, which reflects corneal viscosity, and corneal resistance factor, that relates to the elastic properties of the cornea.(67)

Understanding of corneal biomechanical parameters is important because minimal changes in the corneal shape can induce significant variations in the optical properties of the eye. Changes due to refractive surgery or corneal diseases also occur in the mechanical properties of the cornea, not

just the optical properties. It is essential to understand the consequences of modifications in geometry of the cornea to improve the diagnosis and management of ectatic corneal disorders such as keratoconus, and to understand the biomechanics of intraocular pressure after surgical procedures.

Decreases in corneal hysteresis and corneal resistance factor have been reported after refractive surgery. These findings may be related with weakening of the corneal structure induced by laser ablation. Alteration of corneal biomechanics by LASIK flap creation and excimer laser ablation affects the postoperative measurement of intraocular pressure by Goldmann applanation tonometry; however, other devices like the ORA have lower standard deviations in its measurements and provide useful complementary clinical data.(67) It has also been frequently considered that corneas with CCT below 510μm have a greater weakness for excimer laser refractive procedures,(68) however other reports have shown safety and effectiveness in patients with CCT values <500μm.(69).

Factors influencing corneal topography and biomechanics

External factors:
Lids
Extraocular muscles
Atmospheric pressure

Corneal factors:

Corneal stroma:
Collagen fibrils arrangement
Proteoglycans
Endothelial integrity
Corneal hydration

Biomechanics:
Central corneal thickness
Hysteresis: viscosity
Corneal resistance factor: elasticity

Internal factors:
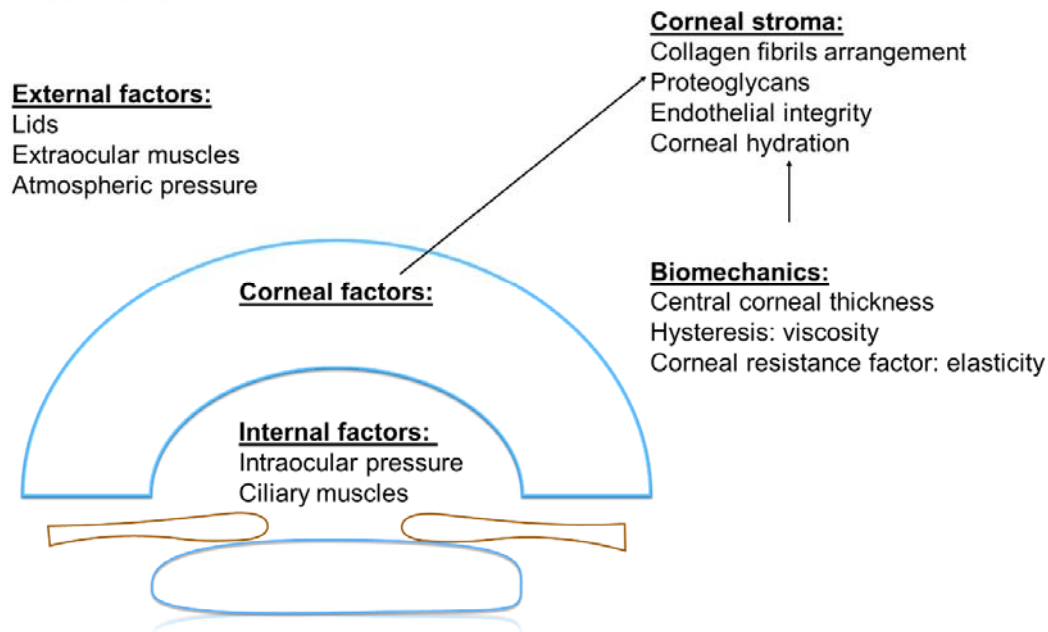Intraocular pressure
Ciliary muscles

Figure 2. Factors influencing corneal topography and biomechanics. Figure presenting the factors that influence corneal topography by dividing them in external factors, internal factors and corneal factors. Corneal factors are directly related to the components of the corneal stroma. Biomechanical properties of the cornea such as central corneal thickness and hysteresis, are in turn also dependent on these components.

The understanding of corneal anatomy and physiology are useful for the understanding of the underlying mechanisms responsible for corneal biomechanics. It is of great importance to further study corneal biomechanics because minimal changes can alter optical properties of the cornea and weaken its structure making the cornea more susceptible to conditions such as ectasia or alter postoperative measurement of parameters such as intraocular pressure. Corneal biomechanics give a global vision of the way the cornea behaves and the effects surgical treatments or diseases have on the cornea; however, this is a field still growing with new findings changing the boundaries of what is known and can be done with safety regarding corneal stability.

7.5 Clinical significance of CCT values

Corneal thickness is a determinant of corneal refractive power, which contributes to normal vision (31) and variations in this parameter have relevance in several ophthalmologic conditions. Certain eye conditions seem to have an association with thinner or thicker corneas. For example, eyes with congenital glaucoma may have thinner corneas, while eyes that have had cataract surgery, Sturge-Weber Syndrome, or aniridia, often have thicker corneas (70). Reduced CCT is also important for the diagnosis and progression of primary open-angle glaucoma (71). Thin corneas are also present in keratoconus, a corneal ectasia with a prevalence of 1:2000 in general population (7) CCT could be abnormal in corneal dystrophies, some genetic diseases like Ehlers-Danlos syndrome, Brittle corneal syndrome (BCS) or Osteogenesis Imperfecta, as well as seen in herpes simplex keratitis.(72) CCT is also important in determining person's suitability for laser refractive surgery, and in the assessment of intraocular pressure (IOP) values in patients undergoing refractive and corneal transplant surgery, as well as in contact lens wearers.(73,74)

Table 1 summarizes some of the main clinical implications of CCT. This section will give a more in depth review of these subjects.

Perhaps one of the most studied implications of CCT is its impact on the assessment of IOP and on the diagnosis and management of glaucoma (3). Applanation tonometry is influenced by CCT. Thicker corneas give an overestimation of IOP readings when measured with applanation tonometry.(75) In a similar sense, thin corneas lead to an underestimation of intraocular pressure.(73) Findings such as these, have made the use of corneal pachymetry in the management of patients at risk for or with glaucoma increasingly recognized as important and necessary.(76) Several correction algorithms have been described, however the consensus is that regardless of the models and correction algorithms studied, adjustments for IOP based on CCT are

critical for clinical management.(2)

The Ocular Hypertension Treatment Study, a multicenter randomized trial designed to evaluate safety and efficacy of topical ocular hypotensive medication in delaying or preventing the onset of primary open-angle glaucoma, showed that a thin CCT measurement was a strong predictor for the development of primary open-angle glaucoma in patients with ocular hypertension.(3) For every 40μm decrease in CCT the relative risk was 1.71, and individuals with CCTs of 555 μm or less were found to have 3times greater risk of developing glaucoma compared with patients with CCTs of greater than 588 μm.(2)

Another aspect in which CCT has various implications is in patients undergoing refractive surgery. One of the options available for refractive surgery is LASIK.   Given the high satisfaction rates of LASIK and its widespread use, patients have high expectations of this procedure; however, there are several risk factors that can lead to complications or retreatment of the patients.(77) Among the complications of this procedure is the development of corneal ectasia, which has been defined as a progressive steepening and thinning of the cornea after excimer laser corneal refractive surgery that reduces uncorrected and even best spectacle-corrected visual acuity.   This complication has been frequently reported in patients with risk factors such as keratoconnus, forme fruste keratoconus and high myopia;(5) however, it has also been described in patients without these risk factors, leading to the development of scores to predict the development of ectasia. One such score is the Ectasia Risk Score System proposed by Randleman et al. which among its parameters considers preoperative corneal thickness and residual stromal bed thickness. (4) Santhiago also described a relationship between the percent tissue altered and the risk of developing ectasia in patients with normal preoperative topographic pattern. The percent tissue altered calculation also takes into account the patient's preoperative central corneal thickness. (78) These data demonstrate that corneal thickness is a relevant parameter in

determining if a patient is a candidate for LASIK surgery or should undergo a different procedure. Patients with thin corneas where stromal residual bed after LASIK would be less than 300 μm and patients with flat or steep corneas, are considered better candidates for photorefractive keratectomy (PRK)(79) However, patients with a final central corneal thickness <400 μm are not considered candidates for PRK of LASIK. These limits are controversial and different corneal thickness cutoffs have been proposed. Frequently, corneas below 510μm are considered as thin and therefore as corneas with biomechanical liability or weakness for excimer laser refractive procedures (LASIK, PRK). However, there is increasing evidence concerning the safety and effectiveness of LASIK surgery in patients with CCT values <500μm, which suggest that there are other factors that affect corneal structural stability independently of CCT. Hence, in order to consider a cornea as "normal", the entire topography (topographic pattern, pachymetry map and elevation maps) along with the expected CCT for a given population, should be taken into account (80).

In line with the topic of refractive surgery, there is a growing concern that the process of removing corneal tissue during this surgery will lead to an increased difficulty in diagnosing glaucoma. Since removing of corneal tissue leads to a thinner corneal thickness, this surgery tends to alter IOP measurements and may in turn require greater emphasis on the assessment of the optic disc and visual fields for the diagnosis and treatment of glaucoma (6).

Corneal thickness is also an important feature of keratoconus, a condition in which the cornea assumes an irregular conical shape secondary to non-inflammatory thinning of the corneal stroma. The thinning of the cornea induces irregular astigmatism, myopia and protrusion, leading to impairment in the quality of vision.(7,81) In fact, one of the treatment options available for this condition is cross-linking, which uses riboflavin and UVA light in order to form new covalent bonds, or cross-links, between collagen fibrils thus strengthening and stabilizing the cornea.(28) The

result of such treatment is an increase in resistance against enzymatic degeneration of the cornea, increase in the diameter of collagen fibrils and improvement in visual acuity.(82)   There have been several studies about the genetics behind keratoconus, and while there is still work to be done to confirm the specific roles of the genes implicated in the disease,   among the genes that have been identified are visual system homeobox1 (*VSX1)* and superoxide dismutase 1   (*SOD1*), collagen crosslinking enzyme lysyl oxidase (*LOX*), *COL5A1, FOXO1,* zinc finger protein 469 *(ZNF469),* among others.(31,83–86)

Reduced CCT has also been associated with some genetic diseases such as congenital glaucoma, osteogenesis imperfecta, Down syndrome, X-linked megalocornea, keratoconus, Marfan syndrome, and Ehlers-Danlos syndrome, whereas increased CCT has been found in patients with congenital aniridia (70).

Taking on account the different conditions presented, it can be seen that CCT has importance in several scenarios, from being a factor influencing in the measurement of clinical parameters, to being a risk factor for certain diseases, or determining if a patient can undergo a certain type of surgery or not. These implications encourage to the establishment of pachymetry as an important element when approaching the ophthalmologic patient. The broad spectrum of implications of this parameter encourages further investigation of the factors involved in its expression and other clinical implications it may have, not just in the corneal and refractive surgery field but in other areas of ophthalmology as well.

7.6   "Normal" CCT values

Once the clinical importance of the CCT has been discussed, the question that comes to mind is: ¿What are the "normal" parameters of corneal thickness?   It is known that CCT values vary between ethnic groups, and that there are several factors either extrinsic or intrinsic that can

influence it (these factors are discussed in another section of the review), however several studies have been made trying to find a value for what can be taken as a normal CCT.

Although there are racial variations, the average adult CCT is 550 μm (87) In a meta-analysis by Doughty and Zaman they reported CCT value in normal eyes with a mean of 536±31 μm (75). It has been questioned if corneal thickness by itself could affect the measurement of IOP and vice versa. This meta-analysis also revealed a significant association between the interrelationship of IOP and CTT; it was found that the difference in IOP was significant in patients in the category with "chronic disease", highly variable in patients with acute onset disease and this difference was smaller for eyes designated as healthy.(75)

Doughty & Zaman established that it is hard to compare the CCT of different races since some conditions (such glaucoma, hypertension and diabetes) and their prevalence are known to cause changes in CCT (75). Currently, there's considerable research dedicated to investigate the mean CCT value of different ethnic groups and populations that indicate strong evidence of ethnic differences in CCT. **Table 2** summarizes most of the populations studies conducted in this regard (80,88–103). There are differences between ethnic groups that have been measured using ultrasound pachymetry showing a wide distribution between the ethnic groups, for example the Turkish population had the lowest CCT (500 ± 347) while the Chinese subjects the thickest (555.96 ±32.41). It is essential to compare information obtained from studies using similar methods in aim to draw meaningful assumptions. It has been recognized that genetic classifications of ancestry could serve as a more accurate estimate of ethnicity groups to detect true biological differences. (104)

Table 1: Population based studies on CCT

Ethnic goup	Country	Number of participants	Mean CCT ± SD (µm)	Mean age ± SD (years)	Glaucome included	Device	Reference
African	USA	107	521.0 ± 3.9		YES	US Pach	57
African	USA	84	529.3		YES	ORA	58
Asian	China	157	555.6 ± 3.4		YES	US Pach	57
Asian	Japan	121	531.7 ± 4.1		YES	US Pach	57
Asian	Hong Kong	74	555.96 ±32.41		NO	US Pach	59
Asian	Korea	1259	530.0 ± 31.5		YES	US Pach	60
Asian	Nepal	152	540 ± 30		NO	US Pach	61
Asian	Philippines	114	550.6 ± 3.8		YES	US Pach	57
Black	Nigeria	95	547.0 ± 29.5		NO	Not Found	62
Black	R.Cameroon	85	528.74 ± 35.89		NO	US Pach	63
Black	Nigeria	130	548.97 ± 34.28		NO	US Pach	62
Caucasian	USA	186	550.4 ± 3.2		YES	US Pach	57
Caucasian	Germany	390	548 ± 37		NO	Orbscan	64
Caucasian	Spain	357	548.21 ± 30.7		NO	US Pach	65
Caucasian	Australia	84	541 ± 31		NO	US Pach	66
Caucasian	Yemen	2,304	521.7 ± 31.62		NO	US Pach	67
Hispanic	USA	96	544.7 ± 38.9	61.6 ± 12	YES	ORA	58
Hispanic	Brazil	90	547.5 ± 32	35.80 ± 12.83	NO	PETCAM	68
Hispanic	USA	116	548.1		YES	US Pach	57

Hispanic	Mexico	93	545.69 ± 36.88	32.54 ± 12.04	NO	AccuPach VI	43
Indian	India	101	528.1±35.0	69.2±10.9	NO	PETCAM	69
Indian	India	4711	514+/-33		NO	US	70
Indian	Pakistan	100	531.29±33.33	44.29 +/- 15.18	NO	US Pach	71
Aborigean	Australia	91	511 ± 34		NO	US Pach	66
Latin	USA	634	546.9 +/- 33.5		YES	US Pach	72
Turkish	Turkey	517	500 ± 37	68.46 +/-10.4	NO	US Pach	73
White	USA	90	549.9		YES	ORA	58

7.7 Genetic aspects of CCT

Studies have been made with genes affecting corneal architecture, in which a relation between genes and the CCT has been found. Of the first candidate genes to be studied were the ones related with the corneal architecture and that were associated with genetic diseases such as osteogenesis imperfecta or Ehlers Danlos. Genes associated with the development of the anterior segment have also been studied, such as *PAX6,* forkhead box 01 *(FOXC1)* and zinc finger 469 *(ZNF469)*. Genome-wide association studies (GWAS) have identified some candidate genes, such as *COL5A1* and *ZNF469*, both have been described in diverse population. Others have been described in specific population, such as autogenous vein graft remodeling associated protein 8 *(AVGR8)*, which has been associated to Caucasians, *COL8A2* to Asians and American Caucasians; *IBTK* to Asians; *AKAP13* to Caucasians; *CHSY1* to Asians, and *FOXO1* to Caucasians and Latino (USA).(71)

From those mentioned above, there are four main genes known to influence CCT: *COL5A1*, *FOXO1*,

AVGR8, and *ZNF469*.

Collagen is the most abundant protein in the body and its fibrils are responsible for the functional integrity of tissues and contribute a framework within which the tissue functions. They closely relate to proteoglycans, hybrid-protein-polysaccharide molecules that form an interfibrillary matrix. The relative proportion of collagen to interfibrillary matrix and the nature of this interaction impart characteristic features to tissues, also accounting for the water content of the tissue. Particular chemical groupings on the collagen molecule determines its physiological characteristics and the methods by which they impart tissue specificity (105). In the cornea, collagen is the principal component of the stroma. The arrangement of the regularly orientated collagen fibrils, which is maintained by chondroitin sulphate and keratan sulphate with interspaced keratocytes; is critical to optical clarity (19). Collagen type 5 determines the diameter of the corneal collagen fibrils. *COL5A1* (OMIM: *120215) is located at 9q34.3, has 66 exons and encodes for α1 (V) chain of type V collagen. *COL5A2* (OMIM: *120190) is located at 2q32.2, has 54 exons and encodes for α 2(V) chain of type V collagen. These genes are present in over 50% of the families with classic Ehlers Danlos. Collagen V determines 15-20% of the fibrillary collagens in corneal tissue.(106) In the Col5a1+/- mouse cornea, type V collagen content decrease by approximately 49 % and stromal thickness by approximately 26%. Total collagen deposition in Col5a1 (+/-) corneas also decrease. Collagen fibril diameters are increased, but fibril density decrease throughout the stroma at all developmental stages.(71,106,107) In patients with classic Ehlers-Danlos syndrome, the mean CCT is 435.75μm ± 12.51 μm (range, 415–448 μm), the corneas are thin, steep and transparent with floppy eyelids (106).

Additionally, there are reports of two SNPs, rs1536482 and rs7044529, located near and within COL5A1 associated with reduced CCT.(31,108) In a study conducted with three independent cohorts of patients in which selected SNPs located within or near *COLA5A1* (including those

associated with CCT) for genotyping for association with keratoconus, rs1536482 and rs7044529 SNPs were found to be associated with keratoconus and CCT.(109) Corneal thinning is one of the hallmarks of keratoconus; however, it is not clear whether the *COL5A1* association with keratoconus is an independent finding or is due to association with corneal thinning in general. In this study, although the difference in CCT between the genotypes was not statistically significant for rs1536482 and rs7044529, the effect size of the risk allele was −3 and −10μm respectively, suggesting that the association between keratoconus and this gene may be independent of CCT.

ZNF469 (OMIM *612078) is located at 16q24, has a single exon and encodes for a zinc protein finger 469. Its function is unknown. However, this protein has a 30% homology to the helical parts of COL1A2, COL4A1, COL1A1, all which are highly expressed in the cornea. The transparency and strength of the cornea requires maintenance of structural organization, as well as the precise regulation of fibril and matrix assembly. *ZNF469* either could act as a nuclear transcription factor or as an extra-nuclear regulatory molecule involved in the synthesis and/or organization of these collagen fibers (110). There is another gene related to brittle cornea syndrome (BCS), *PRDM5* (OMIM *614161), located at 4q27, which encodes for a transcription factor, but still has not been identified by GWAS as a contributor to CCT. It is the most frequent genetic cause of BCS,(111) and close variants may contribute to CCT variation.(72) Mutations in *PRDM5* and *ZNF469* have been correlated with disarray of collagens I and III, fibronectin, and their receptor α2β1 and α5β1 integrin in vitro through shared molecular pathways.(112) In keratoconus, heterozygous alleles of *ZNF469* have been associated with the disease development with a relative risk of 12.0.(113) This evidence highlights *ZNF469* as the main genetic factor of keratoconus.

FOXO1 (OMIM *136533) is a protein coding gene located at 13q14. Its protein is the main target of insulin signaling and regulates metabolic homeostasis in response to oxidative stress. *FOXO1* expresses in the cornea, although it has no proven function in ocular development it is one of the

targets for transcriptional regulation by *FOXC1*, which play a critical role in corneal development. Mutations in *FOXC1* are associated with various anterior segment malformations and glaucoma in Axenfeld-Rieger syndrome. Two recent different studies conducting GWAS have reported the SNP rs2721051 in the genomic region of *FOXO1* with strong association with a risk of keratoconus (odd ratio of 1.62 and 1.4).(86,114) Further evaluation of the clinical relevance of these SNP along with analysis implicating the collagen and extracellular matrix in the regulation of CCT will allow understanding the molecular pathways of CCT.

Vitart described the locus defined by rs1034200 as a factor related with CCT (31). This locus was found 5kb from *AVGR8* gene, encoding a putative transcription factor with typical ZNF and KRAB domains, in chromosomal region 13q12.11. The *AVGR8* gene appears to be a transcription factor of unknown function with a Krueppel-associated box (KRAB) domain and at least five prototypical C2H2 ZNF domains. Although only a few genes regulating corneal gene expression are known, it is believed that *AVGR8* could play a role in the correct assembly and organization of the corneal structure. In a study reported in 2012, the same locus rs1034200 near from *AVGR8* showed relation with Fuchs dystrophy. However, the effect was much large in CCT than in Fuchs. This study estimated that along with three SNPs in *ZNF469* and with rs1409832 between *COL5A1* and *RXRA*, *AVGR8* is associated with an 8- to 16-μm change in corneal thickness (115).

Additional GWAS have identified a number of genes and SNPs associated with CCT, **Table 3** summarizes the findings of the genes described as well as some of the reports on these other genes and SNPs that could be related to CCT (115–121). Together with *COL5A1*, *FOXO1*, *AVGR8*, and *ZNF469*, the analysis of the influence of these genes over CCT will eventually provide a catalog of common genetic variation affecting corneal structure and their relevance in the treatment of corneal diseases.

Table 2: Genes associated with CCT variations

Gene	Experimental model	Experimental strategy	Results	Reference
Col8a1, Col8a2	Mice	Gene inactivation	Disgenesis of anterior segment of the eye Thinner Descemet's membrane Enlarged corneal endothelial cells and reduced in number, decreased ability to proliferate in response to different growth factors in vitro	Hopfer et al, 2005
Col8a2, TCF4	Human FECD & control corneal specimens	Genotyping (SNPs)	The G allele of rs613872 in *TCF4* was associated with increasing corneal thickness (each copy conferring an expected 18.6-μm increase) Each copy of the minor allele of rs4652900 was associated with a 14.8-μm decrease in CCT The minor T allele of SNP rs6084312 was associated with an increase of ~14 μm	Igo et al, 2012
Col8a1, Col8a2 in POAG patients	Human POAG and control bucal specimens	The entire coding region of *COL8A1* and *COL8A2* was sequenced	Three patients with CCT less than 513 μm and advanced POAG have missense changes in *COL8A2* Missense changes were not found in any of the patients with CCT>513 μm and missense changes in the *COL8A1* gene were not found in any patient	Desronvil et al, 2010
Pax6	*Pax6*$^{+/-}$ mice	Fetal and postnatal corneal histopathology, adult corneal thickness, and the distribution of K12-immunostained cells were compared in wild-type and *Pax6*$^{+/-}$ mice	The corneal stroma was thicker centrally, with an irregular lamellar alignment	Ramaesh et al, 2003

Lumican	*Lum⁻/⁻* mice	Confocal microscopy through focusing	Corneal stromal and epithelial thickness was reduced in *Lum⁻/⁻* mice as compared to WT mice	Meij et al, 2007
Bcl2, Bax	Adult Bcl-2 transgenic and Bax knockout mice and wild-type controls	Polymerase chain reaction was used to confirm genotype In vivo tandem scanning confocal microscopy	Stromal thicknesses were greater in the Bcl-2 transgenic group compared to wild-type and decreased in the Bax knockout Homozygosity of the disrupted gene led to substantial reductions in thickness	Roberts on et al, 2006
Col1a1, Col1a2	mouse model of Osteogenesis imperfecta with a *col1a2* mutation	CCT measurement with noncontact optical low coherence reflectometer (OLCR; Haag-Streit, USA). SNP's (tissue samples from the tails)	Oim/oim mice showed CCT descreased of ~15% when compared with the control Wt/oim mice showed CCT decrease of ~8% The addition of each *oim* mutant allele resulted in a 7.8% reduction in CCT Polymorphism rs2696297 in *COL1A1* and a three SNP haplotype in *COL1A2* were all significantly associated with normal CCT variation	Dimasi et al, 2009

7.8   Factors influencing CCT

In addition to the influence of genetic factors on CCT, several other extrinsic factors are known to have influence on CCT. Among these factors are the age of the patient, physiologic diurnal variations, UV radiation, altitude, chronic contact lens use, and various diseases. This section will briefly review the evidence reported regarding the influence of some of these factors on CCT.

Age. Reports on a relationship between CCT and age are contradictory. While some studies report a statistically significant inverse relationship between these variables,(88) others indicate there is

no statistical significant relationship between these variables.(96) Overall, the evidence from published studies made in whites suggests that for the majority of individuals there is no substantial change in CCT beyond the infant years, however studies done in different ethnic groups like those of Japanese and Eskimo prove there is a significant difference.(75,88)

Diurnal variation of CCT. Corneal thickness can also increase due to net water influx. Pachymetry indirectly reflects endothelial function because the endothelium maintains corneal thickness and transparency by regulating the flux of water and solutes across the posterior corneal surface.(1,64) Because of the changes in corneal thickness due to hydration, there is a diurnal physiological variability on CCT. Data confirm an increase of corneal thickness during sleep having its peak value at 4 am, but considerable variation during waking hours has also been reported.(122) Corneal thickness may increase immediately after waking up due to overnight corneal hydration. This is consequence of diminished evaporation of water from closed lids and reduced nocturnal metabolic activity of the endothelium. Corneal hydration during sleep is caused because the cornea experiences hypoxia beneath closed eyelids. This reduction in oxygen increases anaerobic metabolism causing accumulation of lactate within the stroma, followed by an osmotic influx of water.(123) Reports about the percentage of diurnal changes in CCT vary depending on the study, however it is consistently found to be significant.(123–125) A 5.5% overnight increase, with a 7.2% of diurnal variation was reported in 1996 by Harper and collaborators.(123) Du Toit and collaborators reported in 2003 a variation of 3.9% over 24 hours with an overnight swelling of around 2.9%, concluding that baseline CCT can be measured at any time from 7 hours of eye opening.(124)

UV radiation: The entire anterior eye segment can be damaged when exposed to UV-B, the parts that receive most damage are the cornea and the lens. Repeated exposure to UV-B radiation has shown to damage the corneal epithelium and disturb corneal metabolites.(126) It has been known

that UV radiation may cause photokeratitis, also known as snow blindness, which is a transitory inflammatory condition caused by damage to the corneal epithelium.(87,127) UV-B irradiation may also cause or promote changes in the endothelium associated with aging.(128) Another effect of UV radiation on the cornea is an increase in biomechanical stiffness when used in combination with riboflavin.(28,129) This effect is due to the increase in the collagen crosslinks in the corneal stroma, this technique has been exploited specially in the treatment of conditions such as keratoconus.(28,130)

Altitude: The human eye, like several other organs, is affected by hypoxia at high altitude. Hypoxia makes the cornea shift to anaerobic metabolism, with a subsequent increase in extracellular metabolic byproducts, causing a hydration pressure shift into the extracellular stromal spaces.(131) This hydration secondary to hypoxia results in increased CCT. The cornea returns to its initial thickness after descent. In other studies, individuals with more acute mountain sickness-related symptoms have been found to have thicker corneas, suggesting that CCT could be used as a parameter to indicate if a person is susceptible to acute mountain syndrome (132).

Chronic contact lens use: Chronic use of contact lenses and dry eye can also increase CCT (122). Differences between morning and afternoon CCT readings may be exaggerated in contact lens wearers. The lens type and the period of lens wear can be important factors for the changes in CCT after contact lens use (75).

Diseases: Corneal thickness vary in several diseases, or can have impact on the severity of an ophthalmologic condition. One such disease is glaucoma, in which as presented before, lower CCT is associated with worsened advanced glaucoma and greater risk of developing glaucoma (2,133). Another condition associated with abnormalities in corneal thickness is keratoconus. This is a non-inflammatory disease of the cornea that mainly affects the central cornea and is characterized

by thinning and ectasia (134). Corneal thinning in this condition is a result of the loss of its structural components (7). With increasing keratoconus severity, the cornea becomes thinner, and as presented above, this thinning of the cornea induces irregular astigmatism, myopia and protrusion, leading to impairment in the quality of vision. Diabetes has been associated with alterations in the corneal endothelium. Among the disorders observed in diabetic patients are decreased endothelial cell density, glycation of membrane ATPases, and a decrease in Na+/K+-ATPase activity (135). These changes influence the endothelial pump action and hence induce dysfunction. As presented above, the pump function of the endothelial layer is responsible for the active dehydration of the cornea and its alteration correlates with thickening of the cornea (64) CCT in diabetic patients is significantly thicker than in control groups, (136) and there has also been a correlation between duration of diabetes mellitus and CCT (135,137). Congenital glaucoma also relates with changes in corneal thickness. Pediatric patients with congenital cataract have been reported to have thicker central corneas when compared to contralateral healthy eye and a normal population (138,139). This increase in corneal thickness in the eyes with cataract may be a consequence of delayed development and maturation of the cornea (140). Another ophthalmologic disease related with endothelial cell dysfunction is Fuch's endothelial corneal dystrophy. The endothelial dysfunction present in this disease results in corneal edema and hence an increase in CCT.(141) Thickening presents mainly in the later stages of the disease and its physiological basis has been attributed to alteration in Na+/K+-ATPase activity and breakdown in the barrier function of the endothelium.(142) It has been found that the point at which the compensatory mechanisms of the corneal endothelium fail in Fuch's dystrophy, and corneal edema results, is when the central endothelial cell density reaches around 700-400 cells/mm^2.(38,39) Other ophthalmologic diseases that are related with changes in CCT are Behçet's disease and retinal vein occlusion. Eyes with active Behçet's disease have increased CCT

probably related to active inflammation that returns to normal after treatment (143). Patients with central retinal vein occlusion have thinner CCT than controls, however the pathophysiology underlying this association is unclear (144).

While some of the factors influencing CCT are related with delayed development, inflammation or altered arrangement of collagen fibrils, most of them are related to alteration in endothelial integrity and permeability. Diurnal variation, altitude and contact lens related changes in CCT directly relates with corneal hydration. Likewise, the effects of UV-B radiation relate to endothelial damage and the consequent increased corneal hydration. Even some of the diseases studied, such as diabetes and Fuch's endothelial corneal dystrophy, also increase CCT by altering the endothelium's barrier or pump function. This is in line with the statement that pachymetry indirectly reflects endothelial function (64). However, there remains work to be done to fully understand the pathophysiology underlying the relationship with other factors such as central vein occlusion.

7.9 Heritability

Corneal central thickness is highly heritable. There is no clear genetic correlation between a thinner cornea and primary open angle glaucoma (POAG). There are genetic variants that had been proved to contribute to CCT, most of which are population specific. Further genomic studies from each population will lead to the finding of genetic variants associated to CCT. Therefore, these studies are useful as tools to evaluate corneal health status. Additive genetic effects appear to be the major contributor to the variation of CCT (70,145). Familial and twin studies suggest CCT heritability could be as high as 0.95 (70). Further data supporting heritability is the high prevalence of glaucoma in some populations in which the CCT tends to be lower, compared against other groups. At first, it was thought that CCT and POAG could be genetically related,

because of their close relation. Thus, if CCT genes were found, it could be possible to find POAG genes also. However, no such relation has been found so far.

7.10   Conclusion

Corneal thickness is a parameter of the cornea that has important implications in several aspects of ophthalmology, from its effect on the measurement of IOP to its impact on refractive surgery and diseases like keratoconus. This review has addressed the subject of corneal thickness trying to broadly cover all parameters that influence or have implications in CCT in order to fill in the gap between scholar articles and more specific and advanced ones found in the literature. In order to do so, general concepts regarding corneal anatomy and physiology were reviewed initially for the better understanding of their relevance in the areas of corneal biomechanics and corneal topography, which are helpful tools in the study of corneal structure and the effects surgical treatment and therapies have on the physiological conditions of human cornea such as its optical properties and general structure. The importance of CCT in several clinical scenarios was reviewed, with it being a factor influencing in the measurement of clinical parameters, to being a risk factor for several diseases, and determining if a patient can undergo a certain type of surgery or not. A revision of the studies about average adult CCT was done, showing a comparison between different population studies in order to reflect the variations among different ethnicities as well as illustrating what is generally considered as an average CCT value. An analysis of the genes known to influence CCT was done, with main emphasis in COL5A1, FOXO1, AVGR8, and ZNF469, which are the most related with corneal thickness, however other promising genes in this field were also mentioned. In addition to the influence of genetics, several other extrinsic factors known to have influence on CCT were reviewed including the age of the patient, physiologic diurnal variations, UV radiation, altitude, chronic contact lens use, and various diseases. While some of the factors

influencing CCT are related with delayed development, inflammation or altered arrangement of collagen fibrils, most of them are related to a lack of endothelial integrity, permeability and corneal hydration.

Even though extensive research on this topic has been done, the broad spectrum of clinical implications of CCT encourages further investigation of the factors involved in its expression and other clinical implications it may have, not just in the corneal and refractive surgery field but in other areas of ophthalmology as well. There is still work to be done especially in areas like biomechanics, which continue to push the boundaries of what is known about structure and functioning, as well as about what is done in terms of safety regarding surgical procedures.

7.11   Discussion

CCT is a critical parameter in the assessment of IOP in glaucoma patients, and its measurement is also compulsory in patients undergoing corneal refractive surgery and during the postoperative follow up of corneal transplant. It is known that CCT values vary between ethnic groups, and that there are several factors either extrinsic (i.e. UV radiation, altitude, humidity) and intrinsic (age, gender, ethnicity, hereditability and genetics) have an effect influence it.[17,22,24,25,31,32]

8. Sección II.

Correlacion de la edad, curvtura corneal y equivalente esferico.

8.1 Justificación.

La estructura normal de la cornea es actualmente motivo de invetigación para un mayor entendimiento de su conformación y de su comportamiento en entidades aptologicas como ante situacione clinicas com pudiesen ser los eventos quirurgicos. Un elemento que ha sucitad la atención de nuestro grupo de ionvestigación es el espesor corneal. He mos heco una amplia busqueda de los diferente facotres que actuan para dare las caracteristicas normales. Despues de nuetra primera proximación sabeos que el espesor corneal varia de acuerdo a la edad y grupo etnico, por ejemplo, pero ademas, que los valores de normalidad deberan ajustarse de acuerdo acada población. No existe información suficiente de los valores normales paquimétricos en nuestra población y el efecto que tiene sobre ella factores como: la edad, la curvatura corneal y el equivalente esférico.

8.2 HIPÓTESIS

Hipotesis de trabajo:

El espesor corneal se correlaciona con la edad, la curvatura corneal y el equivalente esferico.

Hipotesis nula:

El espesor corneal no se correlaciona con la edad, la curvatura corneal y el equivalente esferico.

8.3   OBJETIVOS

8.3.1. Objetivo principal

Objetivo General:

Determinar la correlacion entre es espesor corneal central, la edad, la curvatura corenal y el equivalente esferico.

8.3.2. Objetivos específicos

1.   Determinar la normalidad del espesor corneal en paciente candidatos a cirugía refractiva.

2.   Relación entre espesor, defecto refractivo y curvatura promedio.

3.   Establecer los valores paquimetricos normales en nuestra población

8.4 Correlation of age, corneal curvature and spherical equivalent with central corneal thickness

Introduction

Central corneal thickness (CCT) is one of the major parameters for measuring corneal health.[1,2] Its measurement is essential in the assessment, management and follow up of corneal ectatic diseases (i.e. keratoconus, post-LASIK ectasia) and corneal endothelium dysfunction, since the changes in the corneal thickness are directly associated with the severity of the disease.[3–6] CCT measurement is also essential in the management of glaucoma patients, given that applanation tonometry underestimates the intraocular pressure (IOP) in eyes with thin corneas and it overestimates this in thick corneas.[7,8] CCT has also been used as a predictor of graft survival and cell density measurement after penetrating keratoplasty, thicker corneas have shown a tendency to develop graft failure within 5 years post-surgery.[3] Thin corneas, along with low residual stromal bed thickness (<300µm), deep ablation and abnormal corneal topography, have been considered as preoperative risk factors in corneal refractive surgery for developing corneal ectasia.[9–11] However, there is ongoing debate surrounding the precept that "thinner" corneas are indeed "weaker" corneas with biomechanical liability, since the influence of CCT over the long-term stability of LASIK procedures has not been demonstrated.[12,13]

Normal CCT values have been established by different research groups.[7] However, a large variability among different ethnic groups has been reported.[14–17] Age,[7,18,19] gender,[20]

the transition from lower to higher humidity, UV radiation exposure, hereditability,[21,22] genetics,[23,24] altitude have also been associated with changes and variability in CCT.[25,26] Additionally, the correlation of different ocular parameters with CCT has been studied, including corneal radius and curvature,[27] anterior chamber depth, axial length,[28] the spherical equivalent,[29] visual acuity, and IOP.[30]

All the factors mentioned before and the controversial results regarding the use of CCT as a predictive parameter for different ocular procedures indicate that the "normality" concept for CCT needs to be re-evaluated so it can be used appropriately as a clinical parameter. In this study, we aimed to measure the CCT among healthy Hispanic patients, and to determine its correlation with age, gender, curvature, and spherical equivalent.

8.4.1 Materials and methods

A retrospective analysis of pachymetric measurements conducted between February 2012 and November 2012 at the Ophthalmology and Visual Sciences Institute (Tecnologico de Monterrey, School of Medicine, Monterrey, Mexico) was performed. Data from 93 healthy patients were obtained after calculating the optimal sample size using Raosoft® (Raosoft, Inc., Seattle, WA, USA) with a confidence interval (CI) of 90% and an error margin of 5% in a population of 600 patients. Patients with abnormal topography (inferior steepening, irregular pattern, non-orthogonal bowtie), contact lens users or with history of refractive

surgery were excluded. The CCT was obtained using ultrasonic pachymetry (AccuPach VI; Accutome, Inc., Malvern, PA, USA). Briefly, the cornea was anesthetized with topical 1% tetracaine and the patient was asked to adopt a face up position on the examination chair and solicited to fixate a target on the ceiling. The pachymeter probe was brought in contact with the cornea centrally and perpendicularly over the visual axis. CCT was recorded as the average of 9 consecutive acquisitions. This process was repeated for every individual CCT measurement.

Age, gender, mean simulated keratometry (SimK) (Orbscan II Software version 4.1, Bausch&Lomb, Rochester, NY, USA), and spherical equivalent data were also obtained. Patients with any ocular or corneal pathology as well as history of ocular surgery were excluded. Patients with diagnosis of cataract, but who did not have surgery, were included. Statistical analysis was performed using IBM SPSS® version 21 (IBM Corporation, Armonk, NY, USA). A descriptive analysis and Spearman's correlation of the variables were performed. The mean of the CCT values and their distribution were established via the Anderson–Darling, Shapiro–Wilk, and Kolmogorov–Smirnov tests. The sample was divided by the following age groups: <20 years, ≥20 and ≤40 years, and >than 40 years to perform a descriptive and comparative analysis by analysis of variance (ANOVA), as well as to conduct an independent samples t-test.

8.4.2 Results

A total of 93 patients (186 eyes) were included in the study, 43% (n=40) were female. The mean age of the patients was 32.54±12.04 years (range 21–54 years). The mean keratometry was 43.56±1.90 diopters (D) and the mean spherical equivalent was −2.54±3.15D.

The mean CCT was 545.69±36.88μm (range 458–640μm). The CCT showed a bimodal distribution with the first peak occurring at 540μm and the second at 580μm (Fig. 1). No association was observed between the pachymetry measurements and the mean keratometry, spherical equivalent, and age when analyzed with the Anderson–Darling (p=0.006), Shapiro–Wilk (p=0.043), and Kolmogorov–Smirnov (p=0.01) tests. Pearson's test showed a correlation of −0.08 between pachymetry and age, 0.099 between pachymetry and keratometry, and 0.033 between pachymetry and the spherical equivalent. The correlation between age and keratometry was −0.259 and the correlation between age and the spherical equivalent was −0.2 (Fig. 2).

 CCT histogram. The analyzed population did not exhibit a normal distribution. The first peak can be noted at 540μm, and the second at 580μm.
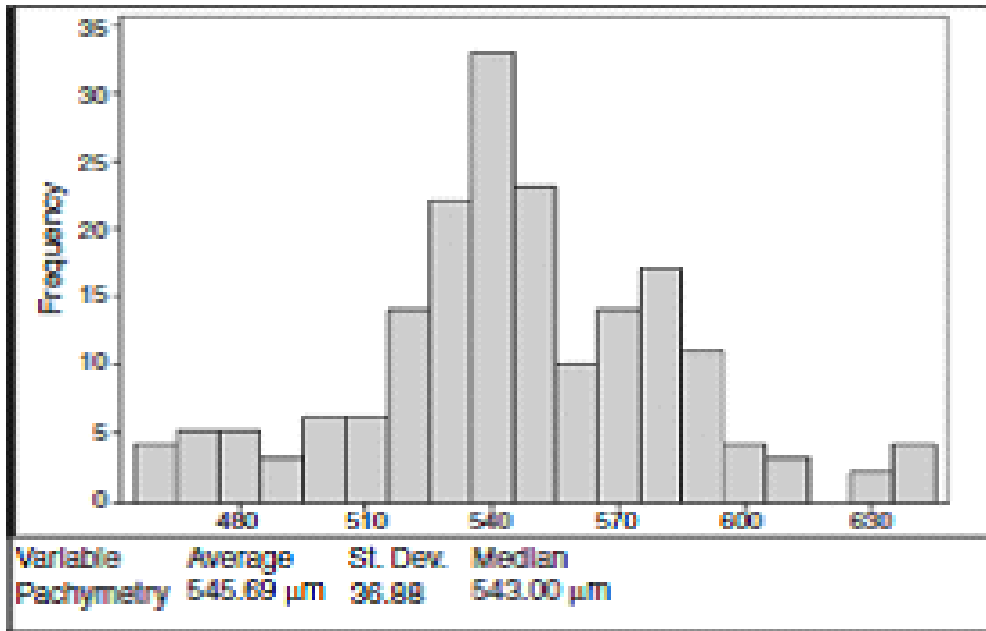
Figure 1. CCT histogram. The analyzed population did not exhibit a normal distribution. The first peak can be noted at 540μm, and the second at 580μm.

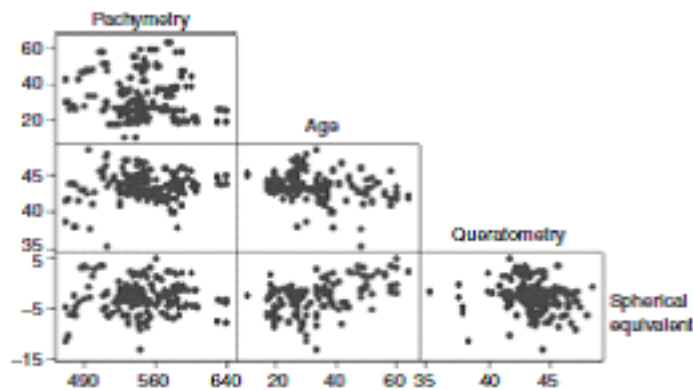**Figure 2.** Matrix plot showing the correlation between CCT and the age, keratometry, and spherical equivalent variables.

The sample was divided in three age groups: <20 years, from 20 to 40 years, and >40 years

(Table 1). Although the mean CCT for the group <20 years was 558.82±37.398μm, 42.8%

(n=12) of the eyes in this group had a CCT ≥580µm, while 14.4% (n=17) and 14.2% (n=6)

of the eyes in the groups from 20 to 40 years and over 40 years had CCT ≥580µm. The

mean CCT between age groups <20 years and >40 years showed a significant difference

(p=0.016). No difference was detected between the age groups <20 years and 20–40 years

(p=0.094), and >40 years (p=0.17). A positive correlation with CCT was observed in the

group <20 years (ρ=0.596, p=0.001), a negligible correlation between CCT and age was

detected in for the age group ≥20 and ≤40 years (ρ=0.091, p=0.326) and a non-significant

positive correlation in the group over 40 years (ρ=0.255, p=0.103).

Table 1 Central corneal thickness by age group.

Age group (years)	n	Mean CCT	Standard deviation	Range (µm)
<20	28	558.82	37.398	507–640
≥20–≤40	114	545.84	36.321	458–640
>40	44	536.93	36.256	458–600

CCT = central corneal thickness, n = number.

Table 1. Central corneal thickness by age group.

We observed an average CCT of 545.69±36.88µm, similar to that of previous studies

conducted with Hispanic subjects. Hahn et al.19 in 2003 reported a mean CCT of 546.9µm;

Erickson et al.33 in 2010 obtained a mean CCT of 541.8µm; and recently, Valbon et al.34

found a CCT of 547.5µm. Our sample also exhibited a wide range of CCT values (ranging

from 458 to 640µm), this was superior to the ranks reported by Hahn et al.

(479.7–613.4µm) and Valbon et al. (490–647µm). Additionally, our results showed a

bimodal distribution with the first peak reflecting the mean CCT for the whole sample (545.69μm) and the second peak attributed to the eyes (n=35) with thick corneas (CCT ≥580μm), primarily at the expense of the younger group of patients <20 years (42.8%). Other authors have made similar observations with regard to a trend over a higher prevalence of thicker corneas in younger ages.[27,35]

The wide range of CCT values, as well as the high frequency in values around 540μm, might lead us to redefine the concept of "normality" for corneal thickness in our population. Frequently, corneas below 510μm are considered as thin and, and therefore as corneas with biomechanical liability or weakness for excimer laser refractive procedures (LASIK, PRK).[10–12,36,37] However, there is increasing evidence with regards to the safety and effectiveness of LASIK surgery in patients with CCT values <500μm.[13,38,39] Since collagen tension disruption affects corneal biomechanics in refractive surgery,[40,41] this contradictory evidence leads us to believe that there are other factors that impact corneal structural stability independently of CCT. In this respect, it has been suggested that ultrastructural changes observed in ectatic corneas are related to mechanical stress, which leads to greater modifications in collagen fibrils and not directly to the CCT.[42,43] Hence, in order to consider a cornea as "normal", the entire topography (topographic pattern, pachymetry map and elevation maps) along with the expected CCT for a given population, should be taken into account.

In agreement with other reports,[28,29] we did not observe a correlation between CCT and the variables age, keratometry, and spherical equivalent. However, when the population was subdivided into age groups, a significant difference was noticed between the CCT of individuals under 20 years and those over 40 years. Younger patients registered thicker corneas with a mean difference of 20µm from those patients over 40 years, and a positive correlation was observed for both groups (only significant for the group <20 years). This is in accordance with numerous studies that have reported decreasing values of CCT in relation to older age.[14,44] In a meta-analysis that included populations from different ethnicities, Doughty and Zaman,[7] reported an inverse relationship between age and CCT for non-white population. This age/CCT correlation could be explained by the decrease in interfibrillar spacing due to age-related non-enzymatic crosslinking, which has been suggested to cause reductions in stromal thickness.[35,45]

8.4.3 Discussion

A bimodal distribution in the CCT was observed in this cross-sectional study, with the first peak at 540µm and a second minor peak at 580µm, the latter attributed mainly to younger patient measurements. No association between age, corneal curvature and spherical equivalent was observed, but when analyzed by age groups a positive correlation was detected for age group <20 years and age group >40 years. To our knowledge, this is the first study that describes pachymetric values and their correlation with other factors in this specific population. The findings regarding the lack of normality,

the higher frequency of the samples in the first peak, and the relationship between age

and decreasing CCT, may lead us to redefine the "normal" pachymetric parameters in our

population so they can be used properly for clinical purposes.

9. Sección III.

Seguridad y Eficacia de la Queratomileusis in Situ asistida por láser miopica (LASIK) en corneas delgadas.

9.1 Justificación

Sabemos que el espesor corneal puede ser afectdo por diversos factores y por algunos estados patologicos. Es también conocido que los rangos de normalidad varian de acuerdo al grupo poblacional al que hagamos referencia y que el rango de valores considerados es mas o menos amplio. Tradicionalmente se ha establecido al grosor (espesor) corneal central como un factor importante al considerar una cornea como normal o patologica, inclusive se utiliza para determinar si un paciente es suceptible de sometido a cirugía refractiva, excluyendo aquellos pacientes que no presenten un valor minimo paquimetrico. En la presente tesis desafiamos esta practica, tomando en cuenta nuestros hallazgos de la sección anterior la presente tesis en la que evidenciamos el amplio rango de valores normales paquimetricos de nuestra póblación. Con el proposito de analizar el comportamiento de un grupo de pacientes con la caracteristica de tener un groso corneal menor al promedio analizamos su comportamiento postoepratorio y evaluamos parametros de seguridad y eficacia del procedimiento. Hasta donde es de nuestro

conocimiento, existe poca evidencia publicada en nuestro medio al respecto.

9.2 HIPÓTESIS

Hipotesis de trabajo:

El espesor corneal tiene efecto sobre el resultado refractivo en pacientes sometidos a queratomileusis in situ asisitida por laser.

Hipotesis nula:

El espesor corneal no tiene efecto sobre el resultado refractivo en pacientes sometidos a queratomileusis asisitida por laser.

9.3 OBJETIVOS.

    9.3.1. Objetivo principal

Objetivo General:

Determinar el efecto que el espesor corneal tiene sobre el resultado refractivo en los pacientes sometidos a queratomileusis in situ asistida por laser a largo plazo.

9.3. 2. Objetivos específicos

1.   Comparación de resultado refractivos en ablaciones miopicas con corneas limítrofes (delgadas vs gruesas).

2.   Comparación de resultado refractivos en ablaciones hipermetropicas en corneas limitrofes.

3.   Determinar si el espesor corneal disminuido (paquimetria) es un factor de riesgo independiente en la cirugía refractiva.

9.4 Safety and Efficacy of Myopic LASIK performed on Thin Corneas

Introduction

Laser in situ keratomileusis has been the treatment of choice for correcting corneal refractive errors since its introduction in early 1990 [1,2].   Resulting in immediate high quality visual outcomes and having an excellent efficacy, predictability, stability and safety profiles, it's no wonder why LASIK surgery has become one of today's most popular elective procedures, with more than 28 million procedures performed worldwide [3,4]. As with any other surgical procedure, an increased frequency and widespread use is also associated with a grown incidence of complications.

Although effective methods to treat most of the complications related to LASIK have emerged (either with eye drops or with surgical correction) [5,6] post-LASIK ectasia is one of the most feared complications since its treatment often involves extensive management strategies that go from intrastromal corneal rings [7] and crosslinking8 to

keratoplasty [9].

Specific risk factors for developing corneal ectasia after LASIK have been identified and they include deep ablation, residual stromal bed thickness lower than 300μm, abnormal topography and central corneal thickness (CCT) less than 500μm [10–12].   Randleman et al. also considered factors as young age and high refractive correction to develop an Ectasia Risk Score System (ERSS) with the objective to assess the preoperative risk for developing ectasia after LASIK.13   Recently, the role of the percent tissue altered (PTA) has been emphasized by Santhiago et al. as a robust risk indicator for developing ectasia after LASIK in eyes with normal topography [14].

Either directly (ERSS) or indirectly (PTA), thin corneas have been considered as corneas with biomechanical liability and therefore to have an increased risk for developing ectasia after ablative surgery [13,14].   However, recent evidence shows not only that thin corneas (<500μm) have not an increased risk for ectasia but that LASIK is as effective, safe and stable as in corneas with 500μm or greater [15,16]. In this study we assessed the visual outcomes and safety of myopic LASIK performed in patients with corneas with central thickness below average <540 μm and normal topography.

9.4.1 Methods

A retrospective analysis was performed on the records of Hispanic patients who underwent myopic LASIK between January 2014 and January 2015, at the

Zambrano-Hellion Medical Center, Tec de Monterrey (Monterrey, México). The analysis followed the tenets of the Declaration of Helsinki, informed consent was obtained from all patients after details of the surgical procedure were explained. Inclusion criteria for the initial treatment were: age over 18 years; stable refraction with spherical component up to -8.50D, a cylindrical component between up to -6.50D; corrected visual acuity ≥ 20/20 (Snellen visual acuity chart) a central corneal thickness (CCT) < 540μm and at least 12 months follow up. Patients with LASIK surgery general contraindications as autoimmune diseases, diabetes, pregnancy, and ocular diseases including glaucoma, cataract, retinal diseases, and dry eye were excluded.

Preoperative examination included uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), manifest refraction, cyclopegic refraction, intraocular pressure measurement (Goldmann applanation tonometer), ultrasonic pachymetry (Accutome AccuPach V, Malvern, PA, USA), corneal topography (Orbscan IIz, Bausch and Lomb, Rochester, NY, USA) and slit lamp examination. The CCT was obtained using ultrasonic pachymetry (Accutome 4sight pachymeter module; Accutome, Inc., Malvern, PA, USA). Briefly, the cornea was anesthetized with topical 1% tetracaine and the patient was asked to adopt a face up position on the examination chair and solicited to fixate a target on the ceiling. The pachymeter probe was brought in contact with the cornea centrally and perpendicularly over the visual axis. CCT was recorded as the average of 9 consecutive acquisitions. This process was repeated for every individual CCT measurement.

Postoperative protocol consisted on moxifloxacin 0.5% ophthalmic solution (Vigamoxi,

Alcon Laboratories, Fort Worth TX, US) every 6 hours for 7 days and fluorometholone 0.1 opthalmic suspension (Flumetol, Sophia , Jalisco, Mexico) in dose reduction for 2 weeks. Postoperative visits included UDVA, CDVA, manifest refraction, corneal topography, Goldmann tonometry, slit lamp biomicroscopy and Visante AS-OCT (Carl Zeiss Meditec Inc, Version 3.0, Dublin, CA, US) on postoperative week 1 to measure the thickness of the corneal flap.

LASIK procedures were performed by the same surgeon using a Technolas-217 Excimer workstation (Technolas Perfect Vision GmbH, München, Germany) using the standard technique. Briefly, under topical anesthesia with tetracaine chlorhidrate 0.5% (Ponti ofteno, Sophia , Jalisco, México), the cornea was marked with gentian violet and a superior hinge was performed using a Hansatome XP Microkeratome (Bausch & Lomb, Rochester, NY). When indicated both eyes were operated the same day, with the refractive target to emmetropia. A 6.0 mm optical zone and a 120 microns flap with a superior hinge and average diameter of 9.5 mm (an 8.5 mm diameter ring was used in eyes with mean keratometry > 45D) was used in every case. Zyoptix Tissue Saving-2 ablation profile was used to ensure a residual stromal bed $\geq$ 300µm. Standard visual outcomes and percent tissue altered (PTA) analysis were obtained. The preoperative and postoperative data were compared using Student's t test. Statistical analysis was implemented with the SPSS software (version 20.0, IBM Inc., NY, USA) for Windows, a p value <0.05 was considered statistically significant. Visual acuity was measured using Snellen´s visual acuity chart and then converted to LogMAR for statistical analysis.

9.4.2 Results

A total of 51 patients (102 eyes) were included in the study, 56% (n=57) were female. The mean age was 26.52 ± 8.06 (range 18 to 55 years) with a mean follow up of 13.9 ± 1.2 months. Preoperatively, CCT was 515.44 ± 17.87µm (range 452-539µm), the mean refractive spherical equivalent (MRSE) was -4.06 ± 1.85 D (range -0.75 to -9.75 D) with a mean refractive cylinder of -1.44 ± 1.29 D (range 0.00 to -5.75 D). On postoperative week 1, the mean central thickness of the corneal flap was (128.66 ± 17.09µm). The analysis of PTA showed a mean value of 0.35 ± 0.04 (range 0.22 to 0.44). Figure 1 shows the Standard Graphs for Reporting Refractive Surgery.

The mean predictability of postoperative SEQ was -0.20 ± 0.40 D (range -1.25 to +1.25) at the end of the follow up. Postoperative SEQ was ±0.50 D in 71% and ±1.00 D in 93% of the eyes. Preoperative CDVA was 20/20 or better in 93% of the eyes. Postoperative uncorrected distance visual acuity was 20/20 or better in 78% and 20/25 or better 95%. One line of CDVA was lost in 3% of eyes and none of the eyes lost more than 2 lines of CDVA. Over the follow up (from postoperative month 3 to postoperative month 12), only 4% of the eyes changed >0.50D. A strong squared correlation (R2=0.981) was observed between attempted and achieved SEQ correction.
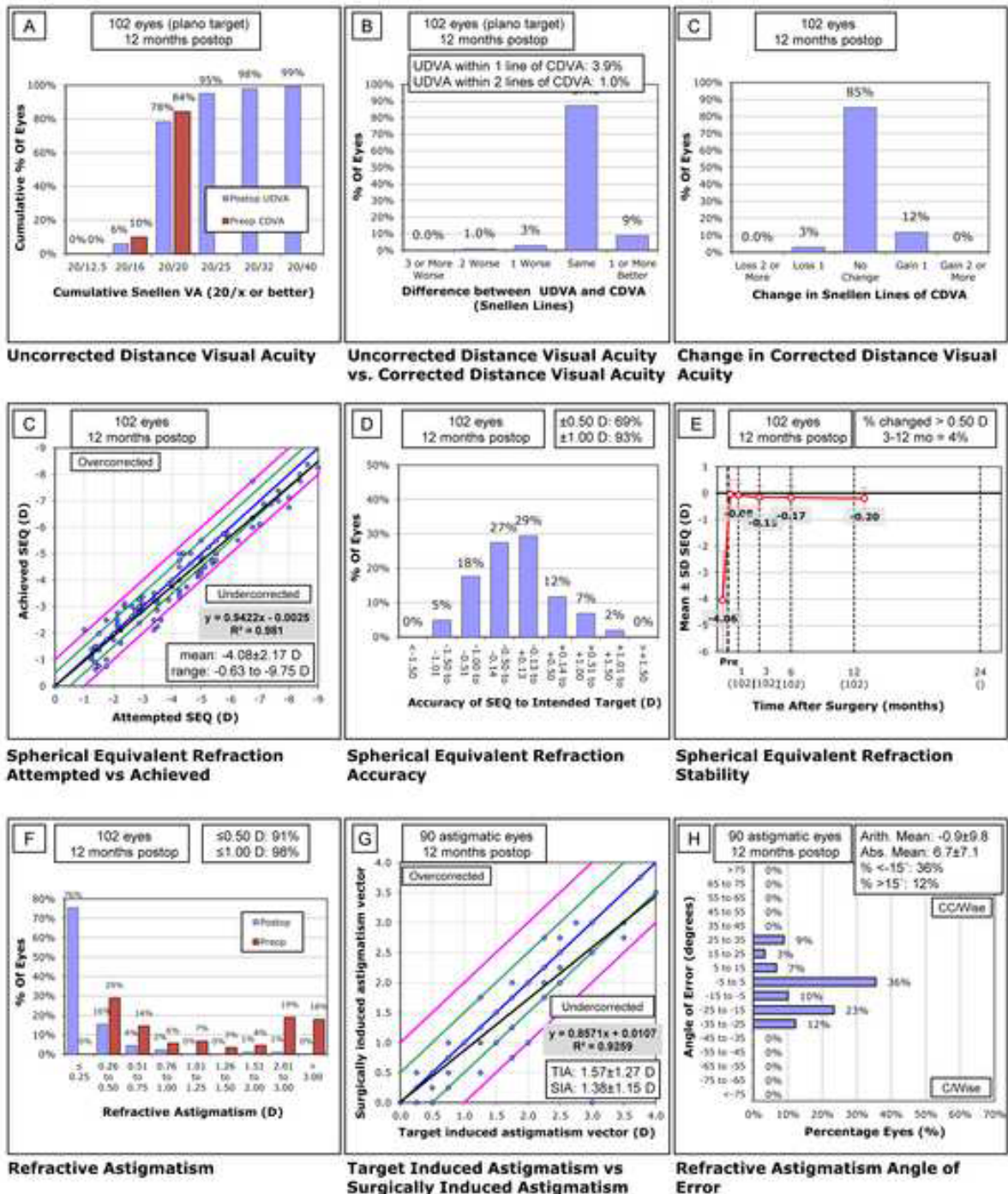
Figure 1. Nine standard graphs for reporting refractive surgery showing the visual and refractive outcomes for 102 myopic eyes treated with Hansatome XP Microkeratome (Bausch & Lomb, Rochester, NY) and Technolas-217 Excimer workstation (Technolas Perfect Vision GmbH, München, Germany), using Zyoptix Tissue Saving-2 ablation. UDVA= uncorrected distance visual acuity; CDVA= corrected distance visual acuity; D = diopters; Postop = postoperative; Preop = preoperative; SEQ = spherical equivalent refraction; TIA = target-induced astigmatism; SIA = surgically induced astigmatism.

Table 1 shows the changes in visual and refractive outcomes before and after the lasik procedure. Intraoperative complications consisted on epithelial defect in 3 cases (3% of total) and flap striae that required flap re-lifting in 1 eye (1%). No ectasia cases were observed during follow-up.

TABLE 1

Visual and Refractive Outcomes Before and After Myopic LASIK in Thin Corneas

Parameter	UDVA (LogMAR) a	CDVA (LogMAR) a	SEQ (D) a	Keratometry (D)
Preoperative	0.84 ± 0.45	0.00 ± .05	-4.06 ± 1.85	-1.44 ± 1.29
6 months FwUp	0.00 ± .08	0.00 ± .04	-0.17 ± 0.41	-0.47 ± 0.40
End point FwUp	0.00 ± .05	0.00 ± .02	-0.20± 0.40	-0.36 ± 0.39
P valueb	<.001	<.001	<.001	<.001
P valuec	.78	.81	.13	.08

UDVA = uncorrected distance visual acuity; CDVA = corrected distance visual acuity; D = diopters; FwUp= Follow Up; LogMAR= Logarithm of the Minimum Angle of Resolution; a Values reported as mean ± standard deviation; b Mean comparison between preoperative and 6 months follow up; c Mean comparison between 6 months follow-up and end point follow-up.

9.4.3 Discussion

Post LASIK ectasia is rare, but even with a prevalence rate of 0.02% to 0.6% it remains as one of the most feared complications in refractive surgery [17,18]. Risk factors for developing this condition have been previously identified [12,14], amongst them thin corneas (<500μm) have been historically considered as corneas with biomechanical frailty and therefore as corneas predisposed to develop ectasia [19, 20]. Evidence shows that

factors as race [21,22], age and gender [22,23] altitude [24] and UV light exposure [25] may influence CCT, hence different "normal" corneal thickness have been stablished among various research groups.   In a meta-analysis conducted by Doughty et al. [23] an average CCT of 536 ± 29 µm was stablished for normal healthy eyes.   In a Hispanic population, Valdez et al. observed a mean CCT of 545.69 ± 36.88 µm (mode of 540 µm) in healthy corneas of Hispanic patients [26].   In this study we evaluate the visual outcome, safety and predictability of LASIK performed on a large cohort of corneas thinner than "normal", defining the latter as corneas <540 µm accordingly to the reported values (statistical mean and mode) in our population, at a 12 month follow up.

Against the old paradigm that thin corneas have a biomechanical liability, recent evidence has shown not only the absence of keratectasia during follow up but also no difference in visual outcomes, safety and predictability when LASIK is performed on thin corneas with normal topography when compared with preoperative corneas with average or normal thickness.   Tomita et al, assessed the 6 year-follow up outcomes of thin-flap LASIK in eyes with thin corneas (CCT<500 µm) but normal topography and compared them with the outcomes of LASIK performed on corneas with CCT 500 µm or greater [16]   They observed no difference in visual, refractive and topographic outcomes at long-term between both groups.   At their last follow-up 83% of the eyes in the thin cornea group achieved a UDVA of 20/20 or better, 63% were stable or gained lines of CDVA and had refractive stability with a MRSE change of -0.17 ± 0.42 D over time [16].   Similarly, we observed 78% of the patients with UDVA ≥20/20, 97% of the eyes were stable or gained lines of CDVA at the last follow up and a refractive stability with a MRSE change of -0.20 ±

0.40 over time.   Likewise, we observed a non-significant difference on visual and refractive outcomes when comparing 6 month follow-up with the final follow up (Table 1), suggesting visual an refractive stability.

Caster et al, performed a retrospective analysis of 109 eyes with preoperative central corneal thickness of ≤ 500 µm and otherwise normal topography that underwent LASIK, having a postoperative follow up of at least 12 months [15].   As in Tomita et al [16], and the present study, refractive stability was observed during the follow up period with no incidence of postoperative keratectasia.   Previously, Binder et al. examined a database of 9700 eyes that underwent myopic lasik and he found 117 eyes with corneal pachymetry <500 microns and a follow up of at least 2 years with no report of corneal ectasia [17]. Kymionis et al, also showed the results of 124 eyes with thin corneas less than 500 microns that underwent excimer laser cornea refractive surgery (either PRK or LASIK) observing a good predictability (mean predictability of 0.08 ± 0.40 D for PRK group, 0.14 ± 0.55D for the LASIK group) and no ectasia during the follow-up (1 year) [27].

Corneal thickness has been considered as an inherent sign of structural stability, hence different authors have included thin corneas as a risk factor to develop postoperative keratectasia after excimer laser corneal refractive surgery [13,17,27–30].   However the question if thin corneas should be considered as "weak" corneas and therefore as an independent risk for post-LASIK ectasia is yet in dispute.   Recent evidence, including the present study, has failed to categorize thinner than normal corneas as independent risk for developing keratectasia after LASIK or PRK, since not only thin corneas perform as efficiently and safely than normal thickness corneas after refractive surgery but they have

not showed a trend over time to evolve in to ectasia. Focusing on a flap thickness tailored to the initial corneal thickness and to the amount of ablation has been a more important issue on the debate, since the evidence from the work of Santhiago et al [14], have shown that the percent of tissue altered ≥40% (obtained from the quotient of the sum of flap thickness and ablation depth over the central corneal thickness) was a more robust indicator that other individual variables (included CCT <510µm) for the development of corneal ectasia after LASIK in eyes with normal topography. In our series a mean PTA of 0.35 ± 0.04 was achieved and although the recommendation in these patients is to create flaps of precise thickness using the femtosecond laser, we observed an acceptable flap thickness using a mechanical microkeratome (postoperative flap thickness 128.66 ± 17.09µm).

A weakness of this study is its retrospective nature and the limited follow up to 13 months. However it is a large retrospective cohort of patients eyes with thinner than "normal" corneas and normal topography that underwent LASIK and along with previous studies of Caster [15] (109 eyes), Kymionis [27] (56 eyes with LASIK and 68 with PRK), Binder [11] (107 eyes) and Tomita [16] (291 eyes, case control) it contributes with evidence arguing against thin corneas as an independent risk factor for keratectasia after ablative corneal surgery.

In conclusion, we observed that LASIK surgery in patients with corneas thinner that "normal" (<540µm) is safe, efficient and predictable at 1 year follow up for myopic refractive corrections with no evidence of postoperative keratectasia. Evidence in this and similar works suggest that LASIK surgery in eyes with preoperative thinner than

normal cornea and normal topography may not be a risk factor if a fair residual stromal bed (at least 300 μm) and a PTA <40% is ensured.   Longer follow up and larger cohorts of patients are needed to support and reinforce the proposition that thinner than normal corneas perform as efficiently and safely than normal thickness corneas after excimer refractive surgery.

10. CONCLUSIONES / CONCLUSIONS

Español / Spanish

I. El espesor corneal es determinado por varios factores y entre otros, varía con la etnicidad y edad y existe un ampio rango de valores normales de espesor corneal central en la población estudiada.

II. Un espesor corneal "delgado" no esta asociado con patología y no puede ser considerado individualmente como factor de riesgo para cirugía fotorefractiva.

III. Sujetos con espesores centrales corneales delgados (menores al promedio de nuestra población), tuvieron un desempeño normal al ser sometidos a Cirugía Fotorefractiva (Queratomileusis in Situ asitida por Laser) y en el tiempo de seguimiento estudiado no se presento ningúna ectasia corneal.

Inglés / English

I. Corneal thickness is determined by several factors and among others, varies with ethnicity and age and there is a wide range of normal values of central corneal thickness in the population studied.

II. A "thin" corneal thickness is not associated with pathology and can not be considered individually as a risk factor for photorefractive surgery

III. Subjects with thin corneal central thickness (less than the average for the population of the study), had normal performance when undergoing Photorefractive Surgery (Keratomileusis Situ Situated by Laser) and no corneal ectasia was detected within the follow-up of the study.

11. FUTUROS PROYECTOS DE INVESTIGACIÓN

Nuestro conocimiento del comportamiento de corneas consideradas delgadadas es poco aun, por lo que consideramos que debemos aumentarlo a través del comprtamiento en diferentes situaciones clinicas y con mayor tiempo de seguimiento. Por lo que en un futuro proximo se planea comparar los pacientes con corneas delgadas sometidos a queratomileusis asisitida por laser con aquellos en los que se realizo una fotoqueratectomia refractiva de superfcie. Tambén el valorar aquellas corneas por debajo de 500 micras que es considerado como un parametro ablsoluto para no ser sometido a cirugía fotorefractiva.

12.BIBLIOGRAFÍA.

Sección I.

Factors Influencing Central Corneal Thickness

1. Farjo AA, Brumm M V., Soong HK. Corneal Anatomy, Physiology, and Wound Healing. In: Yanoff M, Duker JS, editors. Ophthalmology. 4th ed. Elsevier Inc.; 2014. p. 163–7.

2. Shih CY, Graff Zivin JS, Trokel SL, Tsai JC. Clinical Significance of Central Corneal Thickness in the Managementof Glaucoma. Arch Ophthalmol. 2004 Sep 1;122(9):1270.

3. Gordon MO, Beiser JA, Brandt JD, Heuer DK, Higginbotham EJ, Johnson CA, et al. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. Arch Ophthalmol (Chicago, Ill 1960). 2002 jun;120(6):714-20-30.

4. Randleman JB, Woodward M, Lynn MJ, Stulting RD. Risk Assessment for Ectasia after Corneal Refractive Surgery. Ophthalmology. 2008 Jan;115(1):37–50.

5. Tabbara K, Kotb A. Risk Factors for Corneal Ectasia after LASIK. Ophthalmology. 2006 Sep;113(9):1618–22.

6. Emara B, Probst LE, Tingey DP, Kennedy DW, Willms LJ, Machat J. Correlation of intraocular pressure and central corneal thickness in normal myopic eyes and after laser in situ keratomileusis. J Cataract Refract Surg. 1998 Oct; 24(10):1320–5.

7. Rabinowitz YS. Keratoconus. Surv Ophthalmol. 1998;42(4):297–319.

8. Rüfer F, Schröder A, Erb C. White-to-white corneal diameter: normal values in healthy humans obtained with the Orbscan II topography system. Cornea. 2005 Apr;24(3):259–61.

9.   Khng C, Osher RH. Evaluation of the relationship between corneal diameter and lens diameter. J Cataract Refract Surg. 2008 Mar;34(3):475–9.

10. Beebe DC. Maintaining transparency: A review of the developmental physiology and pathophysiology of two avascular tissues. Semin Cell Dev Biol. 2008 Apr;19(2):125–33.

11. Schmoll T, Unterhuber A, Kolbitsch C, Le T, Stingl A, Leitgeb R. Precise thickness measurements of Bowman's layer, epithelium, and tear film. Optom Vis Sci. 2012 May;89(5):E795-802.

12. Hanna C, Bicknell DS, O'Brien JE. Cell turnover in the adult human eye. Arch Ophthalmol (Chicago, Ill   1960). 1961 May;65:695–8.

13. Tao A, Wang J, Chen Q, Shen M, Lu F, Dubovy SR, et al. Topographic thickness of Bowman's layer determined by ultra-high resolution spectral domain-optical coherence tomography. Invest Ophthalmol Vis Sci. 2011 Jun 1;52(6):3901–7.

14. Patel S, McLaren J, Hodge D, Bourne W. Normal human keratocyte density and corneal thickness measurement by using confocal microscopy in vivo. Invest Ophthalmol Vis Sci. 2001 Feb;42(2):333–9.

15. Reinstein DZ, Archer TJ, Gobbe M, Silverman RH, Coleman DJ. Stromal Thickness in the Normal Cornea: Three-Dimensional Display with Artemis Very High-Frequency Digital Ultrasound. J Refract Surg. 2009 Sep 1;25(9):776–86.

16. Radner W, Zehetmayer M, Aufreiter R, Mallinger R. Interlacing and cross-angle distribution of collagen lamellae in the human cornea. Cornea. 1998 Sep;17(5):537–43.

17. Birk DE. Type V collagen: heterotypic type I/V collagen interactions in the regulation of fibril

assembly. Micron. 2001 Apr;32(3):223–37.

18. Rawe IM, Zhan Q, Burrows R, Bennett K, Cintron C. Beta-ig. Molecular cloning and in situ hybridization in corneal tissues. Invest Ophthalmol Vis Sci. 1997 Apr;38(5):893–900.

19. Bowling B, Kanski J. Kanski's Clinical Ophthalmology A Systematic Approach. 8th ed. Elsevier Health Sciences, editor. Elsevier; 2016. 928 p.

20. Cogan DG, Kuwabara T. Growth and regenerative potential of Descemet's membrane. Trans Ophthalmol Soc U K. 1971;91:875–94.

21. Waring GO, Bourne WM, Edelhauser HF, Kenyon KR. The corneal endothelium. Normal and pathologic structure and function. Ophthalmology. 1982 Jun;89(6):531–90.

22. Zavala J, López Jaime GR, Rodríguez Barrientos CA, Valdez-Garcia J. Corneal endothelium: developmental strategies for regeneration. Eye (Lond). 2013 May 8;27(5):579–88.

23. Dua HS, Faraj LA, Said DG, Gray T, Lowe J. Human corneal anatomy redefined: a novel pre-Descemet's layer (Dua's layer). Ophthalmology. 2013 Sep;120(9):1778–85.

24. Zaki AA, Elalfy MS, Said DG, Dua HS. Deep anterior lamellar keratoplasty--triple procedure: a useful clinical application of the pre-Descemet's layer (Dua's layer). Eye (Lond). 2015 Mar 31;29(3):323–6.

25. McKee HD, Irion LCD, Carley FM, Brahma AK, Jafarinasab MR, Rahmati-Kamel M, et al. Re: Dua et al.: Human corneal anatomy redefined: a novel pre-Descemet layer (Dua's layer) (Ophthalmology 2013;120:1778-85). Ophthalmology. 2014 May;121(5):e24-5.

26. Ashwin PT, McDonnell PJ. Collagen cross-linkage: a comprehensive review and directions for future research. Br J Ophthalmol. 2010 Aug 1;94(8):965–70.

27. Barnard K, Light ND, Sims TJ, Bailey AJ. Chemistry of the collagen cross-links. Origin and partial characterization of a putative mature cross-link of collagen. Biochem J. 1987 Jun 1;244(2):303–9.

28. Hovakimyan M, Guthoff RF, Stachs O. Collagen cross-linking: current status and future directions. J Ophthalmol. 2012;2012:406850.

29. Siegel RC. Collagen cross-linking. Synthesis of collagen cross-links in vitro with highly purified lysyl oxidase. J Biol Chem. 1976 Sep 25;251(18):5786–92.

30. Albert DM, Jakobiec FA, Miller JW. Principles and practice of ophthalmology. Saunders W B Co, editor. Saunders/Elsevier; 2008. 5461 p.

31. Vitart V, Bencić G, Hayward C, Skunca Herman J, Huffman J, Campbell S, et al. New loci associated with central cornea thickness include COL5A1, AKAP13 and AVGR8. Hum Mol Genet. 2010 Nov 1;19(21):4304–11.

32. Fratzl P. Collagen - Structure and Mechanics. Springer Science & Business Media, editor. New York: Springer; 2008. 506 p.

33. Elsheikh A, Wang D, Brown M, Rama P, Campanelli M, Pye D. Assessment of corneal biomechanical properties and their variation with age. Curr Eye Res. 2007 Jan 2;32(1):11–9.

34. Seiler T, Huhle S, Spoerl E, Kunath H. Manifest diabetes and keratoconus: a retrospective case-control study. Graefes Arch Clin Exp Ophthalmol. 2000 Oct;238(10):822–5.

35. Carlson EC, Liu C-Y, Chikama T, Hayashi Y, Kao CW-C, Birk DE, et al. Keratocan, a cornea-specific keratan sulfate proteoglycan, is regulated by lumican. J Biol Chem. 2005 Jul 8;280(27):25541–7.

36.   Ihanamäki T, Pelliniemi LJ, Vuorio E. Collagens and collagen-related matrix components in the human and mouse eye. Prog Retin Eye Res. 2004 Jul;23(4):403–34.

37.   Müller LJ, Pels L, Vrensen GF. Ultrastructural organization of human corneal nerves. Invest Ophthalmol Vis Sci. 1996 Mar;37(4):476–88.

38.   Bonanno JA. Identity and regulation of ion transport mechanisms in the corneal endothelium. Prog Retin Eye Res. 2003 Jan;22(1):69–94.

39.   Edelhauser HF. The balance between corneal transparency and edema: the Proctor Lecture. Invest Ophthalmol Vis Sci. 2006 May 1;47(5):1754–67.

40.   DelMonte DW, Kim T. Anatomy and physiology of the cornea. J Cataract Refract Surg. 2011 Mar;37(3):588–98.

41.   Marfurt CF, Cox J, Deek S, Dvorscak L. Anatomy of the human corneal innervation. Exp Eye Res. 2010 Apr;90(4):478–92.

42.   Müller LJ, Marfurt CF, Kruse F, Tervo TMT. Corneal nerves: structure, contents and function. Exp Eye Res. 2003 May;76(5):521–42.

43.   Spadea L, Salvatore S, Vingolo EM. Corneal Sensitivity in Keratoconus: A Review of the Literature. Sci World J. 2013;2013:1–7.

44.   Zander E, Weddell G. Observations on the innervation of the cornea. J Anat. 1951 Jan;85(1):68–99.

45.   Kraff CR, Robin JB. Normal Corneal Topography. In: Schanzlin DJ, Robin JB, editors. Corneal Topography   Measuring and Modifying the Cornea. New York: Springer New York; 1992. p. 33–8.

46. González-Pérez J, González-Méijome JM, Rodríguez Ares MT, Parafita MA. Central corneal thickness measured with three optical devices and ultrasound pachometry. Eye Contact Lens. 2011 Mar;37(2):66–70.

47. Nguyen TD, Jones RE, Boyce BL. A nonlinear anisotropic viscoelastic model for the tensile behavior of the corneal stroma. J Biomech Eng. 2008 Aug;130(4):41020.

48. Comaish IF, Lawless MA. Progressive post-LASIK keratectasia: biomechanical instability or chronic disease process? J Cataract Refract Surg. 2002 Dec;28(12):2206–13.

49. Pinheiro MN, Bryant MR, Tayyanipour R, Nassaralla BA, Wee WR, McDonnell PJ. Corneal integrity after refractive surgery. Effects of radial keratotomy and mini-radial keratotomy. Ophthalmology. 1995 Feb;102(2):297–301.

50. Wang JQ, Zeng YJ, Li XY. Influence of some operational variables on the radial keratotomy operation. Br J Ophthalmol. 2000 Jun;84(6):651–3.

51. Müller LJ, Pels E, Vrensen GF. The specific architecture of the anterior stroma accounts for maintenance of corneal curvature. Br J Ophthalmol. 2001 Apr;85(4):437–43.

52. Wilson SE, Hong JW. Bowman's layer structure and function: critical or dispensable to corneal function? A hypothesis. Cornea. 2000 Jul;19(4):417–20.

53. Belin MW, Khachikian SS. An introduction to understanding elevation-based topography: how elevation data are displayed - a review. Clin Experiment Ophthalmol. 2009 Jan;37(1):14–29.

54. Brody J, Waller S, Wagoner M. Corneal topography: history, technique, and clinical uses. Int Ophthalmol Clin. 1994;34(3):197–207.

55. American Academy of Ophthalmology. Corneal topography. American Academy of Ophthalmology. Ophthalmology. 1999 Aug;106(8):1628–38.

56. Belin MW, Zloty P. Accuracy of the PAR corneal topography system with spatial misalignment. CLAO J. 1993 Jan;19(1):64–8.

57. Belin MW, Litoff D, Strods SJ, Winn SS, Smith RS. The PAR Technology Corneal Topography System. Refract Corneal Surg. 1992;8(1):88–96.

58. Lackner B, Schmidinger G, Skorpik C. Validity and repeatability of anterior chamber depth measurements with Pentacam and Orbscan. Optom Vis Sci. 2005 Sep;82(9):858–61.

59. O'Donnell C, Maldonado-Codina C. Agreement and repeatability of central thickness measurement in normal corneas using ultrasound pachymetry and the OCULUS Pentacam. Cornea. 2005 Nov;24(8):920–4.

60. Schultze RL. Accuracy of corneal elevation with four corneal topography systems. J Refract Surg. 1998;14(2):100–4.

61. Uçakhan OO, Ozkan M, Kanpolat A. Corneal thickness measurements in normal and keratoconic eyes: Pentacam comprehensive eye scanner versus noncontact specular microscopy and ultrasound pachymetry. J Cataract Refract Surg. 2006 Jun;32(6):970–7.

62. Piñero DP, Alcón N. Corneal biomechanics: a review. Clin Exp Optom. 2015 Mar;98(2):107–16.

63. Liu J, Roberts CJ. Influence of corneal biomechanical properties on intraocular pressure measurement: quantitative analysis. J Cataract Refract Surg. 2005 Jan;31(1):146–55.

64. Ehlers N, Hjortdal J. Corneal thickness: Measurement and implications. Experimental Eye

Research. 2004.

65. Chen MC, Lee N, Bourla N, Hamilton DR. Corneal biomechanical measurements before and after laser in situ keratomileusis. J Cataract Refract Surg. 2008 Nov;34(11):1886–91.

66. Wang D, Liu M, Chen Y, Zhang X, Xu Y, Wang J, et al. Differences in the Corneal Biomechanical Changes After SMILE and LASIK. J Refract Surg. 2014 Oct 1;30(10):702–7.

67. Pepose JS, Feigenbaum SK, Qazi MA, Sanderson JP, Roberts CJ. Changes in corneal biomechanics and intraocular pressure following LASIK using static, dynamic, and noncontact tonometry. Am J Ophthalmol. 2007 Jan;143(1):39–47.

68. Garcia-Gonzalez M, Teus MA, Juhasz E. Flap thickness in femtosecond laser. J Refract Surg. 2015 Feb 1;31(2):140.

69. Tatar MG, Aylin Kantarci F, Yildirim A, Uslu H, Colak HN, Goker H, et al. Risk Factors in Post-LASIK Corneal Ectasia. J Ophthalmol. 2014;2014:1–4.

70. Toh T, Liew SHM, MacKinnon JR, Hewitt AW, Poulsen JL, Spector TD, et al. Central Corneal Thickness Is Highly Heritable: The Twin Eye Studies. Investig Opthalmology Vis Sci. 2005 Oct 1;46(10):3718.

71. Hoehn R, Zeller T, Verhoeven VJM, Grus F, Adler M, Wolfs RC, et al. Population-based meta-analysis in Caucasians confirms association with COL5A1 and ZNF469 but not COL8A2 with central corneal thickness. Hum Genet. 2012 Nov 20;131(11):1783–93.

72. Lu Y, Dimasi DP, Hysi PG, Hewitt AW, Burdon KP, Toh T, et al. Common genetic variants near the Brittle Cornea Syndrome locus ZNF469 influence the blinding disease risk factor central corneal thickness. PLoS Genet. 2010 May 13;6(5):e1000947.

73.   Hassan M ul, Rehman A ur, Abbas M, Fawad U, Bhatti N, Daud A. Relationship between Central Corneal Thickness and Intraocular Pressure in Selected Pakistani Population. Pakistan J Ophthalmol. 2010;26(2):79–82.

74.   Patwardhan AA, Khan M, Mollan SP, Haigh P. The importance of central corneal thickness measurements and decision making in general ophthalmology clinics: a masked observational study. BMC Ophthalmol. 2008 Jan 20;8(1):1.

75.   Doughty MJ, Zaman ML. Human corneal thickness and its impact on intraocular pressure measures: a review and meta-analysis approach. Surv Ophthalmol. 2000;44(5):367–408.

76.   Thomas R, Korah S, Muliyil J. The role of central corneal thickness in the diagnosis of glaucoma. Indian J Ophthalmol. 2000 Jun;48(2):107–11.

77.   Valdez-García JE, Hernandez-Camarena JC, Martínez-Muñoz R. 3-Year follow-up after Lasik: assessing the risk factors for retreatment. Int Ophthalmol. 2016 Feb 19;36(1):91–6.

78.   Santhiago MR, Smadja D, Gomes BF, Mello GR, Monteiro MLR, Wilson SE, et al. Association Between the Percent Tissue Altered and Post–Laser In Situ Keratomileusis Ectasia in Eyes With Normal Preoperative Topography. Am J Ophthalmol. 2014 Jul;158(1):87–95.e1.

79.   Torricelli AAM, Bechara SJ, Wilson SE. Screening of Refractive Surgery Candidates for LASIK and PRK. Cornea. 2014 Oct;33(10):1051–5.

80.   Valdez-García JE, Hernandez-Camarena JC, Lozano-Ramírez JF, Zavala J, Loya-García D, Merayo-Lloves J. Correlation of age, corneal curvature and spherical equivalent with central corneal thickness. Rev Mex Oftalmol. 2016; http://doi.org/10.1016/j.mexoft.2016.05.005

81.   Valdez-García JE, Sepúlveda R, Salazar-Martínez JJ, Lozano-Ramírez JF. Prevalence of

keratoconus in an adolescent population. Rev Mex Oftalmol. 2014;88(3):95–8.

82. Farjadnia M, Naderan M. Corneal cross-linking treatment of keratoconus. Oman J Ophthalmol. 2015;8(2):86–91.

83. Bykhovskaya Y, Margines B, Rabinowitz YS. Genetics in Keratoconus: where are we? Eye Vis. 2016 Dec 27;3(1):16.

84. Gao X, Gauderman WJ, Liu Y, Marjoram P, Torres M, Haritunians T, et al. A Genome-Wide Association Study of Central Corneal Thickness in Latinos. Investig Opthalmology Vis Sci. 2013 Apr 1;54(4):2435.

85. Gordon-Shaag A, Millodot M, Shneor E, Liu Y. The Genetic and Environmental Factors for Keratoconus. Biomed Res Int.;2015:1–19.

86. Lu Y, Vitart V, Burdon KP, Khor CC, Bykhovskaya Y, Mirshahi A, et al. Genome-wide association analyses identify multiple loci associated with central corneal thickness and keratoconus. Nat Genet. 2013 Feb 6;45(2):155–63.

87. Roberts JE. Ocular phototoxicity. J Photochem Photobiol B. 2001 Nov 15;64(2–3):136–43.

88. Aghaian E, Choe JE, Lin S, Stamper RL. Central corneal thickness of Caucasians, Chinese, Hispanics, Filipinos, African Americans, and Japanese in a glaucoma clinic. Ophthalmology. 2004;111(12):2211–9.

89. Haseltine SJ, Pae J, Ehrlich JR, Shammas M, Radcliffe NM. Variation in corneal hysteresis and central corneal thickness among black, hispanic and white subjects. Acta Ophthalmol. 2012 Dec;90(8):e626–31.

90. Wong AC-M, Wong C-C, Yuen NS-Y, Hui S-P. Correlational study of central corneal thickness

measurements on Hong Kong Chinese using optical coherence tomography, Orbscan and ultrasound pachymetry. Eye. 2002 Nov 13;16(6):715–21.

91.   Hwang YH, Kim HK, Sohn YH, Namil Study Group, Korean Glaucoma Society. Central Corneal Thickness in a Korean Population: The Namil Study. Investig Opthalmology Vis Sci. 2012 Oct 5;53(11):6851.

92.   Godar ST, Kaini KR, Khattri JB. Factors Affecting the Central Corneal Thickness in Nepalese Population. Nepal J Med Sci. 2012;1(1):7–10.

93.   Iyamu E, Iyamu JE, Oghovwerha L. Anthropometry, amplitude of accommodation, and spherical equivalent refractive error in a nigerian population. ISRN Ophthalmol. 2012:295613.

94.   Eballe AO, Epée E, Godefroy K, Bella AL. Analysis of central corneal thickness in black Cameroonian children. Clin Optom. 2010 Nov; 2:113–7.

95.   Rüfer F, Sander S, Klettner A, Frimpong-Boateng A, Erb C. Characterization of the Thinnest Point of the Cornea Compared With the Central Corneal Thickness in Normal Subjects. Cornea. 2009 Feb;28(2):177–80.

96.   Gros-Otero J, Arruabarrena-Sánchez C, Teus M. [Central corneal thickness in a healthy Spanish population]. Arch Soc Esp Oftalmol. 2011 Mar;86(3):73–6.

97.   Landers JA, Billing KJ, Mills RA, Henderson TR, Craig JE. Central Corneal Thickness of Indigenous Australians Within Central Australia. Am J Ophthalmol. 2007 Feb;143(2):360–2.

98.   Bamashmus MA, Saleh MF, Mousa A, Abdulrahman M, Fawzi M. Central corneal pachymetry in Yemeni patients undergoing refractive surgery. Saudi Med J. 2014

Jan;35(1):56–62.

99.   Valbon BF, Ambrósio R, Fontes BM, Luz A, Roberts CJ, Alves MR. Ocular biomechanical metrics by CorVis ST in healthy Brazilian patients. J Refract Surg. 2014 Jul 1;30(7):468–73.

100.   Nangia V, Jonas JB, Sinha A, Matin A, Kulkarni M. Central corneal thickness and its association with ocular and general parameters in Indians: the Central India Eye and Medical Study. Ophthalmology. 2010 Apr;117(4):705–10.

101.   Channa R, Mir F, Shah MN, Ali A, Ahmad K. Central corneal thickness of Pakistani adults. J Pak Med Assoc. 2009 Apr;59(4):225–8.

102.   Hahn S, Azen S, Ying-Lai M, Varma R, Los Angeles Latino Eye Study Group. Central corneal thickness in Latinos. Invest Ophthalmol Vis Sci. 2003 Apr;44(4):1508–12.

103.   Goktas A, Gumus K, Mirza GE, Crockett C, Karakucuk S, Cavanagh HD. Corneal endothelial characteristics and central corneal thickness in a population of Turkish cataract patients. Eye Contact Lens. 2012 May;38(3):142–5.

104.   Yaeger R, Avila-Bront A, Abdul K, Nolan PC, Grann VR, Birchette MG, et al. Comparing genetic ancestry and self-described race in african americans born in the United States and in Africa. Cancer Epidemiol Biomarkers Prev. 2008 Jun 1;17(6):1329–38.

105.   Watson PG, Hazleman BL, McCluskey, Peter M. MD, Pavesio, Carlos E. MD. The Sclera and Systemic Disorders. 3th ed. London: Jp Medical Ltd; 2012. 366 p.

106.   Segev F, Héon E, Cole WG, Wenstrup RJ, Young F, Slomovic AR, et al. Structural abnormalities of the cornea and lid resulting from collagen V mutations. Invest Ophthalmol Vis Sci. 2006 Feb 1;47(2):565–73.

107. Wenstrup RJ, Florer JB, Brunskill EW, Bell SM, Chervoneva I, Birk DE. Type V collagen controls the initiation of collagen fibril assembly. J Biol Chem. 2004 Dec 17;279(51):53331–7.

108. Vithana EN, Aung T, Khor CC, Cornes BK, Tay W-T, Sim X, et al. Collagen-related genes influence the glaucoma risk factor, central corneal thickness. Hum Mol Genet. 2011 Feb 15;20(4):649–58.

109. Li X, Bykhovskaya Y, Canedo ALC, Haritunians T, Siscovick D, Aldave AJ, et al. Genetic association of COL5A1 variants in keratoconus patients suggests a complex connection between corneal thinning and keratoconus. Invest Ophthalmol Vis Sci. 2013 Apr 12;54(4):2696–704.

110. Abu A, Frydman M, Marek D, Pras E, Nir U, Reznik-Wolf H, et al. Deleterious Mutations in the Zinc-Finger 469 Gene Cause Brittle Cornea Syndrome. Am J Hum Genet. 2008;82(5):1217–22.

111. Rohrbach M, Spencer HL, Porter LF, Burkitt-Wright EMM, Bürer C, Janecke A, et al. ZNF469 frequently mutated in the brittle cornea syndrome (BCS) is a single exon gene possibly regulating the expression of several extracellular matrix components. Mol Genet Metab. 2013 Jul;109(3):289–95.

112. Burkitt Wright EMM, Spencer HL, Daly SB, Manson FDC, Zeef LAH, Urquhart J, et al. Mutations in PRDM5 in brittle cornea syndrome identify a pathway regulating extracellular matrix development and maintenance. Am J Hum Genet. 2011 Jun 10;88(6):767–77.

113. Lechner J, Porter LF, Rice A, Vitart V, Armstrong DJ, Schorderet DF, et al. Enrichment of pathogenic alleles in the brittle cornea gene, ZNF469, in keratoconus. Hum Mol Genet.

2014 Oct 15;23(20):5527–35.

114. Abu-Amero K, Kondkar A, Chalam K. An Updated Review on the Genetics of Primary Open Angle Glaucoma. Int J Mol Sci. 2015 Dec 4;16(12):28886–911.

115. Igo RP, Kopplin LJ, Joseph P, Truitt B, Fondran J, Bardenstein D, et al. Differing roles for TCF4 and COL8A2 in central corneal thickness and fuchs endothelial corneal dystrophy. den Hollander AI, editor. PLoS One. 2012 Oct 23;7(10): e46742.

116. Robertson DM, Ladage PM, Yamamoto N, Jester J V, Petroll WM, Cavanagh HD. Bcl-2 and Bax regulation of corneal homeostasis in genetically altered mice. Eye Contact Lens. 2006 Jan;32(1):3–7.

117. Dimasi DP, Chen JY, Hewitt AW, Klebe S, Davey R, Stirling J, et al. Novel quantitative trait loci for central corneal thickness identified by candidate gene analysis of osteogenesis imperfecta genes. Hum Genet. 2010 Jan 28;127(1):33–44.

118. Ramaesh T, Collinson JM, Ramaesh K, Kaufman MH, West JD, Dhillon B. Corneal abnormalities in Pax6+/- small eye mice mimic human aniridia-related keratopathy. Invest Ophthalmol Vis Sci. 2003 May;44(5):1871–8.

119. Desronvil T, Logan-Wyatt D, Abdrabou W, Triana M, Jones R, Taheri S, et al. Distribution of COL8A2 and COL8A1 gene variants in Caucasian primary open angle glaucoma patients with thin central corneal thickness. Mol Vis. 2010 Oct 29; 16:2185–91.

120. Hopfer U, Fukai N, Hopfer H, Wolf G, Joyce N, Li E, et al. Targeted disruption of Col8a1 and Col8a2 genes in mice leads to anterior segment abnormalities in the eye. FASEB J. 2005 Aug 1;19(10):1232–44.

121. Meij JTA, Carlson EC, Wang L, Liu C-Y, Jester J V, Birk DE, et al. Targeted expression of a lumican transgene rescues corneal deficiencies in lumican-null mice. Mol Vis. 2007 Oct 18;13:2012–8.

122. Kaushik S, Singh Pandav S. Measuring Intraocular Pressure: How Important is the Central Corneal Thickness? J Curr Glaucoma Pract. 2007;1(1):21–4.

123. Harper CL, Boulton ME, Bennett D, Marcyniuk B, Jarvis-Evans JH, Tullo AB, et al. Diurnal variations in human corneal thickness. Br J Ophthalmol. 1996 Dec;80(12):1068–72.

124. du Toit R, Vega JA, Fonn D, Simpson T. Diurnal variation of corneal sensitivity and thickness. Cornea. 2003 Apr;22(3):205–9.

125. Hon Y, Wan K, Chen G-Z, Lu S-H, Lam DCC, Lam AKC. Diurnal Variation of Corneal Tangent Modulus in Normal Chinese. Cornea. 2016 Aug 17;35(12):1600–4.

126. Cejka C, Pláteník J, Sirc J, Ardan T, Michálek J, Brůnová B, et al. Changes of corneal optical properties after UVB irradiation investigated spectrophotometrically. Physiol Res. 2010;59(4):591–7.

127. Young AR. Acute effects of UVR on human eyes and skin. Prog Biophys Mol Biol. 2006 Sep;92(1):80–5.

128. Riley M V, Susan S, Peters MI, Schwartz CA. The effects of UV-B irradiation on the corneal endothelium. Curr Eye Res. 1987 Aug;6(8):1021–33.

129. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. Am J Ophthalmol. 2003 May;135(5):620–7.

130. Meek KM, Hayes S. Corneal cross-linking - a review. Ophthalmic Physiol Opt. 2013

Mar;33(2):78–93.

131.   Morris DS, Somner JEA, Scott KM, McCormick IJC, Aspinall P, Dhillon B. Corneal Thickness at High Altitude. Cornea. 2007 Apr;26(3):308–11.

132.   Karakucuk S, Mujdeci M, Baskol G, Arda H, Gumus K, Oner A. Changes in central corneal thickness, intraocular pressure, and oxidation/antioxidation parameters at high altitude. Aviat Space Environ Med. 2012 Nov;83(11):1044–8.

133.   Herndon LW, Weizer JS, Stinnett SS. Central Corneal Thickness as a Risk Factor for Advanced Glaucoma Damage. Arch Ophthalmol. 2004 Jan 1;122(1):17.

134.   Wolffsohn JS, Safeen S, Shah S, Laiquzzaman M. Changes of Corneal Biomechanics With Keratoconus. Cornea. 2012 Aug;31(8):849–54.

135.   Urban B, Raczyńska D, Bakunowicz-Łazarczyk A, Raczyńska K, Krętowska M. Evaluation of Corneal Endothelium in Children and Adolescents with Type 1 Diabetes Mellitus. Mediators Inflamm. 2013; 2013:1–6.

136.   Roszkowska AM, Tringali CG, Colosi P, Squeri CA, Ferreri G. Corneal endothelium evaluation in type I and type II diabetes mellitus. Ophthalmologica. 1999;213(4):258–61.

137.   Lee JS, Oum BS, Choi HY, Lee JE, Cho BM. Differences in corneal thickness and corneal endothelium related to duration in Diabetes. Eye. 2006 Mar 15;20(3):315–8.

138.   Gul A, Cinal A, Caglar C, Yasar T, Kilic A. Comparing biometry in normal eyes of children with unilateral cataract/corneal disease to age-matched controls. Nepal J Ophthalmol. 2015 Jul 25;7(14):108–16.

139.   Khan S, Ali M, Zaheer N. Comparison of pre-operative central corneal thickness in pediatric

cataract cases versus normal. J Coll Physicians Surg Pak. 2014 Aug;24(8):561–4.

140. Lin D, Chen J, Liu Z, Wu X, Long E, Luo L, et al. Prevalence of Corneal Astigmatism and Anterior Segmental Biometry Characteristics Before Surgery in Chinese Congenital Cataract Patients. Sci Rep. 2016 Feb 25; 6:22092.

141. Burns RR, Bourne WM, Brubaker RF. Endothelial function in patients with cornea guttata. Invest Ophthalmol Vis Sci. 1981 Jan;20(1):77–85.

142. Kopplin LJ, Przepyszny K, Schmotzer B, Rudo K, Babineau DC, Patel S V, et al. Relationship of Fuchs Endothelial Corneal Dystrophy Severity to Central Corneal Thickness. Arch Ophthalmol. 2012 Apr 1;130(4):433–9.

143. Ozdamar Y, Berker N, Ertugrul G, Gurlevik U, Karakaya J, Ozkan SS. Is there a change of corneal thickness in uveitis with Behçet disease? Cornea. 2010 Nov;29(11):1265–7.

144. Wanichwecharungruang B, Laophulsuk V, Sopitanont S, Vanichvaranont S, Harncharoen K. Central corneal thickness in the central retinal vein occlusion fellow eyes. J Med Assoc Thai. 2010 Aug;93(8):943–9.

145. Zheng Y, Ge J, Huang G, Zhang J, Liu B, Hur Y-M, et al. Heritability of central corneal thickness in Chinese: the Guangzhou Twin Eye Study. Invest Ophthalmol Vis Sci. 2008 Oct 1;49(10):4303–7.

Sección II.

Correlation of age, corneal curvature and spherical equivalent with central corneal thickness

1.Ehlers N, Hjortdal J. Corneal thickness: measurement and implications. Exp Eye Res. 2004; 78:543---8.

2. Dutta D, Rao HL, Addepalli UK, et al. Corneal thickness in keratoconus: comparing optical, ultrasound, and optical coherence tomography pachymetry. Ophthalmology. 2013; 120:457---63.

3. Verdier DD, Sugar A, Baratz K, et al. Corneal thickness as a predictor of corneal transplant outcome. Cornea. 2013; 32:729---36.

4. Kettesy B, Nemeth G, Kemeny-Beke A, et al. Assessment of endothelial cell density and corneal thickness in corneal grafts an average of 5 years after penetrating keratoplasty. Wien Klin

Wochenschr. 2014; 126:286---90.

5. Kamiya K, Ishii R, Shimizu K, et al. Evaluation of corneal elevation, pachymetry and keratometry in keratoconic eyes with respect to the stage of Amsler---Krumeich classification. Br J Ophthalmol. 2014; 98:459---63.

6. Demir S, Ortak H, Yeter V, et al. Mapping corneal thickness using dual-scheimpflug imaging at different stages of keratoconus. Cornea. 2013; 32:1470---4.

7. Doughty MJ, Zaman ML. Human corneal thickness and its impact on intraocular pressure measures: a review and meta-analysis approach. Surv Ophthalmol. 2000; 44:367---408.

8. Browning AC, Bhan A, Rotchford AP, et al. The effect of corneal thickness on intraocular pressure measurement in patients with corneal pathology. Br J Ophthalmol. 2004; 88:1395---9.

9. Binder PS. Analysis of ectasia after laser in situ keratomileusis: risk factors. J Cataract Refract Surg. 2007; 33:1530---8.

10. Binder PS, Trattler WB. Evaluation of a risk factor scoring system for corneal ectasia after LASIK in eyes with normal topography. J Refract Surg. 2010; 26:241---50.

11. Randleman JB, Russell B, Ward MA, et al. Risk factors and prognosis for corneal ectasia after LASIK. Ophthalmology. 2003; 110:267---75.

12. Tatar MG, Aylin Kantarci F, Yildirim A, et al. Risk factors in Post- LASIK corneal ectasia. J Ophthalmol. 2014; 2014:204191.

13. Tomita M, Watabe M, Mita M, et al. Long-term observation and evaluation of femtosecond laser-assisted thin-flap laser in situ keratomileusis in eyes with thin corneas but normal topography. J Cataract Refract Surg. 2014; 40:239---50.

14. Aghaian E, Choe JE, Lin S, et al. Central corneal thickness of Caucasians, Chinese, Hispanics, Filipinos, African Americans, and Japanese in a glaucoma clinic. Ophthalmology. 2004; 111:2211---9.

15. Haseltine SJ, Pae J, Ehrlich JR, et al. Variation in corneal hysteresis and central corneal thickness among black, hispanic and white subjects. Acta Ophthalmol. 2012;90: e626---31.

16. Wong AC-M, Wong C-C, Yuen NS-Y, et al. Correlational study of central corneal thickness measurements on Hong Kong Chinese using optical coherence tomography, Orbscan and ultrasound pachymetry. Eye (Lond). 2002; 16:715---21.

17. Gros-Otero J, Arruabarrena-Sánchez C, Teus M. Central corneal thickness in a healthy Spanish population. Arch Soc Española Oftalmol. 2011; 86:73---6.

18. Iyamu E, Osuobeni E. Age, gender, corneal diameter, corneal curvature and central corneal thickness in Nigerians with normal intra ocular pressure. J Optom. 2012; 5:87---97.

19. Hahn S, Azen S, Ying-Lai M, et al. Central corneal thickness in Latinos. Invest Ophthalmol Vis Sci. 2003; 44:1508---12.

20. Galgauskas S, Juodkaite G, Tutkuvien˙e J. Age-related changes in central corneal thickness in normal eyes among the adult Lithuanian population. Clin Interv Aging. 2014; 9:1145---51.

21. Toh T, Liew SHM, MacKinnon JR, et al. Central corneal thickness is highly heritable: the twin eye studies. Invest Ophthalmol Vis Sci. 2005; 46:3718---22.

22. Zheng Y, Ge J, Huang G, et al. Heritability of central corneal thickness in Chinese: the Guangzhou Twin Eye Study. Invest Ophthalmol Vis Sci. 2008; 49:4303---7.

23. Hoehn R, Zeller T, Verhoeven VJM, et al. Population-based metaanalysis in Caucasians confirms association with COL5 A1 and ZNF469 but not COL8 A2 with central corneal thickness. Hum

Genet. 2012; 131:1783---93.

24. Segev F, Héon E, Cole WG, et al. Structural abnormalities of the cornea and lid resulting from collagen V mutations. Invest Ophthalmol Vis Sci. 2006; 47:565---73.

25. Morris DS, Somner JEA, Scott KM, et al. Corneal thickness at high altitude. Cornea. 2007; 26:308---11.

26. Riley MV, Susan S, Peters MI, et al. The effects of UV-B irradiation on the corneal endothelium. Curr Eye Res. 1987; 6:1021---33.

27. Suzuki S, Suzuki Y, Iwase A, et al. Corneal thickness in an ophthalmologically normal

Chen M-J, Liu Y-T, Tsai C-C, et al. Relationship between central corneal thickness, refractive error, corneal curvature, anterior chamber depth and axial length. J Chin Med Assoc.

2009; 72:133---7.

29. Prasad A, Fry K, Hersh PS. Relationship of age and refraction to central corneal thickness.

Cornea. 2011; 30:553---5.

30. Weizer JS, Stinnett SS, Herndon LW. Longitudinal changes in central corneal thickness and their relation to glaucoma status: an 8 year follow up study. Br J Ophthalmol. 2006;90: 732---6.

31. Siegfried CJ, Shui Y-B, Bai F, et al. Central corneal thickness correlates with oxygen levels in the human anterior chamber angle. Am J Ophthalmol. 2015; 159:457---62, e1.

32. Cohen SR, Polse KA, Brand RJ, Mandell RB. Humidity effects on corneal hydration. Invest Ophthalmol Vis Sci. 1990;31: 1282---7.

33. Erickson DH, Goodwin D, Anderson C, Hayes JR. Ocular pulse amplitude and associated glaucomatous risk factors in a healthy Hispanic population. Optometry. 2010;81: 408---13.

34. Valbon BF, Ambrósio R, Fontes BM, Luz A, Roberts CJ, Alves MR. Ocular biomechanical metrics by CorVis ST in healthy Brazilian patients. J Refract Surg. 2014; 30:468---73.

35. Elsheikh A, Wang D, Brown M, Rama P, Campanelli M, Pye D. Assessment of corneal biomechanical properties and their variation with age. Curr Eye Res. 2007; 32:11---9.

36. Groden LR, Shah VC. Safe LASIK: a primer. Int Ophthalmol Clin. 2006; 46:83---90.

37. Randleman JB, Woodward M, Lynn MJ, et al. Risk assessment for ectasia after corneal refractive surgery. Ophthalmology. 2008; 115:37---50.

38. Tatar MG, Aylin Kantarci F, Yildirim A, et al. Risk factors in post- LASIK corneal ectasia. J Ophthalmol. 2014:2014.

39. Caster AI, Friess DW, Potvin RJ. Absence of keratectasia after LASIK in eyes with preoperative central corneal thickness of 450 to 500 microns. J Refract Surg. 2007; 23:782---8.

40. Chen MC, Lee N, Bourla N, et al. Corneal biomechanical measurements before and after laser in situ keratomileusis. J Cataract Refract Surg. 2008; 34:1886---91.

41. Wang D, Liu M, Chen Y, et al. Differences in the corneal biomechanical changes after SMILE and LASIK. J Refract Surg. 2014; 30:702---7.

42. Akhtar S, Alkatan H, Kirat O, et al. Ultrastructural and threedimensional study of post-LASIK ectasia cornea. Microsc Res Tech. 2014; 77:91---8.

43. Abahussin M, Hayes S, Edelhauser H. A microscopy study of the structural features of post-LASIK human corneas. PLoS ONE. 2013;8:e63268.

44. Rüfer F, Sander S, Klettner A, et al. Characterization of the thinnest point of the cornea compared with the central corneal thickness in normal subjects. Cornea. 2009; 28:177---80.

45. Malik NS, Moss SJ, Ahmed N, et al. Ageing of the human corneal stroma: structural and biochemical changes. Biochim Biophys. Acta. 1992; 1138:222---8.

Sección III

Safety and Efficacy of Myopic LASIK performed on Thin Corneas

1. Varley GA, Huang D, Rapuano CJ, et al (2004) LASIK for hyperopia, hyperopic astigmatism, and mixed astigmatism: a report by the American Academy of Ophthalmology. Ophthalmology 111: 1604–17.

2. Sutton G, Lawless M, Hodge C (2014) Laser in situ keratomileusis in 2012: a review. Clin Exp Optom 97: 18–29.

3. Hammond SD, Puri AK, Ambati BK (2004) Quality of vision and patient satisfaction after LASIK. Curr Opin Ophthalmol 15: 328–32.

4. Reinstein DZ, Archer TJ, Gobbe M (2012) The History of LASIK. J Refract Surg 28: 291–298.

5. Gil-Cazorla R, Teus MA, De Benito-Llopis L, Mikropoulos DG (2011) Femtosecond laser vs mechanical microkeratome for hyperopic laser in situ keratomileusis. Am J Ophthalmol 152: 16–21.

6. Kashani S, Rajan M, Gartry D (2009) Wavefront-guided retreatment after primary wavefront-guided laser in situ keratomileusis in myopes and hyperopes: long-term follow-up. Am J Ophthalmol 147: 417–423.e2.

7. Moshirfar M, Fenzl CR, Meyer JJ, et al (2011) Simultaneous and sequential implantation of intacs and verisyse phakic intraocular lens for refractive improvement in keratectasia. Cornea 30: 158–63.

8. Marino GK, Torricelli AA, Giacomin N (2015) Accelerated Corneal Collagen Cross-linking for Postoperative LASIK Ectasia: Two-Year Outcomes. J Refract Surg 31: 380–4.

9. Salouti R, Nowroozzadeh MH, Makateb P (2014) Deep anterior lamellar keratoplasty for keratectasia after laser in situ keratomileusis. J Cataract Refract Surg 40: 2011–8.

10. Kim TH, Lee D, Lee H (2007) The safety of 250 microm residual stromal bed in preventing keratectasia after laser in situ keratomileusis (LASIK). J Korean Med Sci 22: 142–5.

11. Binder, P. S. Ectasia after laser in situ keratomileusis (2003) J Cataract Refract Surg 29: 2419–29.

12. Randleman JB, Russell B, Ward MA, et al (2003) Risk factors and prognosis for corneal

ectasia after LASIK. Ophthalmology 110: 267–275.

13. Randleman JB, Woodward M, Lynn MJ et al (2008) Risk Assessment for Ectasia after Corneal Refractive Surgery. Ophthalmology 115: 37-50.

14. Santhiago MR, Smadja D, Gomes BF et al (2014) Association between the percent tissue altered and post-laser in situ keratomileusis ectasia in eyes with normal preoperative topography. Am J Ophthalmol 158: 87–95. e1.

15. Caster AI, Friess DW, Potvin RJ (2007) Absence of keratectasia after LASIK in eyes with preoperative central corneal thickness of 450 to 500 microns. J Refract Surg 23: 782–8.

16. Tomita M, Watabe M, Mita M et al (2014) Long-term observation and evaluation of femtosecond laser-assisted thin-flap laser in situ keratomileusis in eyes with thin corneas but normal topography. J Cataract Refract Surg 40: 239–50.

17. Binder PS (2007) Analysis of ectasia after laser in situ keratomileusis: risk factors. J Cataract Refract. Surg 33: 1530–8.

18. Chen MC, Lee N, Bourla N et al (2008) Corneal biomechanical measurements before and after laser in situ keratomileusis. J. Cataract Refract. Surg. 34, 1886–1891.

19. Amoils SP, Deist MB, Gous P, Amoils PM (2000) Iatrogenic keratectasia after laser in situ keratomileusis for less than -4.0 to -7.0 diopters of myopia. J. Cataract Refract Surg 26: 967–77.

20. Binder PS, Trattler WB (2010) Evaluation of a Risk Factor Scoring System for Corneal Ectasia After LASIK in Eyes with Normal Topography. J. Refract. Surg. 26: 241–250.

21. Francis BA, Varma R, Chopra V (2008) Intraocular pressure, central corneal thickness, and

prevalence of open-angle glaucoma: the Los Angeles Latino Eye Study. Am J Ophthalmol 146: 741–6.

22. Aghaian E, Choe JE, Lin, S et al (2004) Central corneal thickness of Caucasians, Chinese, Hispanics, Filipinos, African Americans, and Japanese in a glaucoma clinic. Ophthalmology 111: 2211–9.

23. Doughty MJ, Zaman ML (2000) Human corneal thickness and its impact on intraocular pressure measures: a review and meta-analysis approach. Surv Ophthalmol 44: 367–408

24. Morris DS, Mujdeci M, Baskol G (2007) Corneal thickness at high altitude. Cornea 26: 308–11.

25. Riley MV, Susan S, Peters MI et al (1987) The effects of UV-B irradiation on the corneal endothelium. Curr Eye Res 6: 1021–33.

26. Valdez-García JE, Hrnandez-Camarena JC, Lozano-Ramírez JF (2016) Correlation of age, corneal curvature and spherical equivalent with central corneal thickness. Rev Mex Oftalmol http://dx.doi.org/10.1016/j.mexoft.2016.05.005

27. Kymionis GD, Bouzoukis D, Diakonis V (2007) Long-term results of thin corneas after refractive laser surgery. Am J Ophthalmol 144: 181–185.

28. Twa MD, Nichols JJ, Joslin CE (2004) Characteristics of corneal ectasia after LASIK for myopia. Cornea 23: 447–57.

29. Tabbara KF, Kotb AA (2006) Risk factors for corneal ectasia after LASIK. Ophthalmology 113: 1618–22.

13. DIVULGACIÓN CIENTÍFICA

13.1. Artículos científicos

1. Correlation of age, corneal curvature and spherical equivalent with central corneal thickness. Jorge E. Valdez-García, Julio C. Hernandez-Camaren, Juan F. Lozano-Ramíreza, Judith Zavala, Denise Loya-García, Jesús Merayo-Lloves Revista Mexicana de Oftalmologia · June 2016.

CLAVE: A Categoría A (Oftalmología).   Scimago Journal ranking, SJR: 0.101. H index: 5 Posición que ocupa la revista en el área: 100/109 Cuartil: Q4(oftalmología). ISSN: 01874529

2.   3-Year follow-up after Lasik: assessing the risk factors for retreatment. Valdez-García JE, Hernandez-Camarena JC, Martínez-Muñoz R. Int Ophthalmol. 2016 Feb 19;36(1):91–6.

Scimago Journal ranking, SJR: 0.526 H index: 33 Posición que ocupa la revista en el área: 50/109 Cuartil: Q2(oftalmología). ISSN: 01655701, 15732630.

3. Prevalence of keratoconus in an adolescent population**.** Jorge E. Valdez-García, Rubén Sepúlveda, Jessica J. Salazar-Martínez, Juan F. Lozano-Ramírez.   Revista Mexicana de Oftalmologia. 2014;88(3):95---98. Scimago Journal ranking, SJR: 0.101. H index: 5 Posición que ocupa la revista en el área: 100/109 Cuartil: Q4(oftalmología). ISSN: 01874529

13.2. Publicaciones enviadas pendientes de aceptación.

1. Factors Influencing Central Corneal Thickness. Jorge E. Valdez-Garcia, Judith Zavala-Marcos, Rocio Villafuerte-de la Cruz, Jesus Merayo-Lloves, Eduardo Camacho-Marinez, Eric Reyes-Mendoza. Enviado a Eye en abril 2017. Scimago Journal ranking, SJR: 1.132. H index: 71 Posición que ocupa la revista en el área: 20/109 Cuartil: Q1(oftalmología). ISSN: 095022X,14765454

2. Safety and Efficacy of Myopic LASIK performed on Thin Corneas Jorge E. Valdez-García MD, MA , Jesús Merayo-Lloves MD, PhD, MBA, DO, Denise Loya-García MD, Paloma López-Montemayor BN, Julio C. Hernandez-Camarena MD. BMC Ophthalmology. Eniado apublicacion abril 2017. Scimago journal ranking, SJR: 0.938. H index: 29 Posición que ocupa la revista en el área: 29/109 Cuartil: Q2(oftalmología). ISSN: 14712415

13.3 Resumenes Publicados.

1. Pachymetry Average in a Hispanic Population. Judith Zavala; Jorge Valdez; Ubaldo Martínez; Carlos-Alberto Rodríguez-Barrientos; Guillermo Mendoza; Ophthalmology Research Chair. Investigative Ophthalmology & Visual Science (ARVO Abstract) June 2013, Vol.54, 874. doi:

2. Post-Lasik refractive results on eyes with thin corneas. Paloma Lopez; Lorena Lam Franco; Jorge E Valdez; Julio C Hernandez; Jesus Merayo. Investigative Ophthalmology & Visual Science June (ARVO Abstract) 2015, Vol.56, 3950. DOI:

3. Refractive Surgery in the Elderly Population. Paloma Lopez; Julio C Hernandez; Jorge E Valdez. investigative Ophthalmology & Visual Science September (ARVO Abstract) 2016, Vol.57, 4883. doi:

4. Safety and Efficacy of Myopic LASIK performed in Thin Corneas. Jorge E. Valdez, Víctor Preciado-Gómez, Javier Gonzalez Lugo, Julio C Hernandez-Camarena, Jesus Merayo-Lloves. Investigative Ophthalmology & Visual Science September (ARVO Abstract) 2016, Vol.57 doi:

14. ANEXOS

14.1.   Correlation of age, corneal curvature and spherical equivalent with central corneal thickness. Jorge E. Valdez-García, Julio C. Hernandez-Camaren, Juan F. Lozano-Ramíreza, Judith Zavala, Denise Loya-García, Jesús Merayo-Lloves Revista Mexicana de Oftalmologia · June 2016.

14.2.   3-Year follow-up after Lasik: assessing the risk factors for retreatment. Valdez-García JE, Hernandez-Camarena JC, Martínez-Muñoz R. Int Ophthalmol. 2016 Feb 19;36(1):91–6.

14.3.   Prevalence of keratoconus in an adolescent population. Jorge E. Valdez-García, Rubén Sepúlveda, Jessica J. Salazar-Martínez, Juan F. Lozano-Ramírez.   Revista Mexicana de Oftalmologia. 2014;88(3):95---98. Scimago Journal ranking, SJR: 0.101. H index: 5 Posición que ocupa la revista en el área: 100/109 Cuartil: Q4(oftalmología). ISSN: 01874529

14.4.   Factors Influencing Central Corneal Thickness. Jorge E. Valdez-Garcia, Judith Zavala-Marcos, Rocio Villafuerte-de la Cruz, Jesus Merayo-Lloves, Eduardo Camacho-Marinez, Eric Reyes-Mendoza. Enviado a Eye en abril 2017.

14.5.   Safety and Efficacy of Myopic LASIK performed on Thin Corneas Jorge E. Valdez-García MD, MA , Jesús Merayo-Lloves MD, PhD, MBA, DO, Denise Loya-García MD, Paloma López-Montemayor BN, Julio C. Hernandez-Camarena MD. BMC Ophthalmology. Eniado apublicacion abril 2017.

Revista Mexicana de
Oftalmología

www.elsevier.es/mexoftalmo

ORIGINAL ARTICLE

Correlation of age, corneal curvature and spherical equivalent with central corneal thickness[☆]

Jorge E. Valdez-García[a,b,*], Julio C. Hernandez-Camarena[a,b], Juan F. Lozano-Ramírez[a], Judith Zavala[a], Denise Loya-García[b], Jesús Merayo-Lloves[c]

[a] Ophthalmology Research Chair, Tecnológico de Monterrey, School of Medicine, Mexico
[b] Ophthalmology and Visual Sciences Institute, Tecnológico de Monterrey, School of Medicine, Mexico
[c] Instituto Universitario Fernández-Vega, Universidad de Oviedo, Fundación de Investigación Oftalmológica, Mexico

Abstract

Objective: To describe the distribution of the central corneal thickness (CCT) measurements on a healthy Hispanic sample population and its correlation with age, mean simulated keratometry (SimK), and mean refractive spherical equivalent (MRSE).

Methods: Retrospective analysis on the records of healthy patients from the Ophthalmology and Visual Sciences Institute, Tecnologico de Monterrey, January 2015 to August 2015. CCT data, age, gender, corneal curvature, and spherical equivalent was obtained. A descriptive analysis and correlation by the Spearman method was performed. The sample was divided by age subgroups: <20 years old, $\geq$20 and $\leq$40 years, and >than 40 years old and correlation analysis with CCT values was determined.

Results: A total of 93 (186 eyes) patients were included. Mean age: 32.54 ± 12.04 years. 43% were women. Mean CCT: $545.69 \pm 36.88\,\mu m$, mean SimK: $43.56 \pm 1.90\,D$ and MRSE: $-2.54 \pm 3.15\,D$. No correlation was registered between CCT and the variables when analyzed with the Anderson–Darling ($p = 0.006$), Shapiro–Wilk ($p = 0.043$), and Kolmogorov–Smirnov ($p = 0.01$). CCT showed a bimodal distribution with higher density at $540\,\mu m$. Age groups <20 and >40 years showed significant difference in CCT ($p = 0.016$), a positive correlation with CCT was observed in the group <20 ($\rho = 0.596$, $p = 0.001$).

Conclusions: The findings regarding the lack of normality, the bimodal distribution ($540\,\mu m$), and the correlation between age and CCT in younger patients, may lead us to redefine the ''normal'' CCT value in our population in order to be used properly for clinical purposes.

Please cite this article in press as: Valdez-García JE, et al. Correlation of age, corneal curvature and spherical equivalent with central corneal thickness. Rev Mex Oftalmol. 2016. http://dx.doi.org/10.1016/j.mexoft.2016.05.005

PALABRAS CLAVE
Grosor corneal
central;
Distribución bimodal;
Edad;
Queratometría;
Equivalente esférico

Correlación de edad, curvatura corneal y equivalente esférico con el grosor central corneal

Resumen

Objetivo: Describir la distribución de las mediciones del grosor central corneal (GCC) en una población sana de hispanos y analizar su correlación con la edad, queratometría simulada promedio (SimK) y el equivalente esférico refractivo (EE).

Métodos: Análisis retrospectivo, pacientes sanos del Instituto de Oftalmología y Ciencias Visuales, Tecnológico de Monterrey (enero de 2015 a agosto de 2015). Se obtuvo GCC, edad, género, SimK y EE. Se realizó análisis descriptivo de las variables y se utilizó el método de Spearman para correlaciones. La muestra se dividió en 3 subgrupos (<20 años, $\geq$20 y $\leq$40, y > 40 años) para analizar la correlación entre GCC y edad.

Resultados: Se incluyeron un total de 93 pacientes (186 ojos). Edad promedio: 32.54 ± 12.04 años, 43% mujeres. GCC promedio: $545.69 \pm 36.88\,\mu m$, SimK promedio: 43.56 ± 1.90 D y el EE promedio: -2.54 ± 3.15 D. No había correlación entre GCC y edad, género, SimK o EE con análisis Anderson-Darling (p = 0.006), Shapiro-Wilk (p = 0.043) y Kolmogorov-Smirnov (p = 0.01). GCC mostró distribución bimodal, pico principal en $540\,\mu m$. Los subgrupos <20 años y >40 años, mostraron diferencia significativa (p = 0.016) al comparar GCC. Se observó correlación positiva entre grupo <20 años y GCC ($\rho = 0.596$, p = 0.001).

Conclusiones: La falta de normalidad en la distribución del GCC, la distribución bimodal ($540\,\mu m$) y la tendencia a observar mayor GCC en jóvenes, llevan a redefinir los valores «normales» de GCC en nuestra población, con la finalidad de ajustar su uso para propósitos clínicos.

© 2016 Sociedad Mexicana de Oftalmología. Publicado por Masson Doyma México S.A. Este es un artículo Open Access bajo la CC BY-NC-ND licencia (http://creativecommons.org/licencias/by-nc-nd/4.0/).

Introduction

Central corneal thickness (CCT) is one of the major parameters for measuring corneal health.[1,2] Its measurement is essential in the assessment, management and follow up of corneal ectatic diseases (i.e. keratoconus, post-LASIK ectasia) and corneal endothelium dysfunction, since the changes in the corneal thickness are directly associated with the severity of the disease.[3–6] CCT measurement is also essential in the management of glaucoma patients, given that applanation tonometry underestimates the intraocular pressure (IOP) in eyes with thin corneas and it overestimates this in thick corneas.[7,8] CCT has also been used as a predictor of graft survival and cell density measurement after penetrating keratoplasty, thicker corneas have shown a tendency to develop graft failure within 5 years post-surgery.[3] Thin corneas, along with low residual stromal bed thickness (<300 μm), deep ablation and abnormal corneal topography, have been considered as preoperative risk factors in corneal refractive surgery for developing corneal ectasia.[9–11] However, there is ongoing debate surrounding the precept that ''thinner'' corneas are indeed ''weaker'' corneas with biomechanical liability, since the influence of CCT over the long-term stability of LASIK procedures has not been demonstrated.[12,13]

Normal CCT values have been established by different research groups.[7] However, a large variability among different ethnic groups has been reported.[14–17] Age,[7,18,19] gender,[20] the transition from lower to higher humidity, UV radiation exposure, hereditability,[21,22] genetics,[23,24] altitude have also been associated with changes and variability in CCT.[25,26] Additionally, the correlation of different ocular parameters with CCT has been studied, including corneal radius and curvature,[27] anterior chamber depth, axial length,[28] the spherical equivalent,[29] visual acuity, and IOP.[30]

All the factors mentioned before and the controversial results regarding the use of CCT as a predictive parameter for different ocular procedures indicate that the ''normality'' concept for CCT needs to be re-evaluated so it can be used appropriately as a clinical parameter. In this study, we aimed to measure the CCT among healthy Hispanic patients, and to determine its correlation with age, gender, curvature, and spherical equivalent.

Materials and methods

A retrospective analysis of pachymetric measurements conducted between February 2012 and November 2012 at the Ophthalmology and Visual Sciences Institute (Tecnologico de Monterrey, School of Medicine, Monterrey, Mexico) was performed. Data from 93 healthy patients were obtained after calculating the optimal sample size using Raosoft® (Raosoft, Inc., Seattle, WA, USA) with a confidence interval (CI) of 90% and an error margin of 5% in a population of 600 patients. Patients with abnormal topography (inferior steepening, irregular pattern, non-orthogonal bowtie), contact lens users or with history of refractive surgery were excluded. The CCT was obtained using ultrasonic pachymetry (AccuPach VI; Accutome, Inc., Malvern, PA, USA). Briefly, the cornea was anesthetized with topical 1%

tetracaine and the patient was asked to adopt a face up position on the examination chair and solicited to fixate a target on the ceiling. The pachymeter probe was brought in contact with the cornea centrally and perpendicularly over the visual axis. CCT was recorded as the average of 9 consecutive acquisitions. This process was repeated for every individual CCT measurement.

Age, gender, mean simulated keratometry (SimK) (Orbscan II Software version 4.1, Bausch&Lomb, Rochester, NY, USA), and spherical equivalent data were also obtained. Patients with any ocular or corneal pathology as well as history of ocular surgery were excluded. Patients with diagnosis of cataract, but who did not have surgery, were included. Statistical analysis was performed using IBM SPSS® version 21 (IBM Corporation, Armonk, NY, USA). A descriptive analysis and Spearman's correlation of the variables were performed. The mean of the CCT values and their distribution were established via the Anderson–Darling, Shapiro–Wilk, and Kolmogorov–Smirnov tests. The sample was divided by the following age groups: <20 years, $\geq$20 and $\leq$40 years, and >than 40 years to perform a descriptive and comparative analysis by analysis of variance (ANOVA), as well as to conduct an independent samples t-test.

Results

A total of 93 patients (186 eyes) were included in the study, 43% ($n = 40$) were female. The mean age of the patients was 32.54 ± 12.04 years (range 21–54 years). The mean keratometry was 43.56 ± 1.90 diopters (D) and the mean spherical equivalent was -2.54 ± 3.15 D.

The mean CCT was $545.69 \pm 36.88\,\mu m$ (range 458–640 μm). The CCT showed a bimodal distribution with the first peak occurring at 540 μm and the second at 580 μm (Fig. 1). No association was observed between the pachymetry measurements and the mean keratometry, spherical equivalent, and age when analyzed with the Anderson–Darling ($p = 0.006$), Shapiro–Wilk ($p = 0.043$), and Kolmogorov–Smirnov ($p = 0.01$) tests. Pearson's test showed a correlation of -0.08 between pachymetry and age, 0.099 between pachymetry and keratometry, and 0.033 between pachymetry and the spherical equivalent. The
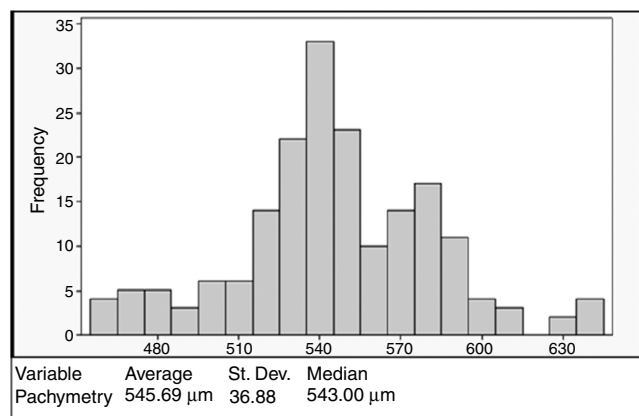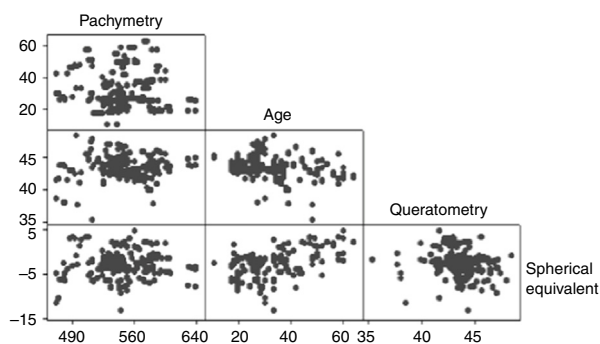

Figure 2 Matrix plot showing the correlation between CCT and the age, keratometry, and spherical equivalent variables.

Table 1 Central corneal thickness by age group.

Age group (years)	n	Mean CCT	Standard deviation	Range (μm)
<20	28	558.82	37.398	507–640
$\geq$20–$\leq$40	114	545.84	36.321	458–640
>40	44	536.93	36.256	458–600

CCT = central corneal thickness, n = number.

correlation between age and keratometry was -0.259 and the correlation between age and the spherical equivalent was -0.2 (Fig. 2).

The sample was divided in three age groups: <20 years, from 20 to 40 years, and >40 years (Table 1). Although the mean CCT for the group <20 years was $558.82 \pm 37.398\,\mu m$, 42.8% ($n = 12$) of the eyes in this group had a CCT $\geq$580 μm, while 14.4% ($n = 17$) and 14.2% ($n = 6$) of the eyes in the groups from 20 to 40 years and over 40 years had CCT $\geq$580 μm. The mean CCT between age groups <20 years and >40 years showed a significant difference ($p = 0.016$). No difference was detected between the age groups <20 years and 20–40 years ($p = 0.094$), and >40 years ($p = 0.17$). A positive correlation with CCT was observed in the group <20 years ($\rho = 0.596$, $p = 0.001$), a negligible correlation between CCT and age was detected in for the age group $\geq$20 and $\leq$40 years ($\rho = 0.091$, $p = 0.326$) and a non-significant positive correlation in the group over 40 years ($\rho = 0.255$, $p = 0.103$).

Discussion

CCT is a critical parameter in the assessment of IOP in glaucoma patients, and its measurement is also compulsory in patients undergoing corneal refractive surgery and during the postoperative follow up of corneal transplant. It is known that CCT values vary between ethnic groups, and that there are several factors either extrinsic (i.e. UV radiation, altitude, humidity) and intrinsic (age, gender, ethnicity, hereditability and genetics) have an effect influence it.[17,22,24,25,31,32]

We observed an average CCT of $545.69 \pm 36.88\,\mu m$, similar to that of previous studies conducted with Hispanic subjects. Hahn et al.[19] in 2003 reported a mean CCT of 546.9 μm; Erickson et al.[33] in 2010 obtained a mean CCT of 541.8 μm; and recently, Valbon et al.[34] found a CCT of 547.5 μm. Our sample also exhibited a wide range of CCT

Variable	Average	St. Dev.	Median
Pachymetry	545.69 μm	36.88	543.00 μm

Figure 1 CCT histogram. The analyzed population did not exhibit a normal distribution. The first peak can be noted at 540 μm, and the second at 580 μm.

values (ranging from 458 to 640 μm), this was superior to the ranks reported by Hahn et al. (479.7–613.4 μm) and Valbon et al. (490–647 μm). Additionally, our results showed a bimodal distribution with the first peak reflecting the mean CCT for the whole sample (545.69 μm) and the second peak attributed to the eyes ($n = 35$) with thick corneas (CCT $\geq$580 μm), primarily at the expense of the younger group of patients <20 years (42.8%). Other authors have made similar observations with regard to a trend over a higher prevalence of thicker corneas in younger ages.[27,35]

The wide range of CCT values, as well as the high frequency in values around 540 μm, might lead us to redefine the concept of ''normality'' for corneal thickness in our population. Frequently, corneas below 510 μm are considered as thin and, and therefore as corneas with biomechanical liability or weakness for excimer laser refractive procedures (LASIK, PRK).[10–12,36,37] However, there is increasing evidence with regards to the safety and effectiveness of LASIK surgery in patients with CCT values <500 μm.[13,38,39] Since collagen tension disruption affects corneal biomechanics in refractive surgery,[40,41] this contradictory evidence leads us to believe that there are other factors that impact corneal structural stability independently of CCT. In this respect, it has been suggested that ultrastructural changes observed in ectatic corneas are related to mechanical stress, which leads to greater modifications in collagen fibrils and not directly to the CCT.[42,43] Hence, in order to consider a cornea as ''normal'', the entire topography (topographic pattern, pachymetry map and elevation maps) along with the expected CCT for a given population, should be taken into account.

In agreement with other reports,[28,29] we did not observe a correlation between CCT and the variables age, keratometry, and spherical equivalent. However, when the population was subdivided into age groups, a significant difference was noticed between the CCT of individuals under 20 years and those over 40 years. Younger patients registered thicker corneas with a mean difference of 20 μm from those patients over 40 years, and a positive correlation was observed for both groups (only significant for the group <20 years). This is in accordance with numerous studies that have reported decreasing values of CCT in relation to older age.[14,44] In a meta-analysis that included populations from different ethnicities, Doughty and Zaman,[7] reported an inverse relationship between age and CCT for non-white population. This age/CCT correlation could be explained by the decrease in interfibrillar spacing due to age-related non-enzymatic crosslinking, which has been suggested to cause reductions in stromal thickness.[35,45]

Conclusion

A bimodal distribution in the CCT was observed in this cross-sectional study, with the first peak at 540 μm and a second minor peak at 580 μm, the latter attributed mainly to younger patient measurements. No association between age, corneal curvature and spherical equivalent was observed, but when analyzed by age groups a positive correlation was detected for age group <20 years and age group >40 years. To our knowledge, this is the first study that describes pachymetric values and their correlation

with other factors in this specific population. The findings regarding the lack of normality, the higher frequency of the samples in the first peak, and the relationship between age and decreasing CCT, may lead us to redefine the ''normal'' pachymetric parameters in our population so they can be used properly for clinical purposes.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this investigation.

Confidentiality of data. The authors declare that no patient data appears in this article.

Right to privacy and informed consent. The authors declare that no patient data appears in this article.

Conflict of interest

The authors declare no conflicts of interest.

References

1. Ehlers N, Hjortdal J. Corneal thickness: measurement and implications. Exp Eye Res. 2004;78:543–8.
2. Dutta D, Rao HL, Addepalli UK, et al. Corneal thickness in keratoconus: comparing optical, ultrasound, and optical coherence tomography pachymetry. Ophthalmology. 2013;120:457–63.
3. Verdier DD, Sugar A, Baratz K, et al. Corneal thickness as a predictor of corneal transplant outcome. Cornea. 2013;32:729–36.
4. Kettesy B, Nemeth G, Kemeny-Beke A, et al. Assessment of endothelial cell density and corneal thickness in corneal grafts an average of 5 years after penetrating keratoplasty. Wien Klin Wochenschr. 2014;126:286–90.
5. Kamiya K, Ishii R, Shimizu K, et al. Evaluation of corneal elevation, pachymetry and keratometry in keratoconic eyes with respect to the stage of Amsler–Krumeich classification. Br J Ophthalmol. 2014;98:459–63.
6. Demir S, Ortak H, Yeter V, et al. Mapping corneal thickness using dual-scheimpflug imaging at different stages of keratoconus. Cornea. 2013;32:1470–4.
7. Doughty MJ, Zaman ML. Human corneal thickness and its impact on intraocular pressure measures: a review and meta-analysis approach. Surv Ophthalmol. 2000;44:367–408.
8. Browning AC, Bhan A, Rotchford AP, et al. The effect of corneal thickness on intraocular pressure measurement in patients with corneal pathology. Br J Ophthalmol. 2004;88:1395–9.
9. Binder PS. Analysis of ectasia after laser in situ keratomileusis: risk factors. J Cataract Refract Surg. 2007;33:1530–8.

10. Binder PS, Trattler WB. Evaluation of a risk factor scoring system for corneal ectasia after LASIK in eyes with normal topography. J Refract Surg. 2010;26:241–50.

11. Randleman JB, Russell B, Ward MA, et al. Risk factors and prognosis for corneal ectasia after LASIK. Ophthalmology. 2003;110:267–75.

12. Tatar MG, Aylin Kantarci F, Yildirim A, et al. Risk factors in Post-LASIK corneal ectasia. J Ophthalmol. 2014;2014:204191.

13. Tomita M, Watabe M, Mita M, et al. Long-term observation and evaluation of femtosecond laser-assisted thin-flap laser in situ keratomileusis in eyes with thin corneas but normal topography. J Cataract Refract Surg. 2014;40:239–50.

14. Aghaian E, Choe JE, Lin S, et al. Central corneal thickness of Caucasians, Chinese, Hispanics, Filipinos, African Americans, and Japanese in a glaucoma clinic. Ophthalmology. 2004;111:2211–9.

15. Haseltine SJ, Pae J, Ehrlich JR, et al. Variation in corneal hysteresis and central corneal thickness among black, hispanic and white subjects. Acta Ophthalmol. 2012;90:e626–31.

16. Wong AC-M, Wong C-C, Yuen NS-Y, et al. Correlational study of central corneal thickness measurements on Hong Kong Chinese using optical coherence tomography, Orbscan and ultrasound pachymetry. Eye (Lond). 2002;16:715–21.

17. Gros-Otero J, Arruabarrena-Sánchez C, Teus M. Central corneal thickness in a healthy Spanish population. Arch Soc Española Oftalmol. 2011;86:73–6.

18. Iyamu E, Osuobeni E. Age, gender, corneal diameter, corneal curvature and central corneal thickness in Nigerians with normal intra ocular pressure. J Optom. 2012;5:87–97.

19. Hahn S, Azen S, Ying-Lai M, et al. Central corneal thickness in Latinos. Invest Ophthalmol Vis Sci. 2003;44:1508–12.

20. Galgauskas S, Juodkaite G, Tutkuvienė J. Age-related changes in central corneal thickness in normal eyes among the adult Lithuanian population. Clin Interv Aging. 2014;9:1145–51.

21. Toh T, Liew SHM, MacKinnon JR, et al. Central corneal thickness is highly heritable: the twin eye studies. Invest Ophthalmol Vis Sci. 2005;46:3718–22.

22. Zheng Y, Ge J, Huang G, et al. Heritability of central corneal thickness in Chinese: the Guangzhou Twin Eye Study. Invest Ophthalmol Vis Sci. 2008;49:4303–7.

23. Hoehn R, Zeller T, Verhoeven VJM, et al. Population-based meta-analysis in Caucasians confirms association with COL5 A1 and ZNF469 but not COL8 A2 with central corneal thickness. Hum Genet. 2012;131:1783–93.

24. Segev F, Héon E, Cole WG, et al. Structural abnormalities of the cornea and lid resulting from collagen V mutations. Invest Ophthalmol Vis Sci. 2006;47:565–73.

25. Morris DS, Somner JEA, Scott KM, et al. Corneal thickness at high altitude. Cornea. 2007;26:308–11.

26. Riley MV, Susan S, Peters MI, et al. The effects of UV-B irradiation on the corneal endothelium. Curr Eye Res. 1987;6:1021–33.

27. Suzuki S, Suzuki Y, Iwase A, et al. Corneal thickness in an ophthalmologically normal Japanese population. Ophthalmology. 2005;112:1327–36.

28. Chen M-J, Liu Y-T, Tsai C-C, et al. Relationship between central corneal thickness, refractive error, corneal curvature, anterior chamber depth and axial length. J Chin Med Assoc. 2009;72:133–7.

29. Prasad A, Fry K, Hersh PS. Relationship of age and refraction to central corneal thickness. Cornea. 2011;30:553–5.

30. Weizer JS, Stinnett SS, Herndon LW. Longitudinal changes in central corneal thickness and their relation to glaucoma status: an 8 year follow up study. Br J Ophthalmol. 2006;90:732–6.

31. Siegfried CJ, Shui Y-B, Bai F, et al. Central corneal thickness correlates with oxygen levels in the human anterior chamber angle. Am J Ophthalmol. 2015;159:457–62, e1.

32. Cohen SR, Polse KA, Brand RJ, Mandell RB. Humidity effects on corneal hydration. Invest Ophthalmol Vis Sci. 1990;31:1282–7.

33. Erickson DH, Goodwin D, Anderson C, Hayes JR. Ocular pulse amplitude and associated glaucomatous risk factors in a healthy Hispanic population. Optometry. 2010;81:408–13.

34. Valbon BF, Ambrósio R, Fontes BM, Luz A, Roberts CJ, Alves MR. Ocular biomechanical metrics by CorVis ST in healthy Brazilian patients. J Refract Surg. 2014;30:468–73.

35. Elsheikh A, Wang D, Brown M, Rama P, Campanelli M, Pye D. Assessment of corneal biomechanical properties and their variation with age. Curr Eye Res. 2007;32:11–9.

36. Groden LR, Shah VC. Safe LASIK: a primer. Int Ophthalmol Clin. 2006;46:83–90.

37. Randleman JB, Woodward M, Lynn MJ, et al. Risk assessment for ectasia after corneal refractive surgery. Ophthalmology. 2008;115:37–50.

38. Tatar MG, Aylin Kantarci F, Yildirim A, et al. Risk factors in post-LASIK corneal ectasia. J Ophthalmol. 2014:2014.

39. Caster AI, Friess DW, Potvin RJ. Absence of keratectasia after LASIK in eyes with preoperative central corneal thickness of 450 to 500 microns. J Refract Surg. 2007;23:782–8.

40. Chen MC, Lee N, Bourla N, et al. Corneal biomechanical measurements before and after laser in situ keratomileusis. J Cataract Refract Surg. 2008;34:1886–91.

41. Wang D, Liu M, Chen Y, et al. Differences in the corneal biomechanical changes after SMILE and LASIK. J Refract Surg. 2014;30:702–7.

42. Akhtar S, Alkatan H, Kirat O, et al. Ultrastructural and three-dimensional study of post-LASIK ectasia cornea. Microsc Res Tech. 2014;77:91–8.

43. Abahussin M, Hayes S, Edelhauser H. A microscopy study of the structural features of post-LASIK human corneas. PLoS ONE. 2013;8:e63268.

44. Rüfer F, Sander S, Klettner A, et al. Characterization of the thinnest point of the cornea compared with the central corneal thickness in normal subjects. Cornea. 2009;28:177–80.

45. Malik NS, Moss SJ, Ahmed N, et al. Ageing of the human corneal stroma: structural and biochemical changes. Biochim Biophys Acta. 1992;1138:222–8.

3-Year follow-up after Lasik: assessing the risk factors for retreatment

Jorge E. Valdez-García, Julio C. Hernandez-Camarena & Rosa Martínez-Muñoz

ONLINE FIRST

Official Journal of the Society for Ophthalmo-Immuno Infectiology in Europe (SOIE)

International Ophthalmology

The International Journal of Clinical Ophthalmology and Visual Sciences

Submit manuscripts:
http://www.editorialmanager.com/inte

Springer

Free Color Illustrations!

Springer

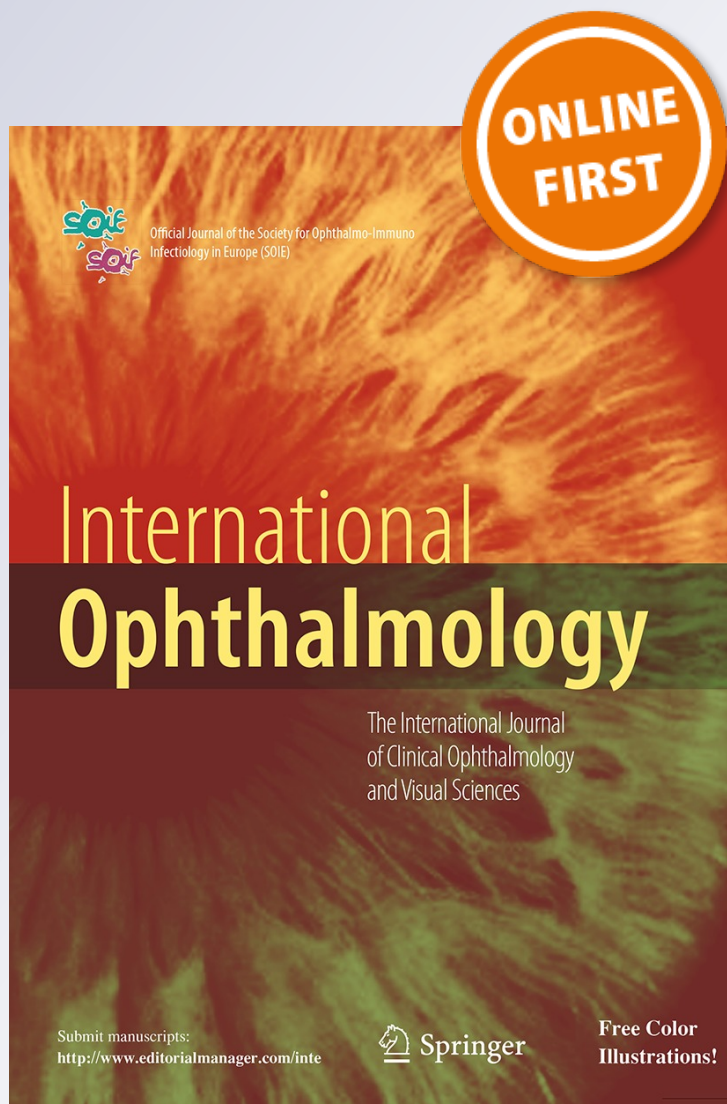Springer

CrossMark

ORIGINAL PAPER

3-Year follow-up after Lasik: assessing the risk factors for retreatment

Jorge E. Valdez-García · Julio C. Hernandez-Camarena · Rosa Martínez-Muñoz

Abstract The purpose of this study was to evaluate the correlation of important risk factors for LASIK retreatment and the retreatment rate. A retrospective cohort study was conducted. Records of patients who underwent LASIK between January 2011 and January 2012 at the Zambrano-Hellion Medical Center, Tec de Monterrey (México), and posteriorly underwent LASIK retreatment were identified and risk factors to receive retreatment were assessed using relative risk. Main outcomes were retreatment rate, risk factors for retreatment, and uncorrected distance visual acuity (UDVA). 482 eyes from 241 patients were available for a 36-month follow-up analysis. 68.5 % had primary myopic LASIK; 37 % were ≤2 diopters (D), 52 % were >2 and <6 D, and 11 % were ≥6 D of myopia. 31.5 % of the eyes had hyperopic LASIK. Retreatment was performed in 6.85 % eyes. Myopia >6 D (RR 4.13), hyperopic refraction (RR 3.18), and age >40 (RR 3.07) were the most important risk factors for retreatment ($P = 0.004$, $P = 0.007$, $P = 0.006$, respectively). UDVA was ≥20/40 in 92.1 % and ≥20/20 in 81.6 % of the retreated eyes and 82 % of the eyes within ±0.50 D of target refraction. Increasing degrees of myopia, followed by hyperopic refraction, and age were the most important associated factors to retreatment. LASIK retreatment was safe and effective.

Keywords LASIK · LASIK retreatment · Risk factors · Refractive surgery

Introduction

Although sometimes overlooked by the clinician, the undercorrection rate is a very important parameter of quality assurance [1–3]. High rates may indicate that changes need to be done to the physician's nomogram and will naturally result in a higher number of unsatisfied patients [3]. Given the high satisfaction rates of LASIK and the widespread use of the procedure, it is quite possible that patients have high expectation. It is therefore important to identify subpopulations of patients with high risk of undercorrection. Awareness of belonging to a high-risk group, as well as the alternative of enhancement and its results, could create more realistic expectations on the patients, therefore, reducing anxiety and dissatisfaction. This paper discusses the correlation of some common, although disputed, risk factors for LASIK

J. E. Valdez-García (✉) · J. C. Hernandez-Camarena
Service of Cornea and Refractive Surgery,
Ophthalmology and Visual Sciences Institute, School of
Medicine of the Tecnologico de Monterrey, Morones
Prieto 3000 Pte., Los Doctores, 64710 Monterrey,
Nuevo Leon, Mexico
e-mail: jorge.valdez@itesm.mx

R. Martínez-Muñoz
School of Medicine of the Tecnologico de Monterrey,
Monterrey, Mexico

🖄 Springer

retreatment in a Hispanic population with a 3-year follow-up after the initial LASIK treatment and reports the results of the enhancement procedures.

Methods

A retrospective analysis was performed on the records of Hispanic patients who underwent LASIK between January 2011 and January 2012, at the Zambrano-Hellion Medical Center, Tec de Monterrey (Monterrey, México). The analysis followed the tenets of the Declaration of Helsinki, and informed consent was obtained from all patients after details of the procedure were explained. Inclusion criteria for the initial treatment were age over 18 years; stable refraction with spherical component in the range of −10.00 to +6.50 D, and a cylindrical component between 0.00 and 6.50 D; corrected visual acuity of 20/20 (Snellen visual acuity chart); and at least 36-month follow-up after the initial treatment. Patients with keratoconus, post-LASIK ectasia, previous eye surgery, and eye trauma were excluded. Patients who underwent LASIK retreatment during this period were identified and charts were analyzed.

Retreatment was defined as a second LASIK procedure due to residual refractive error or patients who were not satisfied with the uncorrected visual acuity due to regression (>0.5 D between two visits separated by at least 2 months) or undercorrection (undercorrection >0.5 D of target refraction the first week after the primary procedure). Initial LASIK procedures were performed by the same surgeon using a Technolas-217 Excimer workstation (Technolas Perfect Vision GmbH, München, Germany) using the standard technique. Briefly, under topical anesthesia with tetracaine chlorhydrate 0.5 % (Ponti ofteno, Sophia ®, Jalisco, México), the cornea was marked with gentian violet and a superior hinge was performed using a Hansatome XP Microkeratome (Bausch & Lomb, Rochester, NY). When indicated both eyes were operated the same day, with the refractive target to emmetropia. A 6.0-mm optical zone was used in every case, with a 120 microns flap with a superior hinge, and average diameter of 9.5 mm (an 8.5-mm-diameter ring was used in eyes with mean keratometries >45) was created. Postoperative medication consisted on moxifloxacin 0.5 % ophthalmic solution (Vigamoxi ®, Alcon Laboratories, Fort Worth TX, US) every 6 h for 7 days and fluorometholone 0.1 opthalmic suspension (Flumetol, Sophia ®, Jalisco, México) in dose reduction for 2 weeks.

The amount of residual refractive error treated was based on subjective refractive measurements. LASIK retreatments were done only when the estimated residual stromal thickness was ≥300 μm. Enhancement was performed by identifying and lifting the prior flap using a Fukasaku LASIK spatula. Statistical analysis was performed with the SPSS software (version 20.0, IBM Inc., NY, USA) for Windows, using Relative Risk (RR) and Chi-square test to determine the association between categorical variables. Visual acuity was measured using Snellen's visual acuity chart and then converted to LogMAR for statistical analysis.

Results

A total of 482 eyes from the records of 241 patients were available for a 36-month follow-up analysis. One hundred and fifty patients (62 %) were female and 91 (38 %) were males. The mean age for the primary intervention was 33.3 (±12.1) years. Patient demographics and refraction at the time of the primary treatment are given on Table 1. Three hundred and thirty eyes (68.5 %) had primary myopic LASIK; 122 eyes (37 %) were ≤2 D, 172 eyes (52 %) were >2 and <6 D, and 36 eyes were ≥6 D of myopia. One hundred and fifty two eyes (31.5 %) had hyperopic LASIK. The uncorrected distance visual acuity after 1 year of the primary procedure was ≥20/40 in 81.1 % of patients and 20/20 in 72.2 %. Retreatment was performed in 33 (6.85 %) eyes. The age at the time of the retreatment was 39.1 (±10.9), 45 % were female. The mean time between the primary treatment and the enhancement was 40.5 (±38.2) months, with a mean follow-up after retreatment of 4.2 (±2.1) months (Table 2). The mean corneal thickness measured at retreatment time was 540 ± 30.2 μm. Of the retreated eyes, 15 (45.5 %) were myopic and 18 (54.5 %) hyperopic corrections. Of the myopic enhancements, one eye (6.2 %) had a baseline refraction <−2 D, eight eyes (56.2 %) were between −2 D and −6 D, and six eyes (37.6 %) were initially >−6 D. The uncorrected distance visual acuity was ≥20/40 in 92.1 % of the eyes and 20/20 in 81.6 % after 3 months of the enhancement treatment. Of the retreated eyes,

Table 1 Patient demographics and refraction

	Preoperative ($n = 482$)	1 year postoperative ($n = 482$)
Gender % (n)	Female 62 % (150)	
Age (years)	33.3 ($\pm$12.1)	
UCVA[a] (SD)	0.9 ($\pm$0.4)	0.1 ($\pm$0.3)
	[20/25]	[20/25]
CDVA[a] (SD)	0.0 ($\pm$0.1)	0.0 ($\pm$0.2)
	[20/20]	[20/20]
SE[b] (SD; range)	-3.25 ($\pm$4.50; $+6.25$ to -8.50)	-0.50 ($\pm$1.50; $+2.25$ to -1.50)
CYL[b] (SD; range)	-1.75 ($\pm$1.50; -0.25 to -5.25)	-0.75 ($\pm$0.75; -0.25 to -2.25)

UCVA uncorrected distance visual acuity, *CDVA* corrected distance visual acuity, *SE* spherical equivalent, *CYL* refractive cylinder, *SD* Standard deviation

[a] Expressed in LogMAR/[Snellen]

[b] Expressed in diopters (D)

Table 2 Patient demographics and refraction at retreatment and 3 months postoperative

	At retreatment ($n = 33$)	3 months after retreatment ($n = 33$)
Gender % (n)	45 % (15)	
Age (years)	39 ($\pm$10.9)	
UCVA[a] (SD)	0.2 ($\pm$0.3)	0.1 ($\pm$0.1)
	[20/30]	[20/25]
CDVA[a] (SD)	0.1 ($\pm$0.2)	0.09 ($\pm$0.1)
	[20/25]	[20/25]
SE[b] (SD; range)	-0.50 ($\pm$1.75; $+2.50$ to -1.75)	-0.50 ($\pm$1.25; $+1.00$ to -1.00)
CYL[b] (SD; range)	-0.75 ($\pm$1.00; -0.25 to -2.25)	-0.55 ($\pm$0.55; -0.25 to -1.25)

UCVA uncorrected distance visual acuity, *CDVA* corrected distance visual acuity, *SE* spherical equivalent, *CYL* refractive cylinder, *SD* Standard deviation

[a] Expressed in LogMAR/[Snellen]

[b] Expressed in diopters (D)

82 % were within $\pm$0.50 D of the target refraction. None of the patients lost lines of corrected distance visual acuity and none of the patients presented epithelial ingrowth or corneal ectasia at the last follow-up.

An association between undercorrection and increasing degrees of myopia ($P = 0.004$) was observed, with eyes >6 diopters of myopia having four times more likely to be retreated (RR = 4.13). Hyperopic refraction had a RR of 3.18 respective to myopia to receive enhancement ($P = 0.007$). Of the patients with an enhancement treatment, 52 % were over 40 years. Age over 40 years old was also significantly associated to undercorrection ($P = 0.006$), and patients in this age group were three times (RR = 3.07) as likely to get excimer surgery enhancement (Fig. 1). Post-treatment visual acuity had no effect on the risk for retreatment ($P = 0.99$). There was no gender difference in the risk for retreatment.

Discussion

Over the past two decades, LASIK has proved to be a safe, an efficient, and a predictable method to correct myopia, astigmatism, and hyperopia, though the results for the latter are generally less predictable [4–6]. However, enhancement rates still are high

ranging from 3.8 to 30 % in eyes with high myopia or hyperopia [7–10]. Retreatment procedures in an attempt to eliminate residual refractive error or to compensate for refractive regression are mostly encouraged by patient visual dissatisfaction in the postoperative period. The current study analyzes the association of the risk factors found in 482 eyes over a period of 3 years after the primary LASIK to receive an enhancement treatment or retreatment.

The overall retreatment rate in the current study was 6.8 %, which is significantly lower than the reported by other authors for moderate to high myopia (ranging from 20 to 30 %) [7, 8, 10] or hyperopia alone (12.8–29 %) [11, 12] and is slightly higher that the reported by other authors for large cohort of post-LASIK eyes (Watson et al. and Yuen et al., retreatment rates of 4.9 and 3.8 %, respectively) [5, 13]. The latter authors explain their low rate of retreatments, as we also could do so, because of the predominance of low to moderate refractive error since regression (especially in myopic eyes) increases with higher corrections. We found the increasing risk for

retreatment with a baseline hyperopic refraction (RR 3.18), this is in agreement with the findings of Randleman et al. who concluded that eyes with hyperopic refractions or astigmatism (≥1 D) were more likely to undergo retreatment [11]. An association between increasing degrees of myopia and retreatment was also found. In this matter, Saeed et al. found that baseline degree of myopia was a significant predictor for regression after both the initial LASIK and retreatment [14]. This is in agreement with Hersh et al. who also defined high initial corrections (>6 D) as risk factors for LASIK retreatment [15]. With regards to age, we found association between older age (>40 years old) and retreatment. In contrast with the results found in the work of Febbraro et al. and Randleman et al. who did not find correlation between age and LASIK retreatment, and in agreement with the results of Hersh et al. who found patients over 40 years at greater risk for retreatment [11, 15, 16]. The retreatment rate was not influenced by the gender, this is in agreement with the results reported by other authors [11].

Fig. 1 Risk factors for LASIK retreatment. a Eyes with high myopia (≥6 diopters) were four times more likely to be retreated (RR 4.32, $P = 0.004$). b Eyes with hyperopic refraction were three times more likely to be retreated (RR 3.18, $P = 0.007$). c Patients over 40 years old were three times more likely to be retreated (RR 3.07, $P = 0.004$)
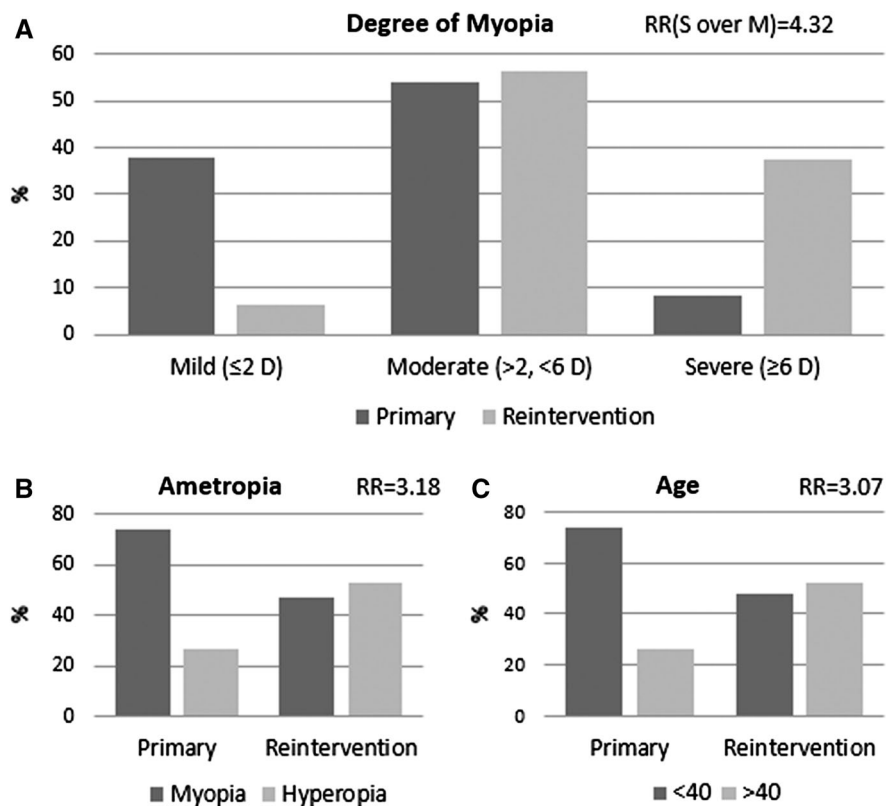
The UDVA [Snellen] of the retreated eyes in our study was 20/40 or better in 92.1 % (30 eyes) and 20/20 or better in 81.6 % (27 eyes), with 82 % of the eyes within ±0.50 D of the target refraction. These results reach and agreement with the reports of Saeed et al. who found and UDVA [Snellen] of 20/30 of better in 88 % of the eyes and 77 % of the eyes within ±0.50 D of the target refraction, considering that his analysis was over a 4-year follow-up after retreatment [14]. Kashani et al. reported a final UCVA [LogMAR] of 0.06 ± 0.13 (Snellen equivalent 20/22) for myopic retreatment and 0.06 ± 0.16 (Snellen equivalent 20/22) for hyperopic retreatment after a mean follow-up of 17.7 months [17]. This is in accordance with the reported UDVA [LogMAR] of 0.1(± 0.1) (Snellen equivalent 20/25) at an early 3-month follow-up in our work. Similarly, McAlinden et al. reported the retreatment results of residual refractive errors with flap lift LASIK. In this study after a 6-month follow-up, 73 and 88.3 % of the eyes had an UDVA [Snellen] of 20/20 and were within ±0.50 D of emmetropia, respectively [18]. Although it was not the main purpose of the study, since the follow-up time after retreatment is short (3 months) and data are insufficient to assure refractive and visual stability, the short-term visual outcomes were excellent and comparable to the reported results of other authors.

One important limitation of this study is absence of cycloplegic refraction during the postoperative visits after LASIK; therefore, in the cases of hyperopic treatments, the analysis of whether the retreatment were due to regression or to facultative hyperopia. Finally, larger sample size and longer follow-up will be necessary for a higher certainty in the visual outcomes after LASIK enhancement.

In conclusion, our retreatment rate was low (6.85 %) and as other authors, we can explain this because of the predominance low to moderate refractive error in our series. Also, the results suggest that in our population increasing degrees of myopia, followed by hyperopic refraction, and age were the most important associated factors to retreatment. These risk factors should always be considered when studying a patient who is a candidate for LASIK surgery in order to set up realistic expectations and to achieve a proper patient selection, finally improving patient satisfaction.

References

1. Tahzib N, Bootsma S, Eggink F et al (2005) Functional outcomes and patient satisfaction after laser in situ keratomileusis for correction for myopia. J Cataract Refract Surg 31:1943–1951
2. Garamendi E, Pesudovs K, Elliot D (2005) Changes in quality of life after laser in situ keratomileusis for myopia. J Cataract Refract Surg 31:1537–1543
3. Jabbur N, Sakatani K, O'Brien T (2004) Survey of complications and recommendations for management in dissatisfied patients seeking a consultation after refractive surgery. J Cataract Refract Surg 30:1867–1874
4. Zadok D, Maskaleris G, Montes M et al (2000) Hyperopic laser in situ keratomileusis with the Nidek EC-5000 excimer laser. Ophthalmology 107:1132–1137
5. Yuen LH, Chan WK, Koh J et al (2010) A 10-year prospective audit of LASIK outcomes for myopia in 37,932 eyes at a single institution in Asia. Ophthalmology 117(6):1236–1244
6. Alió JL, Muftuoglu O, Ortiz D et al (2008) Ten-year follow-up of laser in situ keratomileusis for myopia of up to −10 diopters. Am J Ophthalmol 145(1):46–54
7. Perez-Santoja JJ, Bellot J, Claramonte P et al (1997) Laser in situ keratomileusis to correct high myopia. J Cataract Refract Surg 23:372–385
8. Sugar A, Rapuano CJ, Culbertson WW et al (2002) Laser in situ keratomileusis for myopia astigmatism: safety and efficacy: a report by the American Academy of Ophthalmology. Ophthalmology 109:175–187
9. Knorz MC, Liermann A, Seiberth V et al (1996) Laser in situ keratomileusis to correct myopia of 6.00–29.00 diopter. J Refract Surg 12:575–584
10. Maldonado-Bas A, Onnis R (1998) Results of laser in situ keratomileusis in different degrees of myopia. Ophthalmology 105:606–611
11. Randleman JB, White AJ Jr, Lynn MJ et al (2009) Incidence, outcomes, and risk factors for retreatment after wavefront-optimized ablations with PRK and LASIK. J Refract Surg 25:273–276
12. Alió JL, El Aswad A, Vega-Estrada A et al (2013) Laser in situ keratomileusis for high hyperopia (>5.0 diopters) using optimized aspheric profiles: efficacy and safety. J Cataract Refract Surg 39:519–527
13. Watson SL, Bunce C, Allan BD (2005) Improved safety in contemporary LASIK. Ophthalmology 112(8):1375–1380
14. Saeed A, O'Doherty M, O'Doherty J, O'Keefe M (2007) Analysis of the visual and refractive outcome following laser in situ keratomileusis (LASIK) retreatment over a four-year follow-up period. Int Ophthalmol 27(1):23–29

15. Hersh PS, Fry KL, Bishop DS (2003) Incidence and associations of retreatment after LASIK. Ophthalmology 110:748–754
16. Febbraro JL, Buzard KA, Friedlander MH (2000) Reoperations after myopic laser in situ keratomileusis. J Cataract Refract Surg 26:41–48
17. Kashani S, Rajan M, Gartry D (2009) Wavefront-guided retreatment after primary wavefront-guided laser in situ keratomileusis in myopes and hyperopes: long-term follow-up. Am J Ophthalmol 147(3):417–423
18. McAlinden C, Moore JE (2011) Retreatment of residual refractive errors with flap lift laser in situ keratomileusis. Eur J Ophthalmol 21(1):5–11

Revista Mexicana de
Oftalmología

ORIGINAL ARTICLE

Prevalence of keratoconus in an adolescent population

Jorge E. Valdez-García [a,b,c,*], **Rubén Sepúlveda** [c], **Jessica J. Salazar-Martínez** [c], **Juan F. Lozano-Ramírez** [b,c]

[a] *Instituto de Oftalmología y Ciencias Visuales - TecSalud. Tecnológico de Monterrey, Monterrey, México*
[b] *Catedra de Oftalmología y Ciencias Visuales. Escuela de Medicina y Ciencias de la Salud, Tecnológico de Monterrey, Monterrey, México*
[c] *Escuela de Medicina y Ciencias de la Salud, Tecnológico de Monterrey, Monterrey, México*

Abstract

Introduction: Keratoconus is an idiopathic and progressive disease, where the cornea develops an irregular and conical shape, being the most common form of dystrophy or corneal ectasia, developing between the age of 12 and 20. In Mexico, the epidemiological information about the pathology is scarce.

Purpose: To explore the epidemiology of keratoconus in Mexico among adolescents, and to compare the prevalence with international literature reports. This study identified associated pathologies and examined the management of patients.

Methods: A retrospective study was conducted in an ophthalmology clinic; 500 charts were randomly selected from patients between 10 and 20 years of age in order to acquire information about the identification of the patient; the patient's gender, birthday, and age; three principal diagnoses at the first visit; as well as refraction and visual acuity in both eyes. After this, statistical analysis of the information was done.

Results: The prevalence rate of keratoconus was 1.8%, affecting 66% of females and 33.3% of males. The mean age of presentation was 16.1 years. The most frequently associated refractive error was compound myopic astigmatism (44.4%); 88.8% presented with bilateralism. The majority of patients were being managed conservatively.

Conclusion: Through this study, we found that our statistics matched those of internationally published reports concerning the early age of onset of the disease and its corresponding bilateralism. However, contrary to the international reports, it was evident that this condition was more prevalent among the females in our study sample, and no other associated pathologies were found.

© 2013 Sociedad Mexicana de Oftalmología. Published by Masson Doyma México S.A. All rights reserved.

* Corresponding author at: Av. I Morones Prieto #3000 PTE. Edificio CITES Piso PB Col, Los Doctores Monterrey, NL 64710, Mexico. Tel.: +52 81 8888 2000.
 E-mail address: jorge.valdez@itesm.mx (J.E. Valdez-García).

PALABRAS CLAVE
Queratocono;
Retinoscopía;
Astigmatismo;
Cicloplegia;
Queratoplastia;
Epidemiología

Prevalencia de Queratocono en Población Adolescente

Resumen

Introducción: El queratocono es una enfermedad idiopática y progresiva, donde la cornea adquiere una forma irregular y cónica, siendo la forma más común de distrofia o ectasia corneal desarrollándose entre los 12 y 20 años de edad. En México no se cuenta con suficiente información epidemiológica en cuanto a la patología.

Objetivo: Explorar la epidemiología del queratocono en México en adolescentes y comparar la prevalencia con reportes internacionales. Este estudio identifico patologías asociadas y evaluó el manejo de estos pacientes.

Métodos: Estudio retrospectivo en una clínica oftalmológica; 500 expedientes fueron aleatoriamente seleccionados de pacientes entre 10 y 20 años de edad, obteniendo: identificación del paciente, sexo, fecha de nacimiento y edad, tres diagnósticos principales en su primer visita, refracción y agudeza visual en ambos ojos. Posterior a la captura de datos, se realizo el análisis estadístico.

Resultados: La tasa de prevalencia de queratocono fue de 1.8%, afectando al 66% de las mujeres y el 33% de hombres. La edad media de presentación fue de 16.1 años de edad. El error refractivo asociado a queratocono más común fue astigmatismo miópico compuesto (44.4%); 88.8% se presentó con bilateralidad. La mayoría de los pacientes se trato de manera conservadora.

Conclusión: A través de este estudio, encontramos que nuestros resultados concuerdan con lo publicado internacionalmente en referencia al inicio temprano del queratocono y la bilateralidad. Pero, contrario a lo reportado, fue evidente que esta condición es más prevalente entre las mujeres de nuestra muestra, además no se encontraron patologías asociadas a queratocono.

© 2013 Sociedad Mexicana de Oftalmología. Publicado por Masson Doyma México S.A. Todos los derechos reservados.

Introduction

Keratoconus is a progressive and idiopathic disease in which the cornea develops into an irregular and conic shape. The clinical signs include thinning of the cornea in its central or paracentral region, an apical protrusion, or an elevation of the central zone with an irregular astigmatism, and this condition can progress to the point of corneal perforation in extreme cases[1]; all of these issues can make it difficult to achieve adequate visual correction with the simple use of glasses.[2] Keratoconus is a rare disease, as classified by the Office of Rare Diseases of the National Institute of Health. Despite this, keratoconus is the most common form of dystrophy or corneal ectasia, with an incidence of 50–230 per 100,000 persons.[3]

Some initial studies revealed a greater prevalence of keratoconus among women than men. Today, studies have not been able to find a significant difference between genders, and some studies have even found higher prevalence rate among males.[4,5]

Some reports have documented the age of onset as being as early as birth and up to 51 years of age. However, the vast majority of patients develop the disease between 12 and 20 years of age (it is diagnosed in adolescence and reaches its most severe form between the second and fourth decades of life).[4,5] Based on these reports, we find the need to study this age population in order to define future strategies for diagnosis and treatment.

Keratoconus is a disease that is almost exclusively bilateral, yet asymmetric, as it begins in one eye and after 2–6 years it affects the contralateral eye. It is rare to find a purely unilateral disease. Hall reported that from a total of 288 patients, eight cases were unilateral, while Tuft reported that 4.3% of his sample exhibited unilateral keratoconus.[6,7]

In Mexico, the research on keratoconus is scarce; the articles published show statistics that are similar to those in international literature, which indicates a higher prevalence in male patients with a mean age of 24.5 years.[8] This study will examine a specific population – adolescents. There is debate concerning the prevalence of keratoconus in the general population, but our focus is on the prevalence of keratoconus in the adolescent population visiting an ophthalmology concentration clinic.

Objective

To explore the epidemiology of keratoconus in Mexico among an adolescent population, and to compare the prevalence rates of this condition with international literature reports.

Methods

This study is a retrospective clinical study, which will examine the prevalence rates of keratoconus, for which 500 records were randomly selected. The calculated sample was 221 patients, using Raosoft®, with a 5% margin of error, a 90% confidence interval, and a population of 1200 patients. The patient records used were from patients between the ages of 10–20 years. A database was developed using Microsoft® Excel in which patients' identification, gender, age, three

Table 1 Data concentrate for diagnosis of keratoconus.

	Number of Patients	500
Keratoconus diagnosis		
General prevalence	9	1.8%
Female	6	66.6%
Male	3	33.3%
Mean age at diagnosis		
General	16.1 years	
Female	15.5 years	
Male	17.3 years	
Refractive errors		
Simple Myopia	2	
Compound Myopic Astigmatism	4	
Simple Myopic Astigmatism	2	
Mixed Astigmatism	1	
Treatment		
Corneal transplant	3	
RGP[a] contact lens	5	
Loss to follow-up	1	

[a] RGP = rigid gas permeable.

Table 2 Comparative table indicating keratoconus prevalence per gender in different studies.[5,7,13–15]

Author	Male with KC[a]	Female with KC
Buxton[13]	62%	38%
Woodward[14]	61%	39%
Palimeris[15]	68.9%	30.2%
Kennedy[5]	54.7%	45.3%
Tuft[7]	1.92:1	1:1

[a] KC = keratoconus.

main diagnoses at fist clinic visit, as well as refraction and visual acuity for both eyes were documented. After this, descriptive statistical analysis was performed for prevalence and means. All of the refractions that were documented were performed via skiascopy under cycloplegia. Since this was a general study about the prevalence of keratoconus in a specific population, no exclusion criteria were developed for this study. Before initiating, we received approval from the ethics committee, and the study adheres to the tenets of the Declaration of Helsinki.

Results

Of the 500 records that were examined, keratoconus was diagnosed in 9 patients, with a prevalence rate of 1.8% (Table 1). The proportion of keratoconus per gender was 6 (66.6%) females and 3 (33.3%) males. The mean age at diagnosis was 16.1 years, with 17.3 years of age for males and 15.5 years of age for females.

The refractive errors detected were 2 patients with simple myopia, 2 with simple myopic astigmatism, 4 with compound myopic astigmatism, and 1 with mixed astigmatism. Of the detected patients, 3 (33.3%) had a penetrating keratoplasty and 5 (55.5%) were managed conservatively with rigid gas permeable contact lenses, with periodic adjustments. There was loss to follow-up of 1 (11.1%) patient, after the second visit and no management was appropriately delivered.

Discussion

Our study on keratoconus cannot be compared to an equally designed study from Mexico because no other studies use a similar population. Our 1.8% prevalence rate compares to that of Jonas et al. in India, where they obtained a 2.7%

prevalence rate, sample of 4711 subjects, and in a study conducted in Jerusalem by Millodot et al., who reported a prevalence rate of 2.34% in a sample of 981 volunteers.[9,10] Even though these studies exhibit slightly higher prevalence rates, our results can be regarded as being somewhat similar to those reported in these studies, especially if we compare our prevalence rates to those found by Ihalainen (0.03%).[11]

In relation to gender, we found prevalence rates of 66.6% and 33.3% for women and men, respectively. When we compare these results to those of the study conducted in Cuba by Diaz et al. – who reported similar prevalence rates per gender at 66% for females and 34% for males, had a sample of 73 patients – it is evident that these results are in contrast to those observed in several studies from the United States (Table 2).[5,7,12–15]

The mean age at diagnosis noted in our study was 16.1 years, which can be compared to the mean age at diagnosis found by Olivares and Guerrero, which was 15.39 ± 3.95 years, which had a sample of 74 patients. Even though the mean age reported in our study indicated a younger age, we obtained results that were similar to those found in the general population.[2] When comparing our study's results with those reported by Ruiz-Morales et al., they obtained an age at diagnosis of 24.5 years, study with a sample of 166 patients. While this indicates an older age at diagnosis, it should be considered that the study was conducted on post-transplant patients.[8]

Bilaterality is an important aspect to consider when analyzing a patient with suspected keratoconus. Our study demonstrated bilaterality in 8 (88.8%) patients, although it was asymmetric. Kennedy et al. found an incidence of bilateral involvement to be in 38 (59%) patients at the time of diagnosis.[5] Our results obtained, could indicate a late approach to these patients in our clinic

Theories surrounding the diseases associated with keratoconus can be found in the literature. Some of these theories are based on the effects of hormonal stimulation as the genesis of this pathology. Also, keratoconus is associated with Trisomy 21 and allergic processes, but in our study, no relationships with other diseases were detected.[2]

The relevance of the management of these patients is important to note, as 33.3% of patients ended their treatment in penetrating keratoplasty in our study, clearly indicating that patients are being subjected to radical treatments. The reason behind this is based on the fact that patients at our clinic have already been to other clinics, and they are referred to us (a concentration clinic). Other factors include the fact that this is a population of low socioeconomic status and poor education level; these

factors are often seen in the records in which patients' visual acuity has been significantly affected, and where keratoconus is present and cannot be treated by noninvasive methods.

As the first study using the inclusion criteria specified above, we should highlight the need to perform additional studies. Our study was conducted with a calculated sample of 221 patients. The results are supported by our data, but in order to better compare and extrapolate our epidemiological data, a study that involves a higher number of subjects needs to be performed. In addition to having a larger sample size, other variables should be included such as family history, data concerning atopy, and factors concerning environmental exposure.

The importance of performing similar protocols in populations of this age group is necessary to establish statistics that can help identify the incidence and prevalence of keratoconus in populations of similar geographic areas (this study was conducted in the north of Mexico). Importantly, we can use these studies to establish etiologies, assess proper characteristics, and develop guidelines for the treatment of keratoconus.

Conclusion

Keratoconus identification, diagnosis and treatment are of high importance for primary care physicians, optometrist and ophthalmologist when screening patients in this age group. The incorporation of epidemiology and public health organizations into a future project to identify probable causes can help us understand risk factors for our population, and the best method for detection and timely management.

Funding

Conflict of interest

The authors declare no conflict of interest.

References

1. Lam FC, Bhatt PR, Ramaesh K. Spontaneous perforation of the cornea in mild keratoconus. Cornea. 2011;30(1):103–4.
2. Olivares-Jiménez JL, Guerrero-Jurado JC, Bermudez-Rodriguez FJ, et al. Keratoconus: age of onset and natural history. Optom Vis Sci. 1997;74(3):147–51.
3. Espandar L, Meyer J. Keratoconus: overview and update on treatment. Middle East Afr J Ophthalmol. 2010;17(1):15–20.
4. Abu Ameerh MA, Al Refai RM, Al Bdour MD. Keratoconus patients at Jordan University Hospital: a descriptive study. Clin Ophthalmol. 2012;6:1895–9.
5. Kennedy RH, Bourne WM, Dyer JA. A 48-year clinical and epidemiologic study of keratoconus. Am J Ophthalmol. 1986;101(3):267–73.
6. Hall KG. A comprehensive study of keratoconus. Br J Physiol Opt. 1963;20:215–56.
7. Tuft SJ, Moodaley LC, Gregory WM, et al. Prognostic factors for the progression of keratoconus. Ophthalmology. 1994;101(3):439–47.
8. Ruiz-Morales ML, Verdiguel-Sotelo K, Hernández-López A. Frecuencia del queratocono y transplante de cornea. Rev Med Inst Mex Seguro Soc. 2010;48(3):309–12.
9. Jonas JB, Nangia V, Matin A, et al. Prevalence and associations of keratoconus in rural maharashtra in central India: the central India eye and medical study. Am J Ophthalmol. 2009;148(5):760–5.
10. Millodot M, Shneor E, Albou S, et al. Prevalence and associated factors of keratoconus in Jerusalem: a cross-sectional study. Ophthalmic Epidemiol. 2011;18(2):91–7.
11. Ihalainen A. Clinical and epidemiological features of keratoconus genetic and external factors in the pathogenesis of the disease. Acta Ophthalmol Suppl. 1986;178:1–64.
12. Díaz G, Caíñas A, Jiménez C, et al. Características epidemiológicas en pacientes portadores de queratocono. Rev Cubana Oftalmol. 1999;12:20–6.
13. Buxton JN, Schuman M, Pecego J. Graft reaction after unilateral and bilateral keratoplasty for keratoconus. Ophthalmology. 1981;88(8):771–3.
14. Woodward EG, Moodaley LC, O'Hagan A. Predictors for likelihood of corneal transplantation in keratoconus. Eye. 1990;4(3):493–6.
15. Palimeris G, Droutsas D, Chimonidou E, et al. Some observations on the pathogenesis and management of keratoconus. In: Trevor-Roper PD, editor. The cornea in health and disease. New York: Grune and Stratton; 1981. p. 927–31.

Factors Influencing Central Corneal Thickness

Jorge E. Valdez-García, MD

Corresponding author

Tecnológico de Monterrey, School of Medicine and Health Sciences, Ophthalmology Research

Chair, Monterrey, NL, México.

Ophthalmology and Visual Sciences Institute, Tecnológico de Monterrey, School of Medicine,

Mexico

Address: 3000 Morones Prieto Ave., Col. Los Doctores, Monterrey, N.L., México.

Tel.: +52 81 88882066

E-mail: jorge.valdez@itesm.mx

Judith Zavala, PhD

Ophthalmology Research Chair, Monterrey, NL, México.

Address: 3000 Morones Prieto Ave., Col. Los Doctores, Monterrey, N.L., México.

Tel.: +52 81 88882066

E-mail: judith.zavala@itesm.mx

Rocio Villafuerte-de la Cruz, MD

Developmental biology

Address: 3000 Morones Prieto Ave., Col. Los Doctores, Monterrey, N.L., México.

Tel.: +52 8188882066

E-mail: rociogenetica@gmail.com

Jesús Merayo-Lloves, MD, PhD, MBA

Associate Professor of Ophthalmology. University of Oviedo.

26   Senior Scientist. Ocular Surface & Inflammation Group.

27   Director. Instituto Universitario Fernández-Vega. Universidad de Oviedo. Fundación de

28   Investigación Oftalmológica.

29   Avda Dres Fernández-Vega núm. 34. Oviedo. E-33012 Principado de Asturias. Spain

30   Phone: (+34) 985240141

31   E-mail: merayo@fio.as

32

33   **Eduardo Camacho-Martínez, MD**

34   Address: 3000 Morones Prieto Ave., Col. Los Doctores, Monterrey, N.L., México.

35   Tel.: +52 81 88882066

36   E-mail: a01180527@itesm.mx

37

38   **Eric Reyes-Mendoza, MD**

39   Address: 3000 Morones Prieto Ave., Col. Los Doctores, Monterrey, N.L., México.

40   Tel.: +52 81 88882066

41   E-mail: rrm.eric@gmail.com

42

43   **Conflict of interest:**

44   The authors have no conflicts of interest or funding sources to declare.

45

46

47 **Abstract:**

48 Many factors determine the corneal thickness and our understanding of them is not sufficient. This

49 is of main interest given the significance of this ophthalmological parameter in the management of

50 several clinical conditions like: refractive surgery and high intraocular pressure (IOP). Thin corneas

51 are considered weak and not suitable for surgical procedures, though several studies demonstrate no

52 correlation between thin CCT and development of post-surgical ectasia. Subjacent molecular

53 mechanisms that influence stromal biomechanics, including strength and stability, comprise the role

54 of collagen fibers disposition, keratan sulfate, and proteoglycans. Genetic population studies

55 demonstrate the effect of four specific genes (*COL5A1*, *FOXO1*, *AVGR8*, and *ZNF469*) and several

56 other gene SNPs over CCT. Additionally, factors such as UV radiation, age, humidity, altitude, and

57 certain diseases affect CCT. The analysis of each potential factor that modifies CCT bring us closer

58 to understanding the underlying mechanisms responsible for corneal biomechanics. This will

59 provide a global vision of the way cornea behaves and the effect of surgical treatments or

60 diseases. This review summarizes the factors known to have a role over CCT and the recent genetic

61 analyses that lead to better understanding corneal mechanical properties.

62 **Key Words:**

63 Corneal Thickness

64 Corneal Pachymetry

65 Corneal Thickness Measurement

66 Biomechanics

67 Genetics

68 **Methodology:**

69 The literature review for this article was conducted using a Medline with Pubmed search of

70 references using the following key words: corneal thickness, central corneal thickness, or CCT in

71 combination with genetics, genes, modifiers, factors influencing, normal values, epidemiology. The

72   search also included non-English language articles. Abstracts of the articles were reviewed, and for

73   the ones considered relevant to the review, the full-length articles were reviewed in detail. Manual

74   search of the references of the articles considered relevant was also done. Select articles published

75   before 1990 are included for historical purposes, but the review is based mainly on articles

76   published in the past decade.

77

78

1. Introduction

Central corneal thickness (CCT) is a parameter of high clinical relevance in ophthalmology. The measurement of corneal thickness, also called pachymetry, is not done just because it is something available at hand, but because of the relevance it can have in several fields of study. CCT can be used as an indirect method to evaluate functional status of the endothelial cell layer,(1) and it has been identified as an independent risk factor for developing glaucoma.(2) It also plays an important role in the management of ocular hypertension, since its measurement with some methods such as applanation tonometry can be altered by differences in CCT.(3) Corneal thickness is also of great relevance in the preoperative management of candidate patients for refractive surgery in order to determine which procedure is most suitable for each patient.(4,5) Conditions such as keratoconus and some corneal dystrophies have also been associated with decreased CCT.(6,7) Given the numerous areas in which corneal thickness plays a relevant role, there has been research done about each of these topics in particular. However, there is a gap in the literature when addressing the subject of corneal thickness, the majority of the articles published address very particular populations or specific problems in which corneal thickness play a part, but there is a lack of articles that give a general view of what is central corneal thickness, all the factors that can affect it and its clinical implications. The purpose of the present review is to fill in this gap by approaching the subject of CCT from a stand point that covers all aspects related to central corneal thickness form the anatomical and physiological basis behind it, to the field of biomechanics and corneal topography, it's so called "normal" values, the genetic implications behind it and the factors influencing it. **Figure 1** illustrates some of the factors influencing CCT and the way they relate to thickness, these will be further analyzed throughout the article.

2. Cornea: physiology, structure, function

102   The cornea represents the most anterior part of the human eye. It is a highly specialized transparent

103   tissue situated in front of the iris and the pupil, and inserts into the sclera at the limbus. In the adult,

104   the average horizontal diameter is 11.3–12.1mm(8) and it is approximately 0.8 mm greater than the

105   mean vertical diameter.(9) The cornea is flatter in the periphery and steeper centrally, giving it a

106   shape that makes an aspheric optical system. The cornea is an avascular and highly ordered tissue.

107   Physiologically, the periphery depends more on the blood supply from the vessels that provide

108   oxygen and some nutrients, while the central cornea depends mostly on surrounding fluids, aqueous

109   humor and tear film.(10)

110   There are five layers distinguished in the cornea, from external to internal: the corneal epithelium,

111   Bowman's membrane, the stroma, Descemet's membrane, and the endothelium. The epithelium acts

112   as a barrier of the cornea; it has five or six layers of cells of non-keratinized, non-secretory,

113   stratified squamous epithelium, which give it a thickness of 58μm. The epithelium is covered with a

114   tear film of 5 μm.(11) Together, the tear-air border and the underlying cornea are responsible of

115   two-thirds of the total refractive power of the eye. The corneal epithelium is constantly being

116   regenerated and repaired, complete renewal of corneal epithelial cells is estimated to occur every 7–

117   10 days.(12) The Bowman's membrane is one of the two acellular layers of the cornea. It is a

118   modified portion of the stroma with a tightly intertwined meshwork of collagen fibrils that separates

119   the epithelium from the stroma.(13) Underneath the Bowman's membrane is the corneal stroma,

120   which accounts for about 90% of the corneal thickness (460-500 μm).(14,15) It is composed by

121   extracellular matrix, keratocytes, and proteins.(16) It is responsible of corneal transparency and

122   along with proteins as proteoglycans provide the strength and hydration needed for proper sight

123   function.(17,18) The Descemet's membrane is a discrete layer composed of a fine strips mostly of

124   type IV collagen, laminin, and fibronectin secreted by the corneal endothelium.(19) It is known to

125   have regenerative potential,(20) but its function is not entirely known. The endothelium is the

126   posterior corneal monolayer of hexagonal cells that functions as a system through which nutrients

127 pass in and waste is removed trough simple and facilitated diffusion and active transport. Its main

128 function is to regulate corneal hydration through active ATP bicarbonate-dependent pump, which

129 allows the eye to perform its visual function.(21,22)

130 The existence of a sixth corneal layer has been proposed in recent years. This new corneal layer was

131 discovered thanks to the big bubble technique of deep anterior lamellar keratoplasty (DALK), and is

132 called Dua's layer. It has been defined as an acellular, strong layer in the pre-Descemet's cornea of

133 10.15 ± 3.6 microns composed of 5 to 8 lamellae of predominantly type-1 collagen bundles

134 arranged in transverse, longitudinal, and oblique directions.(23) The discovery of this layer has

135 raised controversy, with some surgeons stating this discovery brings further insight on the field of

136 DALK surgery,(24) while others question the existence of the Dua's layer stating it is stroma and

137 not a new corneal layer.(25) Further research on this subject is needed in order to reach a consensus

138 on the existence of this corneal layer.

139 As stated above, the stroma is the corneal layer that accounts for most of the corneal thickness. Its

140 extracellular matrix is composed mainly of collagen fibrils. Corneal collagen is synthesized by

141 keratocytes in the form of procollagen with two additional peptides, one at each end. Procollagen

142 proteinases located in the extracellular space remove the extension peptides from the precursor

143 molecule and transform it to collagen. The enzyme lysyl oxidase deaminates the lysine or

144 hydroxylisine of the end chains, allowing collagen to form cross-links between fibrils, which then

145 convert during maturation to trivalent cross-links.(26–29) Corneal fibrils are composed mostly of

146 type I collagen that co-assemble into a complex with heterotypic fibrils of type V collagen. The

147 ratio of type V to type I collagen seems to regulate the fibril diameter and the thickness of the

148 corneal stroma.(30,31) Type V collagen co-aggregates with type I collagen and the protruding NH_2

149 terminal domains of this aggregate cause steric hindrance to prevent accretion of more molecules

150 onto the fibril surface. This limits the diameter of the fibrils in the cornea, from 31 to 34 nm.(32)

151 Corneal collagen fibrils are packed in parallel bundles extending from limbus to limbus.(30) These

152 bundles arrange in layers known as lamellae, which assemble in the middle and posterior regions of

153 the stroma at approximate right angles, and those in the anterior stroma at less than right angles.

154 The small diameter of the collagen fibrils and their close, regular packing are responsible for the

155 ability of the cornea to scatter 98% of incoming light. The lamellar organization of the stroma also

156 allows the cornea to maintain intraocular pressure and the appropriate curvature.(30) The difference

157 in the organization of the collagen bundles in the anterior stroma may contribute to a tighter

158 cohesive strength in this area, and may explain why anterior curvature resists change to stromal

159 hydration more than posterior stroma.(1) Another mechanism of cross-linking that influences the

160 strength of the stromal tissue is nonenzymatic glycation, in which prolonged exposure to

161 monosaccharides results in bonding between the reducing sugar and the amino group of a

162 protein.(26,28,33,34)

163 Keratan sulfate proteoglycans are the predominant proteoglycans within the corneal stroma.

164 Lumican and keratocan are the core proteins of keratan sulfate proteoglycans, lumican being a

165 regulatory protein for keratocan expression. These molecules are regulators of collagen matrix

166 organization an assembly in the corneal stroma.(35) Lumican, keratocan and mimecam are believed

167 to play a significant role in corneal transparency due to their specific collagen binding sites.(36)

168 Proteoglycans bind to the exterior surfaces of collagen fibrils, and their glycosaminoglycan side

169 chains attract cations and water molecules, which may cause swelling pressure on collagen fibrils

170 that is balanced by interactions between collagen types I and XII.(30) Keratocytes are the principal

171 cell type of the stroma. They produce the collagen and ground substance and are arranged parallel

172 to the corneal surface and located between the collagen lamellae. There have been differences

173 identified between the anterior and posterior stromal keratocytes, such as fenestrations that indicate

174 heterogeneous functions including facilitating of diffusion and mechanical attachment of collagen

175 fibers. The organization of keratocytes forming closed sheets of communication create equal

176 chances for all light rays to pass and minimize variation in light scattering over the entire

177 cornea.(37)

178 As mentioned, part of the corneal endothelium function is to regulate corneal hydration and as a

179 direct consequence of this, corneal transparency.(21) This pump function of the corneal

180 endothelium is mainly in charge of the transport protein Na^+/K^+- ATPase. A healthy cornea has a

181 density of 4.4 trillion ATPase sites/mm^2, and the cornea has compensatory mechanisms to prevent

182 corneal edema such as increasing the activity or density of the pump sites. Its function can even be

183 clinically assessed by measuring changes in corneal thickness (pachymetry). The point at which the

184 compensatory mechanisms of the corneal endothelium fail, and corneal edema results, is when the

185 central endothelial cell density reaches around 700-400 cells/mm2.(38,39)

186 The cornea is one of the most innervated and sensitive tissues of the human body.(40–42) Epithelial

187 nerve density of the cornea is 300-600 times that of the skin, with corneal sensitivity being most

188 acute in the central cornea and along the horizontal meridian and least sensitive in the vertical

189 meridian.(43,44) Most of the corneal nerves are sensory in origin and are derived from the

190 nasociliary branch of the ophthalmic division of the trigeminal nerve.(40,42) Corneal nerves

191 respond to mechanical, thermal, and chemical stimulation of the cornea, hence protecting the cornea

192 form external threats and stimuli by initiating nerve reflex mechanisms.(37,41) In addition to their

193 sensitive function, corneal nerves have a role in the maintaining of the functional integrity of the

194 ocular surface by releasing trophic substances, such as neuropeptides and growth factors, that

195 promote epithelial homeostasis and by activating brainstem circuits that stimulate tear production

196 and blinking.(41,43) Central corneal nerves do not have a myelin sheath in order to maintain

197 corneal transparency. Also, thick stromal nerve trunks move radially from the periphery towards the

198 center below the anterior third of the stroma in order to preserve the organization of the collagen

199 lamellae.(42)

200   **3. Corneal Topography**

201   The cornea has a complex geometric structure. There are basic anatomic components of the cornea:

202   thickness, radius of curvature and surface irregularity.(45) The measurement and quantification of

203   these components are essential to know the physiologic functions, the diagnosis of corneal diseases

204   and as a screening tool for corrective surgery. Some technologies like corneal tomography, very

205   high frequency ultrasound (VHF), slit scanning, and high-speed anterior segment optical coherence

206   tomography (OCT) are used to measure these components. The ultrasound pachymetry, used to

207   measure the thickness of the cornea, has been considered the gold standard for years.(46)

208   Typically, the shape of the cornea is not spherical; instead, it is considered to have a toroidal shape.

209   Topographically, the anterior cornea is divided in three zones: the apical, peripheral, and limbal

210   zone.(45) The apical zone is also named as the central region of the cornea with a constant radius of

211   curvature, which shows a gradual flattening resulting in an aspheric surface called peripheral zone,

212   and the limbal zone is defined as the junction of the cornea with the sclera.

213   The cornea is characterized by its complex nonlinear anisotropic elastic and viscoelastic

214   properties(47) and the maintenance of the corneal shape and curvature are governed by the intrinsic

215   biomechanical structure and extrinsic environment in a dynamic equilibrium. The intraocular

216   pressure that exerts a force on the inside face of the cornea is the most important extra-corneal

217   factor; less important factors are the external atmospheric pressure, the lids, extraocular and ciliary

218   muscles during accommodation that induce a change in its curvature during accommodation.(48–

219   50) The stroma is responsible for the majority of the cornea's tensile strength and its mechanical

220   properties. It has been established that the most anterior part (120μm) is responsible for the stability

221   and maintenance of its curvature.(51) It has also been discussed if the Bowman's layer has a real

222   function for the maintenance of the corneal curvature, suggesting that it constitutes only a visible

223   indicator of ongoing stromal-epithelial interactions.(52)

224   Corneal topography is the measurement of the corneal shape. There are two different ways of

225   studying topography, one method is called videokeratoscopy and the other is elevation based

226   topography. Videokeratoscopy, also known as Placido-based topography, studies corneal shape by

227   analyzing rings reflected off the corneal surface.(53) Even though this method is better than its

228   precursor keratometry it has some disadvantages.(54) Videokeratoscopy evaluates only about 60%

229   of the total corneal area, which can leave out relevant data of peripheral or para-central pathologies

230   such as keratoconus.(53,55) Another disadvantage of videokeratoscopy is that it doesn't provide

231   information about the posterior corneal surface, which can give information on ectatic disorders

232   before they present on the anterior corneal surface and is key in the development of pachymetric

233   maps, as well as in reconstruction of corneal surface.(53,56) The other method used for the study of

234   corneal topography is called elevation-based topography, and it uses a stereo-triangulation

235   technique to make direct measurements of the corneal surface. Elevation-based topography uses

236   optical cross sectioning to triangulate both the anterior and posterior corneal surfaces, which offers

237   important advances over Placido-based devices, such as the ability to produce pachymetric maps, as

238   well as being more accurate in determining morphology as well as identifying keratoconus.(57–61)

239   This method of topography allows clinicians to view elevation data compared with a best fit sphere,

240   which gives the most useful qualitative map.(53)

241   **4.   Corneal Biomechanics**

242   Biomechanics is the development, extension and application of mechanics for the better

243   understanding of the physiology and physiopathology, as well as the diagnosis and treatment of

244   disease and injury. The aim of biomechanical modelling of human tissues is to predict the results or

245   effects of different surgical treatments or therapies.(62) Corneal biomechanics includes the

246   measurement of central pachymetry, but it also englobes other parameters such as viscosity,

247   elasticity, hydration, regional pachymetry and other factors.(63) As exposed in the corneal

248   physiology section, pachymetry is given mainly by the corneal stroma and its components. Corneal

249   elasticity, curvature and transparency are related to the way collagen fibrils are arranged.

250   Proteoglycans and its relationship with collagen types I and XII are related with corneal

251   hydration,(35) as are endothelial integrity and function.(64) Recalling the anatomical structure of

252   the cornea is important since alteration of the components can affect corneal biomechanics, as can

253   be seen with collagen tension disruption in refractive surgery.(65,66) **Figure 2** summarizes the

254   factors that influence corneal biomechanics.

255   To date, there are only 2 devices available for providing corneal biomechanical data in a clinical

256   setting, the Ocular Response Analyzer (ORA) (Reichert Technologies, Buffalo, New York, USA), a

257   dynamic bidirectional applanation device, and the Corvis ST (Oculus Optikgeräte GmbH, Wetzlar,

258   Germany), a dynamic Scheimpflug analyzer device.(62) Both of these devices report a dynamic

259   assessment of corneal biomechanical properties such as corneal hysteresis, which reflects corneal

260   viscosity, and corneal resistance factor, that relates to the elastic properties of the cornea.(67)

261   Understanding of corneal biomechanical parameters is important because minimal changes in the

262   corneal shape can induce significant variations in the optical properties of the eye. Changes due to

263   refractive surgery or corneal diseases also occur in the mechanical properties of the cornea, not just

264   the optical properties. It is essential to understand the consequences of modifications in geometry of

265   the cornea to improve the diagnosis and management of ectatic corneal disorders such as

266   keratoconus, and to understand the biomechanics of intraocular pressure after surgical procedures.

267   Decreases in corneal hysteresis and corneal resistance factor have been reported after refractive

268   surgery. These findings may be related with weakening of the corneal structure induced by laser

269   ablation. Alteration of corneal biomechanics by LASIK flap creation and excimer laser ablation

270   affects the postoperative measurement of intraocular pressure by Goldmann applanation tonometry;

271   however, other devices like the ORA have lower standard deviations in its measurements and

272   provide useful complementary clinical data.(67) It has also been frequently considered that corneas

273   with CCT below 510μm have a greater weakness for excimer laser refractive procedures,(68)

274   however other reports have shown safety and effectiveness in patients with CCT values

275   <500μm.(69)

276   The understanding of corneal anatomy and physiology are useful for the understanding of the

277   underlying mechanisms responsible for corneal biomechanics. It is of great importance to further

278   study corneal biomechanics because minimal changes can alter optical properties of the cornea and

279   weaken its structure making the cornea more susceptible to conditions such as ectasia or alter

280   postoperative measurement of parameters such as intraocular pressure. Corneal biomechanics give a

281   global vision of the way the cornea behaves and the effects surgical treatments or diseases have on

282   the cornea; however, this is a field still growing with new findings changing the boundaries of what

283   is known and can be done with safety regarding corneal stability.

284   **5.   Clinical significance of CCT values**

285   Corneal thickness is a determinant of corneal refractive power, which contributes to normal

286   vision,(31) and variations in this parameter have relevance in several ophthalmologic conditions.

287   Certain eye conditions seem to have an association with thinner or thicker corneas. For example,

288   eyes with congenital glaucoma may have thinner corneas, while eyes that have had cataract surgery,

289   Sturge-Weber Syndrome, or aniridia, often have thicker corneas.(70) Reduced CCT is also

290   important for the diagnosis and progression of primary open-angle glaucoma.(71) Thin corneas are

291   also present in keratoconus, a corneal ectasia with a prevalence of 1:2000 in general population.(7)

292   CCT could be abnormal in corneal dystrophies, some genetic diseases like Ehlers-Danlos syndrome,

293   Brittle corneal syndrome (BCS) or Osteogenesis Imperfecta, as well as seen in herpes simplex

294   keratitis.(72) CCT is also important in determining person's suitability for laser refractive surgery,

295   and in the assessment of intraocular pressure (IOP) values in patients undergoing refractive and

296   corneal transplant surgery, as well as in contact lens wearers.(73,74) **Table 1** summarizes some of

297   the main clinical implications of CCT. This section will give a more in depth review of these

298   subjects.

299   Perhaps one of the most studied implications of CCT is its impact on the assessment of IOP and on

300   the diagnosis and management of glaucoma.(3) Applanation tonometry is influenced by CCT.

301 Thicker corneas give an overestimation of IOP readings when measured with applanation

302 tonometry.(75) In a similar sense, thin corneas lead to an underestimation of intraocular

303 pressure.(73) Findings such as these, have made the use of corneal pachymetry in the management

304 of patients at risk for or with glaucoma increasingly recognized as important and necessary.(76)

305 Several correction algorithms have been described, however the consensus is that regardless of the

306 models and correction algorithms studied, adjustments for IOP based on CCT are critical for

307 clinical management.(2)

308 The Ocular Hypertension Treatment Study, a multicenter randomized trial designed to evaluate

309 safety and efficacy of topical ocular hypotensive medication in delaying or preventing the onset of

310 primary open-angle glaucoma, showed that a thin CCT measurement was a strong predictor for the

311 development of primary open-angle glaucoma in patients with ocular hypertension.(3) For every

312 40µm decrease in CCT the relative risk was 1.71, and individuals with CCTs of 555 µm or less

313 were found to have 3times greater risk of developing glaucoma compared with patients with CCTs

314 of greater than 588 µm.(2)

315 Another aspect in which CCT has various implications is in patients undergoing refractive surgery.

316 One of the options available for refractive surgery is LASIK. Given the high satisfaction rates of

317 LASIK and its widespread use, patients have high expectations of this procedure; however, there

318 are several risk factors that can lead to complications or retreatment of the patients.(77) Among the

319 complications of this procedure is the development of corneal ectasia, which has been defined as a

320 progressive steepening and thinning of the cornea after excimer laser corneal refractive surgery that

321 reduces uncorrected and even best spectacle-corrected visual acuity. This complication has been

322 frequently reported in patients with risk factors such as keratoconnus, forme fruste keratoconus and

323 high myopia;(5) however, it has also been described in patients without these risk factors, leading

324 to the development of scores to predict the development of ectasia. One such score is the Ectasia

325 Risk Score System proposed by Randleman et al. which among its parameters considers

326 preoperative corneal thickness and residual stromal bed thickness.(4) Santhiago also described a

327 relationship between the percent tissue altered and the risk of developing ectasia in patients with

328 normal preoperative topographic pattern. The percent tissue altered calculation also takes into

329 account the patient's preoperative central corneal thickness.(78) These data demonstrate that

330 corneal thickness is a relevant parameter in determining if a patient is a candidate for LASIK

331 surgery or should undergo a different procedure. Patients with thin corneas where stromal residual

332 bed after LASIK would be less than 300 μm and patients with flat or steep corneas, are considered

333 better candidates for photorefractive keratectomy (PRK).(79) However, patients with a final central

334 corneal thickness <400 μm are not considered candidates for PRK of LASIK. These limits are

335 controversial and different corneal thickness cutoffs have been proposed. Frequently, corneas below

336 510μm are considered as thin and therefore as corneas with biomechanical liability or weakness for

337 excimer laser refractive procedures (LASIK, PRK). However, there is increasing evidence

338 concerning the safety and effectiveness of LASIK surgery in patients with CCT values <500μm,

339 which suggest that there are other factors that affect corneal structural stability independently of

340 CCT. Hence, in order to consider a cornea as "normal", the entire topography (topographic pattern,

341 pachymetry map and elevation maps) along with the expected CCT for a given population, should

342 be taken into account.(80)

343 In line with the topic of refractive surgery, there is a growing concern that the process of removing

344 corneal tissue during this surgery will lead to an increased difficulty in diagnosing glaucoma. Since

345 removing of corneal tissue leads to a thinner corneal thickness, this surgery tends to alter IOP

346 measurements and may in turn require greater emphasis on the assessment of the optic disc and

347 visual fields for the diagnosis and treatment of glaucoma.(6)

348 Corneal thickness is also an important feature of keratoconus, a condition in which the cornea

349 assumes an irregular conical shape secondary to non-inflammatory thinning of the corneal stroma.

350 The thinning of the cornea induces irregular astigmatism, myopia and protrusion, leading to

351   impairment in the quality of vision.(7,81) In fact, one of the treatment options available for this

352   condition is cross-linking, which uses riboflavin and UVA light in order to form new covalent

353   bonds, or cross-links, between collagen fibrils thus strengthening and stabilizing the cornea.(28)

354   The result of such treatment is an increase in resistance against enzymatic degeneration of the

355   cornea, increase in the diameter of collagen fibrils and improvement in visual acuity.(82) There

356   have been several studies about the genetics behind keratoconus, and while there is still work to be

357   done to confirm the specific roles of the genes implicated in the disease, among the genes that have

358   been identified are visual system homeobox1 (*VSX1)* and superoxide dismutase 1 (*SOD1*), collagen

359   crosslinking enzyme lysyl oxidase (*LOX*), *COL5A1, FOXO1,* zinc finger protein 469 *(ZNF469),*

360   among others.(31,83–86)

361   Reduced CCT has also been associated with some genetic diseases such as congenital glaucoma,

362   osteogenesis imperfecta, Down syndrome, X-linked megalocornea, keratoconus, Marfan syndrome,

363   and Ehlers-Danlos syndrome, whereas increased CCT has been found in patients with congenital

364   aniridia.(70)

365   Taking on account the different conditions presented, it can be seen that CCT has importance in

366   several scenarios, from being a factor influencing in the measurement of clinical parameters, to

367   being a risk factor for certain diseases, or determining if a patient can undergo a certain type of

368   surgery or not. These implications encourage to the establishment of pachymetry as an important

369   element when approaching the ophthalmologic patient. The broad spectrum of implications of this

370   parameter encourages further investigation of the factors involved in its expression and other

371   clinical implications it may have, not just in the corneal and refractive surgery field but in other

372   areas of ophthalmology as well.

373   **6. "Normal" CCT values**

374   Once the clinical importance of the CCT has been discussed, the question that comes to mind is:

375   what are the "normal" parameters of corneal thickness? It is known that CCT values vary between

376   ethnic groups, and that there are several factors either extrinsic or intrinsic that can influence it

377   (these factors are discussed in another section of the review), however several studies have been

378   made trying to find a value for what can be taken as a normal CCT.

379   Although there are racial variations, the average adult CCT is 550μm.(87) In a meta-analysis by

380   Doughty and Zaman they reported CCT value in normal eyes with a mean of 536±31μm.(75) It has

381   been questioned if corneal thickness by itself could affect the measurement of IOP and vice versa.

382   This meta-analysis also revealed a significant association between the interrelationship of IOP and

383   CTT; it was found that the difference in IOP was significant in patients in the category with

384   "chronic disease", highly variable in patients with acute onset disease and this difference was

385   smaller for eyes designated as healthy.(75)

386   Doughty & Zaman established that it is hard to compare the CCT of different races since some

387   conditions (such glaucoma, hypertension and diabetes) and their prevalence are known to cause

388   changes in CCT.(75) Currently, there's considerable research dedicated to investigate the mean

389   CCT value of different ethnic groups and populations that indicate strong evidence of ethnic

390   differences in CCT. **Table 2** summarizes most of the populations studies conducted in this

391   regard(80,88–103). There are differences between ethnic groups that have been measured using

392   ultrasound pachymetry showing a wide distribution between the ethnic groups, for example the

393   Turkish population had the lowest CCT (500 ± 347) while the Chinese subjects the thickest (555.96

394   ±32.41). It is essential to compare information obtained from studies using similar methods in aim

395   to draw meaningful assumptions. It has been recognized that genetic classifications of ancestry

396   could serve as a more accurate estimate of ethnicity groups to detect true biological

397   differences.(104)

398   **7.   Genetic aspects of CCT**

399   Studies have been made with genes affecting corneal architecture, in which a relation between

400   genes and the CCT has been found. Of the first candidate genes to be studied were the ones related

401   with the corneal architecture and that were associated with genetic diseases such as osteogenesis

402   imperfecta or Ehlers Danlos. Genes associated with the development of the anterior segment have

403   also been studied, such as *PAX6,* forkhead box 01 *(FOXC1)* and zinc finger 469 *(ZNF469).*

404   Genome-wide association studies (GWAS) have identified some candidate genes, such as *COL5A1*

405   and *ZNF469*, both have been described in diverse population. Others have been described in

406   specific population, such as autogenous vein graft remodeling associated protein 8 *(AVGR8)*, which

407   has been associated to Caucasians, *COL8A2* to Asians and American Caucasians; *IBTK* to Asians;

408   *AKAP13* to Caucasians; *CHSY1* to Asians, and *FOXO1* to Caucasians and Latino (USA).(71)

409   From those mentioned above, there are four main genes known to influence CCT: *COL5A1*,

410   *FOXO1*, *AVGR8*, and *ZNF469*.

411   Collagen is the most abundant protein in the body and its fibrils are responsible for the functional

412   integrity of tissues and contribute a framework within which the tissue functions. They closely

413   relate to proteoglycans, hybrid-protein-polysaccharide molecules that form an interfibrillary matrix.

414   The relative proportion of collagen to interfibrillary matrix and the nature of this interaction impart

415   characteristic features to tissues, also accounting for the water content of the tissue. Particular

416   chemical groupings on the collagen molecule determines its physiological characteristics and the

417   methods by which they impart tissue specificity.(105) In the cornea, collagen is the principal

418   component of the stroma. The arrangement of the regularly orientated collagen fibrils, which is

419   maintained by chondroitin sulphate and keratan sulphate with interspaced keratocytes; is critical to

420   optical clarity.(19) Collagen type 5 determines the diameter of the corneal collagen fibrils. *COL5A1*

421   (OMIM: *120215) is located at 9q34.3, has 66 exons and encodes for α1 (V) chain of type V

422   collagen. *COL5A2* (OMIM: *120190) is located at 2q32.2, has 54 exons and encodes for α 2(V)

423   chain of type V collagen. These genes are present in over 50% of the families with classic Ehlers

424 Danlos. Collagen V determines 15-20% of the fibrillary collagens in corneal tissue.(106) In the

425 Col5a1+/- mouse cornea, type V collagen content decrease by approximately 49 % and stromal

426 thickness by approximately 26%. Total collagen deposition in Col5a1 (+/-) corneas also decrease.

427 Collagen fibril diameters are increased, but fibril density decrease throughout the stroma at all

428 developmental stages.(71,106,107) In patients with classic Ehlers-Danlos syndrome, the mean CCT

429 is 435.75µm ± 12.51 µm (range, 415–448 µm), the corneas are thin, steep and transparent with

430 floppy eyelids.(106)

431 Additionally, there are reports of two SNPs, rs1536482 and rs7044529, located near and within

432 COL5A1 associated with reduced CCT.(31,108) In a study conducted with three independent

433 cohorts of patients in which selected SNPs located within or near *COLA5A1* (including those

434 associated with CCT) for genotyping for association with keratoconus, rs1536482 and rs7044529

435 SNPs were found to be associated with keratoconus and CCT.(109) Corneal thinning is one of the

436 hallmarks of keratoconus; however, it is not clear whether the *COL5A1* association with

437 keratoconus is an independent finding or is due to association with corneal thinning in general. In

438 this study, although the difference in CCT between the genotypes was not statistically significant

439 for rs1536482 and rs7044529, the effect size of the risk allele was −3 and −10µm respectively,

440 suggesting that the association between keratoconus and this gene may be independent of CCT.

441 *ZNF469* (OMIM *612078) is located at 16q24, has a single exon and encodes for a zinc protein

442 finger 469. Its function is unknown. However, this protein has a 30% homology to the helical parts

443 of COL1A2, COL4A1, COL1A1, all which are highly expressed in the cornea. The transparency

444 and strength of the cornea requires maintenance of structural organization, as well as the precise

445 regulation of fibril and matrix assembly. *ZNF469* either could act as a nuclear transcription factor or

446 as an extra-nuclear regulatory molecule involved in the synthesis and/or organization of these

447 collagen fibers.(110) There is another gene related to brittle cornea syndrome (BCS), *PRDM5*

448 (OMIM *614161), located at 4q27, which encodes for a transcription factor, but still has not been

449   identified by GWAS as a contributor to CCT. It is the most frequent genetic cause of BCS,(111)

450   and close variants may contribute to CCT variation.(72) Mutations in *PRDM5* and *ZNF469* have

451   been correlated with disarray of collagens I and III, fibronectin, and their receptor α2β1 and α5β1

452   integrin in vitro through shared molecular pathways.(112) In keratoconus, heterozygous alleles of

453   *ZNF469* have been associated with the disease development with a relative risk of 12.0.(113) This

454   evidence highlights *ZNF469* as the main genetic factor of keratoconus.

455   *FOXO1* (OMIM *136533) is a protein coding gene located at 13q14. Its protein is the main target of

456   insulin signaling and regulates metabolic homeostasis in response to oxidative stress. *FOXO1*

457   expresses in the cornea, although it has no proven function in ocular development it is one of the

458   targets for transcriptional regulation by *FOXC1*, which play a critical role in corneal development.

459   Mutations in *FOXC1* are associated with various anterior segment malformations and glaucoma in

460   Axenfeld-Rieger syndrome. Two recent different studies conducting GWAS have reported the SNP

461   rs2721051 in the genomic region of *FOXO1* with strong association with a risk of keratoconus (odd

462   ratio of 1.62 and 1.4).(86,114) Further evaluation of the clinical relevance of these SNP along with

463   analysis implicating the collagen and extracellular matrix in the regulation of CCT will allow

464   understanding the molecular pathways of CCT.

465   Vitart described the locus defined by rs1034200 as a factor related with CCT.(31) This locus was

466   found 5kb from *AVGR8* gene, encoding a putative transcription factor with typical ZNF and KRAB

467   domains, in chromosomal region 13q12.11. The *AVGR8* gene appears to be a transcription factor of

468   unknown function with a Krueppel-associated box (KRAB) domain and at least five prototypical

469   C2H2 ZNF domains. Although only a few genes regulating corneal gene expression are known, it is

470   believed that *AVGR8* could play a role in the correct assembly and organization of the corneal

471   structure. In a study reported in 2012, the same locus rs1034200 near from *AVGR8* showed relation

472   with Fuchs dystrophy. However, the effect was much large in CCT than in Fuchs. This study

473   estimated that along with three SNPs in *ZNF469* and with rs1409832 between *COL5A1* and *RXRA*,

474   *AVGR8* is associated with an 8- to 16-µm change in corneal thickness.(115)

475   Additional GWAS have identified a number of genes and SNPs associated with CCT, **Table 3**

476   summarizes the findings of the genes described as well as some of the reports on these other genes

477   and SNPs that could be related to CCT(115–121). Together with *COL5A1*, *FOXO1*, *AVGR8*, and

478   *ZNF469*, the analysis of the influence of these genes over CCT will eventually provide a catalog of

479   common genetic variation affecting corneal structure and their relevance in the treatment of corneal

480   diseases.

481   **8. Factors influencing CCT**

482   In addition to the influence of genetic factors on CCT, several other extrinsic factors are known to

483   have influence on CCT. Among these factors are the age of the patient, physiologic diurnal

484   variations, UV radiation, altitude, chronic contact lens use, and various diseases. This section will

485   briefly review the evidence reported regarding the influence of some of these factors on CCT.

486

487   Age. Reports on a relationship between CCT and age are contradictory. While some studies report a

488   statistically significant inverse relationship between these variables,(88) others indicate there is no

489   statistical significant relationship between these variables.(96) Overall, the evidence from published

490   studies made in whites suggests that for the majority of individuals there is no substantial change in

491   CCT beyond the infant years, however studies done in different ethnic groups like those of Japanese

492   and Eskimo prove there is a significant difference.(75,88)

493   Diurnal variation of CCT. Corneal thickness can also increase due to net water influx. Pachymetry

494   indirectly reflects endothelial function because the endothelium maintains corneal thickness and

495   transparency by regulating the flux of water and solutes across the posterior corneal surface.(1,64)

496   Because of the changes in corneal thickness due to hydration, there is a diurnal physiological

497 variability on CCT. Data confirm an increase of corneal thickness during sleep having its peak

498 value at 4 am, but considerable variation during waking hours has also been reported.(122) Corneal

499 thickness may increase immediately after waking up due to overnight corneal hydration. This is

500 consequence of diminished evaporation of water from closed lids and reduced nocturnal metabolic

501 activity of the endothelium. Corneal hydration during sleep is caused because the cornea

502 experiences hypoxia beneath closed eyelids. This reduction in oxygen increases anaerobic

503 metabolism causing accumulation of lactate within the stroma, followed by an osmotic influx of

504 water.(123) Reports about the percentage of diurnal changes in CCT vary depending on the study,

505 however it is consistently found to be significant.(123–125) A 5.5% overnight increase, with a 7.2%

506 of diurnal variation was reported in 1996 by Harper and collaborators.(123) Du Toit and

507 collaborators reported in 2003 a variation of 3.9% over 24 hours with an overnight swelling of

508 around 2.9%, concluding that baseline CCT can be measured at any time from 7 hours of eye

509 opening.(124)

510 UV radiation: The entire anterior eye segment can be damaged when exposed to UV-B, the parts

511 that receive most damage are the cornea and the lens. Repeated exposure to UV-B radiation has

512 shown to damage the corneal epithelium and disturb corneal metabolites.(126) It has been known

513 that UV radiation may cause photokeratitis, also known as snow blindness, which is a transitory

514 inflammatory condition caused by damage to the corneal epithelium.(87,127) UV-B irradiation may

515 also cause or promote changes in the endothelium associated with aging.(128) Another effect of UV

516 radiation on the cornea is an increase in biomechanical stiffness when used in combination with

517 riboflavin.(28,129) This effect is due to the increase in the collagen crosslinks in the corneal stroma,

518 this technique has been exploited specially in the treatment of conditions such as

519 keratoconus.(28,130)

520 Altitude: The human eye, like several other organs, is affected by hypoxia at high altitude. Hypoxia

521 makes the cornea shift to anaerobic metabolism, with a subsequent increase in extracellular

522   metabolic byproducts, causing a hydration pressure shift into the extracellular stromal spaces.(131)

523   This hydration secondary to hypoxia results in increased CCT. The cornea returns to its initial

524   thickness after descent. In other studies, individuals with more acute mountain sickness-related

525   symptoms have been found to have thicker corneas, suggesting that CCT could be used as a

526   parameter to indicate if a person is susceptible to acute mountain syndrome.(132)

527   Chronic contact lens use: Chronic use of contact lenses and dry eye can also increase CCT.(122)

528   Differences between morning and afternoon CCT readings may be exaggerated in contact lens

529   wearers. The lens type and the period of lens wear can be important factors for the changes in CCT

530   after contact lens use.(75)

531   Diseases: Corneal thickness vary in several diseases, or can have impact on the severity of an

532   ophthalmologic condition. One such disease is glaucoma, in which as presented before, lower CCT

533   is associated with worsened advanced glaucoma and greater risk of developing glaucoma.(2,133)

534   Another condition associated with abnormalities in corneal thickness is keratoconus. This is a non-

535   inflammatory disease of the cornea that mainly affects the central cornea and is characterized by

536   thinning and ectasia.(134) Corneal thinning in this condition is a result of the loss of its structural

537   components.(7) With increasing keratoconus severity, the cornea becomes thinner, and as presented

538   above, this thinning of the cornea induces irregular astigmatism, myopia and protrusion, leading to

539   impairment in the quality of vision. Diabetes has been associated with alterations in the corneal

540   endothelium. Among the disorders observed in diabetic patients are decreased endothelial cell

541   density, glycation of membrane ATPases, and a decrease in Na+/K+-ATPase activity.(135) These

542   changes influence the endothelial pump action and hence induce dysfunction. As presented above,

543   the pump function of the endothelial layer is responsible for the active dehydration of the cornea

544   and its alteration correlates with thickening of the cornea.(64) CCT in diabetic patients is

545   significantly thicker than in control groups,(136) and there has also been a correlation between

546   duration of diabetes mellitus and CCT.(135,137) Congenital glaucoma also relates with changes in

547   corneal thickness. Pediatric patients with congenital cataract have been reported to have thicker

548   central corneas when compared to contralateral healthy eye and a normal population.(138,139) This

549   increase in corneal thickness in the eyes with cataract may be a consequence of delayed

550   development and maturation of the cornea.(140) Another ophthalmologic disease related with

551   endothelial cell dysfunction is Fuch's endothelial corneal dystrophy. The endothelial dysfunction

552   present in this disease results in corneal edema and hence an increase in CCT.(141) Thickening

553   presents mainly in the later stages of the disease and its physiological basis has been attributed to

554   alteration in Na+/K+-ATPase activity and breakdown in the barrier function of the

555   endothelium.(142) It has been found that the point at which the compensatory mechanisms of the

556   corneal endothelium fail in Fuch's dystrophy, and corneal edema results, is when the central

557   endothelial cell density reaches around 700-400 cells/mm^2.(38,39) Other ophthalmologic diseases

558   that are related with changes in CCT are Behçet's disease and retinal vein occlusion. Eyes with

559   active Behçet's disease have increased CCT probably related to active inflammation that returns to

560   normal after treatment.(143) Patients with central retinal vein occlusion have thinner CCT than

561   controls, however the pathophysiology underlying this association is unclear.(144)

562   While some of the factors influencing CCT are related with delayed development, inflammation or

563   altered arrangement of collagen fibrils, most of them are related to alteration in endothelial integrity

564   and permeability. Diurnal variation, altitude and contact lens related changes in CCT directly relates

565   with corneal hydration. Likewise, the effects of UV-B radiation relate to endothelial damage and the

566   consequent increased corneal hydration. Even some of the diseases studied, such as diabetes and

567   Fuch's endothelial corneal dystrophy, also increase CCT by altering the endothelium's barrier or

568   pump function. This is in line with the statement that pachymetry indirectly reflects endothelial

569   function.(64) However, there remains work to be done to fully understand the pathophysiology

570   underlying the relationship with other factors such as central vein occlusion.

571   **9. Heritability**

24

572   Corneal central thickness is highly heritable. There is no clear genetic correlation between a thinner

573   cornea and primary open angle glaucoma (POAG). There are genetic variants that had been proved

574   to contribute to CCT, most of which are population specific. Further genomic studies from each

575   population will lead to the finding of genetic variants associated to CCT. Therefore, these studies

576   are useful as tools to evaluate corneal health status. Additive genetic effects appear to be the major

577   contributor to the variation of CCT.(70,145) Familial and twin studies suggest CCT heritability

578   could be as high as 0.95.(70) Further data supporting heritability is the high prevalence of

579   glaucoma in some populations in which the CCT tends to be lower, compared against other groups.

580   At first, it was thought that CCT and POAG could be genetically related, because of their close

581   relation. Thus, if CCT genes were found, it could be possible to find POAG genes also. However,

582   no such relation has been found so far.

583   **10. Conclusion**

584   Corneal thickness is a parameter of the cornea that has important implications in several aspects of

585   ophthalmology, from its effect on the measurement of IOP to its impact on refractive surgery and

586   diseases like keratoconus. This review has addressed the subject of corneal thickness trying to

587   broadly cover all parameters that influence or have implications in CCT in order to fill in the gap

588   between scholar articles and more specific and advanced ones found in the literature. In order to do

589   so, general concepts regarding corneal anatomy and physiology were reviewed initially for the

590   better understanding of their relevance in the areas of corneal biomechanics and corneal

591   topography, which are helpful tools in the study of corneal structure and the effects surgical

592   treatment and therapies have on the physiological conditions of human cornea such as its optical

593   properties and general structure. The importance of CCT in several clinical scenarios was reviewed,

594   with it being a factor influencing in the measurement of clinical parameters, to being a risk factor

595   for several diseases, and determining if a patient can undergo a certain type of surgery or not. A

596   revision of the studies about average adult CCT was done, showing a comparison between different

597   population studies in order to reflect the variations among different ethnicities as well as illustrating

598   what is generally considered as an average CCT value. An analysis of the genes known to influence

599   CCT was done, with main emphasis in COL5A1, FOXO1, AVGR8, and ZNF469, which are the

600   most related with corneal thickness, however other promising genes in this field were also

601   mentioned. In addition to the influence of genetics, several other extrinsic factors known to have

602   influence on CCT were reviewed including the age of the patient, physiologic diurnal variations,

603   UV radiation, altitude, chronic contact lens use, and various diseases. While some of the factors

604   influencing CCT are related with delayed development, inflammation or altered arrangement of

605   collagen fibrils, most of them are related to a lack of endothelial integrity, permeability and corneal

606   hydration.

607   Even though extensive research on this topic has been done, the broad spectrum of clinical

608   implications of CCT encourages further investigation of the factors involved in its expression and

609   other clinical implications it may have, not just in the corneal and refractive surgery field but in

610   other areas of ophthalmology as well. There is still work to be done especially in areas like

611   biomechanics, which continue to push the boundaries of what is known about structure and

612   functioning, as well as about what is done in terms of safety regarding surgical procedures.

613

614

11. References:

1. Farjo AA, Brumm M V., Soong HK. Corneal Anatomy, Physiology, and Wound Healing. In: Yanoff M, Duker JS, editors. Ophthalmology. 4th ed. Elsevier Inc.; 2014. p. 163–7.

2. Shih CY, Graff Zivin JS, Trokel SL, Tsai JC. Clinical Significance of Central Corneal Thickness in the Managementof Glaucoma. Arch Ophthalmol. 2004 Sep 1;122(9):1270.

3. Gordon MO, Beiser JA, Brandt JD, Heuer DK, Higginbotham EJ, Johnson CA, et al. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. Arch Ophthalmol (Chicago, Ill 1960). 2002 Jun;120(6):714-20-30.

4. Randleman JB, Woodward M, Lynn MJ, Stulting RD. Risk Assessment for Ectasia after Corneal Refractive Surgery. Ophthalmology. 2008 Jan;115(1):37–50.e4.

5. Tabbara K, Kotb A. Risk Factors for Corneal Ectasia after LASIK. Ophthalmology. 2006 Sep;113(9):1618–22.

6. Emara B, Probst LE, Tingey DP, Kennedy DW, Willms LJ, Machat J. Correlation of intraocular pressure and central corneal thickness in normal myopic eyes and after laser in situ keratomileusis. J Cataract Refract Surg. 1998 Oct;24(10):1320–5.

7. Rabinowitz YS. Keratoconus. Surv Ophthalmol. 1998;42(4):297–319.

8. Rüfer F, Schröder A, Erb C. White-to-white corneal diameter: normal values in healthy humans obtained with the Orbscan II topography system. Cornea. 2005 Apr;24(3):259–61.

9. Khng C, Osher RH. Evaluation of the relationship between corneal diameter and lens diameter. J Cataract Refract Surg. 2008 Mar;34(3):475–9.

10. Beebe DC. Maintaining transparency: A review of the developmental physiology and pathophysiology of two avascular tissues. Semin Cell Dev Biol. 2008 Apr;19(2):125–33.

11. Schmoll T, Unterhuber A, Kolbitsch C, Le T, Stingl A, Leitgeb R. Precise thickness measurements of Bowman's layer, epithelium, and tear film. Optom Vis Sci. 2012

639   May;89(5):E795-802.

640 12. Hanna C, Bicknell DS, O'Brien JE. Cell turnover in the adult human eye. Arch Ophthalmol

641   (Chicago, Ill 1960). 1961 May;65:695–8.

642 13. Tao A, Wang J, Chen Q, Shen M, Lu F, Dubovy SR, et al. Topographic thickness of

643   Bowman's layer determined by ultra-high resolution spectral domain-optical coherence

644   tomography. Invest Ophthalmol Vis Sci. 2011 Jun 1;52(6):3901–7.

645 14. Patel S, McLaren J, Hodge D, Bourne W. Normal human keratocyte density and corneal

646   thickness measurement by using confocal microscopy in vivo. Invest Ophthalmol Vis Sci.

647   2001 Feb;42(2):333–9.

648 15. Reinstein DZ, Archer TJ, Gobbe M, Silverman RH, Coleman DJ. Stromal Thickness in the

649   Normal Cornea: Three-Dimensional Display with Artemis Very High-Frequency Digital

650   Ultrasound. J Refract Surg. 2009 Sep 1;25(9):776–86.

651 16. Radner W, Zehetmayer M, Aufreiter R, Mallinger R. Interlacing and cross-angle distribution

652   of collagen lamellae in the human cornea. Cornea. 1998 Sep;17(5):537–43.

653 17. Birk DE. Type V collagen: heterotypic type I/V collagen interactions in the regulation of

654   fibril assembly. Micron. 2001 Apr;32(3):223–37.

655 18. Rawe IM, Zhan Q, Burrows R, Bennett K, Cintron C. Beta-ig. Molecular cloning and in situ

656   hybridization in corneal tissues. Invest Ophthalmol Vis Sci. 1997 Apr;38(5):893–900.

657 19. Bowling B, Kanski J. Kanski's Clinical Ophthalmology A Systematic Approach. 8th ed.

658   Elsevier Health Sciences, editor. Elsevier; 2016. 928 p.

659 20. Cogan DG, Kuwabara T. Growth and regenerative potential of Descemet's membrane. Trans

660   Ophthalmol Soc U K. 1971;91:875–94.

661 21. Waring GO, Bourne WM, Edelhauser HF, Kenyon KR. The corneal endothelium. Normal

662   and pathologic structure and function. Ophthalmology. 1982 Jun;89(6):531–90.

663 22. Zavala J, López Jaime GR, Rodríguez Barrientos CA, Valdez-Garcia J. Corneal

664   endothelium: developmental strategies for regeneration. Eye (Lond). 2013 May 8;27(5):579–

665 88.

666 23. Dua HS, Faraj LA, Said DG, Gray T, Lowe J. Human corneal anatomy redefined: a novel

667 pre-Descemet's layer (Dua's layer). Ophthalmology. 2013 Sep;120(9):1778–85.

668 24. Zaki AA, Elalfy MS, Said DG, Dua HS. Deep anterior lamellar keratoplasty--triple

669 procedure: a useful clinical application of the pre-Descemet's layer (Dua's layer). Eye

670 (Lond). 2015 Mar 31;29(3):323–6.

671 25. McKee HD, Irion LCD, Carley FM, Brahma AK, Jafarinasab MR, Rahmati-Kamel M, et al.

672 Re: Dua et al.: Human corneal anatomy redefined: a novel pre-Descemet layer (Dua's layer)

673 (Ophthalmology 2013;120:1778-85). Ophthalmology. 2014 May;121(5):e24-5.

674 26. Ashwin PT, McDonnell PJ. Collagen cross-linkage: a comprehensive review and directions

675 for future research. Br J Ophthalmol. 2010 Aug 1;94(8):965–70.

676 27. Barnard K, Light ND, Sims TJ, Bailey AJ. Chemistry of the collagen cross-links. Origin and

677 partial characterization of a putative mature cross-link of collagen. Biochem J. 1987 Jun

678 1;244(2):303–9.

679 28. Hovakimyan M, Guthoff RF, Stachs O. Collagen cross-linking: current status and future

680 directions. J Ophthalmol. 2012;2012:406850.

681 29. Siegel RC. Collagen cross-linking. Synthesis of collagen cross-links in vitro with highly

682 purified lysyl oxidase. J Biol Chem. 1976 Sep 25;251(18):5786–92.

683 30. Albert DM, Jakobiec FA, Miller JW. Principles and practice of ophthalmology. Saunders W

684 B Co, editor. Saunders/Elsevier; 2008. 5461 p.

685 31. Vitart V, Bencić G, Hayward C, Skunca Herman J, Huffman J, Campbell S, et al. New loci

686 associated with central cornea thickness include COL5A1, AKAP13 and AVGR8. Hum Mol

687 Genet. 2010 Nov 1;19(21):4304–11.

688 32. Fratzl P. Collagen - Structure and Mechanics. Springer Science & Business Media, editor.

689 New York: Springer; 2008. 506 p.

690 33. Elsheikh A, Wang D, Brown M, Rama P, Campanelli M, Pye D. Assessment of corneal

691   biomechanical properties and their variation with age. Curr Eye Res. 2007 Jan 2;32(1):11–9.

692   34.   Seiler T, Huhle S, Spoerl E, Kunath H. Manifest diabetes and keratoconus: a retrospective

693   case-control study. Graefes Arch Clin Exp Ophthalmol. 2000 Oct;238(10):822–5.

694   35.   Carlson EC, Liu C-Y, Chikama T, Hayashi Y, Kao CW-C, Birk DE, et al. Keratocan, a

695   cornea-specific keratan sulfate proteoglycan, is regulated by lumican. J Biol Chem. 2005 Jul

696   8;280(27):25541–7.

697   36.   Ihanamäki T, Pelliniemi LJ, Vuorio E. Collagens and collagen-related matrix components in

698   the human and mouse eye. Prog Retin Eye Res. 2004 Jul;23(4):403–34.

699   37.   Müller LJ, Pels L, Vrensen GF. Ultrastructural organization of human corneal nerves. Invest

700   Ophthalmol Vis Sci. 1996 Mar;37(4):476–88.

701   38.   Bonanno JA. Identity and regulation of ion transport mechanisms in the corneal

702   endothelium. Prog Retin Eye Res. 2003 Jan;22(1):69–94.

703   39.   Edelhauser HF. The balance between corneal transparency and edema: the Proctor Lecture.

704   Invest Ophthalmol Vis Sci. 2006 May 1;47(5):1754–67.

705   40.   DelMonte DW, Kim T. Anatomy and physiology of the cornea. J Cataract Refract Surg.

706   2011 Mar;37(3):588–98.

707   41.   Marfurt CF, Cox J, Deek S, Dvorscak L. Anatomy of the human corneal innervation. Exp

708   Eye Res. 2010 Apr;90(4):478–92.

709   42.   Müller LJ, Marfurt CF, Kruse F, Tervo TMT. Corneal nerves: structure, contents and

710   function. Exp Eye Res. 2003 May;76(5):521–42.

711   43.   Spadea L, Salvatore S, Vingolo EM. Corneal Sensitivity in Keratoconus: A Review of the

712   Literature. Sci World J. 2013;2013:1–7.

713   44.   Zander E, Weddell G. Observations on the innervation of the cornea. J Anat. 1951

714   Jan;85(1):68–99.

715   45.   Kraff CR, Robin JB. Normal Corneal Topography. In: Schanzlin DJ, Robin JB, editors.

716   Corneal Topography Measuring and Modifying the Cornea. New York: Springer New

717   York; 1992. p. 33–8.

718 46. González-Pérez J, González-Méijome JM, Rodríguez Ares MT, Parafita MA. Central

719   corneal thickness measured with three optical devices and ultrasound pachometry. Eye

720   Contact Lens. 2011 Mar;37(2):66–70.

721 47. Nguyen TD, Jones RE, Boyce BL. A nonlinear anisotropic viscoelastic model for the tensile

722   behavior of the corneal stroma. J Biomech Eng. 2008 Aug;130(4):41020.

723 48. Comaish IF, Lawless MA. Progressive post-LASIK keratectasia: biomechanical instability

724   or chronic disease process? J Cataract Refract Surg. 2002 Dec;28(12):2206–13.

725 49. Pinheiro MN, Bryant MR, Tayyanipour R, Nassaralla BA, Wee WR, McDonnell PJ. Corneal

726   integrity after refractive surgery. Effects of radial keratotomy and mini-radial keratotomy.

727   Ophthalmology. 1995 Feb;102(2):297–301.

728 50. Wang JQ, Zeng YJ, Li XY. Influence of some operational variables on the radial keratotomy

729   operation. Br J Ophthalmol. 2000 Jun;84(6):651–3.

730 51. Müller LJ, Pels E, Vrensen GF. The specific architecture of the anterior stroma accounts for

731   maintenance of corneal curvature. Br J Ophthalmol. 2001 Apr;85(4):437–43.

732 52. Wilson SE, Hong JW. Bowman's layer structure and function: critical or dispensable to

733   corneal function? A hypothesis. Cornea. 2000 Jul;19(4):417–20.

734 53. Belin MW, Khachikian SS. An introduction to understanding elevation-based topography:

735   how elevation data are displayed - a review. Clin Experiment Ophthalmol. 2009

736   Jan;37(1):14–29.

737 54. Brody J, Waller S, Wagoner M. Corneal topography: history, technique, and clinical uses.

738   Int Ophthalmol Clin. 1994;34(3):197–207.

739 55. American Academy of Ophthalmology. Corneal topography. American Academy of

740   Ophthalmology. Ophthalmology. 1999 Aug;106(8):1628–38.

741 56. Belin MW, Zloty P. Accuracy of the PAR corneal topography system with spatial

742   misalignment. CLAO J. 1993 Jan;19(1):64–8.

743   57.   Belin MW, Litoff D, Strods SJ, Winn SS, Smith RS. The PAR Technology Corneal

744   Topography System. Refract Corneal Surg. 1992;8(1):88–96.

745   58.   Lackner B, Schmidinger G, Skorpik C. Validity and repeatability of anterior chamber depth

746   measurements with Pentacam and Orbscan. Optom Vis Sci. 2005 Sep;82(9):858–61.

747   59.   O'Donnell C, Maldonado-Codina C. Agreement and repeatability of central thickness

748   measurement in normal corneas using ultrasound pachymetry and the OCULUS Pentacam.

749   Cornea. 2005 Nov;24(8):920–4.

750   60.   Schultze RL. Accuracy of corneal elevation with four corneal topography systems. J Refract

751   Surg. 1998;14(2):100–4.

752   61.   Uçakhan OO, Ozkan M, Kanpolat A. Corneal thickness measurements in normal and

753   keratoconic eyes: Pentacam comprehensive eye scanner versus noncontact specular

754   microscopy and ultrasound pachymetry. J Cataract Refract Surg. 2006 Jun;32(6):970–7.

755   62.   Piñero DP, Alcón N. Corneal biomechanics: a review. Clin Exp Optom. 2015

756   Mar;98(2):107–16.

757   63.   Liu J, Roberts CJ. Influence of corneal biomechanical properties on intraocular pressure

758   measurement: quantitative analysis. J Cataract Refract Surg. 2005 Jan;31(1):146–55.

759   64.   Ehlers N, Hjortdal J. Corneal thickness: Measurement and implications. Experimental Eye

760   Research. 2004.

761   65.   Chen MC, Lee N, Bourla N, Hamilton DR. Corneal biomechanical measurements before and

762   after laser in situ keratomileusis. J Cataract Refract Surg. 2008 Nov;34(11):1886–91.

763   66.   Wang D, Liu M, Chen Y, Zhang X, Xu Y, Wang J, et al. Differences in the Corneal

764   Biomechanical Changes After SMILE and LASIK. J Refract Surg. 2014 Oct 1;30(10):702–

765   7.

766   67.   Pepose JS, Feigenbaum SK, Qazi MA, Sanderson JP, Roberts CJ. Changes in corneal

767   biomechanics and intraocular pressure following LASIK using static, dynamic, and

768   noncontact tonometry. Am J Ophthalmol. 2007 Jan;143(1):39–47.

769   68.   Garcia-Gonzalez M, Teus MA, Juhasz E. Flap thickness in femtosecond laser. J Refract

770   Surg. 2015 Feb 1;31(2):140.

771   69.   Tatar MG, Aylin Kantarci F, Yildirim A, Uslu H, Colak HN, Goker H, et al. Risk Factors in

772   Post-LASIK Corneal Ectasia. J Ophthalmol. 2014;2014:1–4.

773   70.   Toh T, Liew SHM, MacKinnon JR, Hewitt AW, Poulsen JL, Spector TD, et al. Central

774   Corneal Thickness Is Highly Heritable: The Twin Eye Studies. Investig Opthalmology Vis

775   Sci. 2005 Oct 1;46(10):3718.

776   71.   Hoehn R, Zeller T, Verhoeven VJM, Grus F, Adler M, Wolfs RC, et al. Population-based

777   meta-analysis in Caucasians confirms association with COL5A1 and ZNF469 but not

778   COL8A2 with central corneal thickness. Hum Genet. 2012 Nov 20;131(11):1783–93.

779   72.   Lu Y, Dimasi DP, Hysi PG, Hewitt AW, Burdon KP, Toh T, et al. Common genetic variants

780   near the Brittle Cornea Syndrome locus ZNF469 influence the blinding disease risk factor

781   central corneal thickness. PLoS Genet. 2010 May 13;6(5):e1000947.

782   73.   Hassan M ul, Rehman A ur, Abbas M, Fawad U, Bhatti N, Daud A. Relationship between

783   Central Corneal Thickness and Intraocular Pressure in Selected Pakistani Population.

784   Pakistan J Ophthalmol. 2010;26(2):79–82.

785   74.   Patwardhan AA, Khan M, Mollan SP, Haigh P. The importance of central corneal thickness

786   measurements and decision making in general ophthalmology clinics: a masked

787   observational study. BMC Ophthalmol. 2008 Jan 20;8(1):1.

788   75.   Doughty MJ, Zaman ML. Human corneal thickness and its impact on intraocular pressure

789   measures: a review and meta-analysis approach. Surv Ophthalmol. 2000;44(5):367–408.

790   76.   Thomas R, Korah S, Muliyil J. The role of central corneal thickness in the diagnosis of

791   glaucoma. Indian J Ophthalmol. 2000 Jun;48(2):107–11.

792   77.   Valdez-García JE, Hernandez-Camarena JC, Martínez-Muñoz R. 3-Year follow-up after

793   Lasik: assessing the risk factors for retreatment. Int Ophthalmol. 2016 Feb 19;36(1):91–6.

794   78.   Santhiago MR, Smadja D, Gomes BF, Mello GR, Monteiro MLR, Wilson SE, et al.

795   Association Between the Percent Tissue Altered and Post–Laser In Situ Keratomileusis

796   Ectasia in Eyes With Normal Preoperative Topography. Am J Ophthalmol. 2014

797   Jul;158(1):87–95.e1.

798 79. Torricelli AAM, Bechara SJ, Wilson SE. Screening of Refractive Surgery Candidates for

799   LASIK and PRK. Cornea. 2014 Oct;33(10):1051–5.

800 80. Valdez-García JE, Hernandez-Camarena JC, Lozano-Ramírez JF, Zavala J, Loya-García D,

801   Merayo-Lloves J. Correlation of age, corneal curvature and spherical equivalent with central

802   corneal thickness. Rev Mex Oftalmol. 2016;

803 81. Valdez-García JE, Sepúlveda R, Salazar-Martínez JJ, Lozano-Ramírez JF. Prevalence of

804   keratoconus in an adolescent population. Rev Mex Oftalmol. 2014;88(3):95–8.

805 82. Farjadnia M, Naderan M. Corneal cross-linking treatment of keratoconus. Oman J

806   Ophthalmol. 2015;8(2):86–91.

807 83. Bykhovskaya Y, Margines B, Rabinowitz YS. Genetics in Keratoconus: where are we? Eye

808   Vis. 2016 Dec 27;3(1):16.

809 84. Gao X, Gauderman WJ, Liu Y, Marjoram P, Torres M, Haritunians T, et al. A Genome-

810   Wide Association Study of Central Corneal Thickness in Latinos. Investig Opthalmology

811   Vis Sci. 2013 Apr 1;54(4):2435.

812 85. Gordon-Shaag A, Millodot M, Shneor E, Liu Y. The Genetic and Environmental Factors for

813   Keratoconus. Biomed Res Int. 2015;2015:1–19.

814 86. Lu Y, Vitart V, Burdon KP, Khor CC, Bykhovskaya Y, Mirshahi A, et al. Genome-wide

815   association analyses identify multiple loci associated with central corneal thickness and

816   keratoconus. Nat Genet. 2013 Feb 6;45(2):155–63.

817 87. Roberts JE. Ocular phototoxicity. J Photochem Photobiol B. 2001 Nov 15;64(2–3):136–43.

818 88. Aghaian E, Choe JE, Lin S, Stamper RL. Central corneal thickness of Caucasians, Chinese,

819   Hispanics, Filipinos, African Americans, and Japanese in a glaucoma clinic. Ophthalmology.

820   2004;111(12):2211–9.

821   89.   Haseltine SJ, Pae J, Ehrlich JR, Shammas M, Radcliffe NM. Variation in corneal hysteresis

822   and central corneal thickness among black, hispanic and white subjects. Acta Ophthalmol.

823   2012 Dec;90(8):e626–31.

824   90.   Wong AC-M, Wong C-C, Yuen NS-Y, Hui S-P. Correlational study of central corneal

825   thickness measurements on Hong Kong Chinese using optical coherence tomography,

826   Orbscan and ultrasound pachymetry. Eye. 2002 Nov 13;16(6):715–21.

827   91.   Hwang YH, Kim HK, Sohn YH, Namil Study Group, Korean Glaucoma Society. Central

828   Corneal Thickness in a Korean Population: The Namil Study. Investig Opthalmology Vis

829   Sci. 2012 Oct 5;53(11):6851.

830   92.   Godar ST, Kaini KR, Khattri JB. Factors Affecting the Central Corneal Thickness in

831   Nepalese Population. Nepal J Med Sci. 2012;1(1):7–10.

832   93.   Iyamu E, Iyamu JE, Oghovwerha L. Anthropometry, amplitude of accommodation, and

833   spherical equivalent refractive error in a nigerian population. ISRN Ophthalmol.

834   2012;2012:295613.

835   94.   Eballe AO, Epée E, Godefroy K, Bella AL. Analysis of central corneal thickness in black

836   Cameroonian children. Clin Optom. 2010 Nov;2:113–7.

837   95.   Rüfer F, Sander S, Klettner A, Frimpong-Boateng A, Erb C. Characterization of the

838   Thinnest Point of the Cornea Compared With the Central Corneal Thickness in Normal

839   Subjects. Cornea. 2009 Feb;28(2):177–80.

840   96.   Gros-Otero J, Arruabarrena-Sánchez C, Teus M. [Central corneal thickness in a healthy

841   Spanish population]. Arch Soc Esp Oftalmol. 2011 Mar;86(3):73–6.

842   97.   Landers JA, Billing KJ, Mills RA, Henderson TR, Craig JE. Central Corneal Thickness of

843   Indigenous Australians Within Central Australia. Am J Ophthalmol. 2007 Feb;143(2):360–

844   2.

845   98.   Bamashmus MA, Saleh MF, Mousa A, Abdulrahman M, Fawzi M. Central corneal

846   pachymetry in Yemeni patients undergoing refractive surgery. Saudi Med J. 2014

847   Jan;35(1):56–62.

848   99.   Valbon BF, Ambrósio R, Fontes BM, Luz A, Roberts CJ, Alves MR. Ocular biomechanical

849   metrics by CorVis ST in healthy Brazilian patients. J Refract Surg. 2014 Jul 1;30(7):468–73.

850   100.   Nangia V, Jonas JB, Sinha A, Matin A, Kulkarni M. Central corneal thickness and its

851   association with ocular and general parameters in Indians: the Central India Eye and Medical

852   Study. Ophthalmology. 2010 Apr;117(4):705–10.

853   101.   Channa R, Mir F, Shah MN, Ali A, Ahmad K. Central corneal thickness of Pakistani adults.

854   J Pak Med Assoc. 2009 Apr;59(4):225–8.

855   102.   Hahn S, Azen S, Ying-Lai M, Varma R, Los Angeles Latino Eye Study Group. Central

856   corneal thickness in Latinos. Invest Ophthalmol Vis Sci. 2003 Apr;44(4):1508–12.

857   103.   Goktas A, Gumus K, Mirza GE, Crockett C, Karakucuk S, Cavanagh HD. Corneal

858   endothelial characteristics and central corneal thickness in a population of Turkish cataract

859   patients. Eye Contact Lens. 2012 May;38(3):142–5.

860   104.   Yaeger R, Avila-Bront A, Abdul K, Nolan PC, Grann VR, Birchette MG, et al. Comparing

861   genetic ancestry and self-described race in african americans born in the United States and in

862   Africa. Cancer Epidemiol Biomarkers Prev. 2008 Jun 1;17(6):1329–38.

863   105.   Watson PG, Hazleman BL, McCluskey, Peter M. MD, Pavesio, Carlos E. MD. The Sclera

864   and Systemic Disorders. 3th ed. London: Jp Medical Ltd; 2012. 366 p.

865   106.   Segev F, Héon E, Cole WG, Wenstrup RJ, Young F, Slomovic AR, et al. Structural

866   abnormalities of the cornea and lid resulting from collagen V mutations. Invest Ophthalmol

867   Vis Sci. 2006 Feb 1;47(2):565–73.

868   107.   Wenstrup RJ, Florer JB, Brunskill EW, Bell SM, Chervoneva I, Birk DE. Type V collagen

869   controls the initiation of collagen fibril assembly. J Biol Chem. 2004 Dec

870   17;279(51):53331–7.

871   108.   Vithana EN, Aung T, Khor CC, Cornes BK, Tay W-T, Sim X, et al. Collagen-related genes

872   influence the glaucoma risk factor, central corneal thickness. Hum Mol Genet. 2011 Feb

873   15;20(4):649–58.

874   109.   Li X, Bykhovskaya Y, Canedo ALC, Haritunians T, Siscovick D, Aldave AJ, et al. Genetic

875   association of COL5A1 variants in keratoconus patients suggests a complex connection

876   between corneal thinning and keratoconus. Invest Ophthalmol Vis Sci. 2013 Apr

877   12;54(4):2696–704.

878   110.   Abu A, Frydman M, Marek D, Pras E, Nir U, Reznik-Wolf H, et al. Deleterious Mutations in

879   the Zinc-Finger 469 Gene Cause Brittle Cornea Syndrome. Am J Hum Genet.

880   2008;82(5):1217–22.

881   111.   Rohrbach M, Spencer HL, Porter LF, Burkitt-Wright EMM, Bürer C, Janecke A, et al.

882   ZNF469 frequently mutated in the brittle cornea syndrome (BCS) is a single exon gene

883   possibly regulating the expression of several extracellular matrix components. Mol Genet

884   Metab. 2013 Jul;109(3):289–95.

885   112.   Burkitt Wright EMM, Spencer HL, Daly SB, Manson FDC, Zeef LAH, Urquhart J, et al.

886   Mutations in PRDM5 in brittle cornea syndrome identify a pathway regulating extracellular

887   matrix development and maintenance. Am J Hum Genet. 2011 Jun 10;88(6):767–77.

888   113.   Lechner J, Porter LF, Rice A, Vitart V, Armstrong DJ, Schorderet DF, et al. Enrichment of

889   pathogenic alleles in the brittle cornea gene, ZNF469, in keratoconus. Hum Mol Genet. 2014

890   Oct 15;23(20):5527–35.

891   114.   Abu-Amero K, Kondkar A, Chalam K. An Updated Review on the Genetics of Primary

892   Open Angle Glaucoma. Int J Mol Sci. 2015 Dec 4;16(12):28886–911.

893   115.   Igo RP, Kopplin LJ, Joseph P, Truitt B, Fondran J, Bardenstein D, et al. Differing roles for

894   TCF4 and COL8A2 in central corneal thickness and fuchs endothelial corneal dystrophy.

895   den Hollander AI, editor. PLoS One. 2012 Oct 23;7(10):e46742.

896   116.   Robertson DM, Ladage PM, Yamamoto N, Jester J V, Petroll WM, Cavanagh HD. Bcl-2

897   and Bax regulation of corneal homeostasis in genetically altered mice. Eye Contact Lens.

898   2006 Jan;32(1):3–7.

899   117.   Dimasi DP, Chen JY, Hewitt AW, Klebe S, Davey R, Stirling J, et al. Novel quantitative

900   trait loci for central corneal thickness identified by candidate gene analysis of osteogenesis

901   imperfecta genes. Hum Genet. 2010 Jan 28;127(1):33–44.

902   118.   Ramaesh T, Collinson JM, Ramaesh K, Kaufman MH, West JD, Dhillon B. Corneal

903   abnormalities in Pax6+/- small eye mice mimic human aniridia-related keratopathy. Invest

904   Ophthalmol Vis Sci. 2003 May;44(5):1871–8.

905   119.   Desronvil T, Logan-Wyatt D, Abdrabou W, Triana M, Jones R, Taheri S, et al. Distribution

906   of COL8A2 and COL8A1 gene variants in Caucasian primary open angle glaucoma patients

907   with thin central corneal thickness. Mol Vis. 2010 Oct 29;16:2185–91.

908   120.   Hopfer U, Fukai N, Hopfer H, Wolf G, Joyce N, Li E, et al. Targeted disruption of Col8a1

909   and Col8a2 genes in mice leads to anterior segment abnormalities in the eye. FASEB J. 2005

910   Aug 1;19(10):1232–44.

911   121.   Meij JTA, Carlson EC, Wang L, Liu C-Y, Jester J V, Birk DE, et al. Targeted expression of

912   a lumican transgene rescues corneal deficiencies in lumican-null mice. Mol Vis. 2007 Oct

913   18;13:2012–8.

914   122.   Kaushik S, Singh Pandav S. Measuring Intraocular Pressure: How Important is the Central

915   Corneal Thickness? J Curr Glaucoma Pract. 2007;1(1):21–4.

916   123.   Harper CL, Boulton ME, Bennett D, Marcyniuk B, Jarvis-Evans JH, Tullo AB, et al. Diurnal

917   variations in human corneal thickness. Br J Ophthalmol. 1996 Dec;80(12):1068–72.

918   124.   du Toit R, Vega JA, Fonn D, Simpson T. Diurnal variation of corneal sensitivity and

919   thickness. Cornea. 2003 Apr;22(3):205–9.

920   125.   Hon Y, Wan K, Chen G-Z, Lu S-H, Lam DCC, Lam AKC. Diurnal Variation of Corneal

921   Tangent Modulus in Normal Chinese. Cornea. 2016 Aug 17;35(12):1600–4.

922   126.   Cejka C, Pláteník J, Sirc J, Ardan T, Michálek J, Brůnová B, et al. Changes of corneal

923   optical properties after UVB irradiation investigated spectrophotometrically. Physiol Res.

924   2010;59(4):591–7.

925   127.   Young AR. Acute effects of UVR on human eyes and skin. Prog Biophys Mol Biol. 2006

926   Sep;92(1):80–5.

927   128.   Riley M V, Susan S, Peters MI, Schwartz CA. The effects of UV-B irradiation on the

928   corneal endothelium. Curr Eye Res. 1987 Aug;6(8):1021–33.

929   129.   Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for

930   the treatment of keratoconus. Am J Ophthalmol. 2003 May;135(5):620–7.

931   130.   Meek KM, Hayes S. Corneal cross-linking - a review. Ophthalmic Physiol Opt. 2013

932   Mar;33(2):78–93.

933   131.   Morris DS, Somner JEA, Scott KM, McCormick IJC, Aspinall P, Dhillon B. Corneal

934   Thickness at High Altitude. Cornea. 2007 Apr;26(3):308–11.

935   132.   Karakucuk S, Mujdeci M, Baskol G, Arda H, Gumus K, Oner A. Changes in central corneal

936   thickness, intraocular pressure, and oxidation/antioxidation parameters at high altitude.

937   Aviat Space Environ Med. 2012 Nov;83(11):1044–8.

938   133.   Herndon LW, Weizer JS, Stinnett SS. Central Corneal Thickness as a Risk Factor for

939   Advanced Glaucoma Damage. Arch Ophthalmol. 2004 Jan 1;122(1):17.

940   134.   Wolffsohn JS, Safeen S, Shah S, Laiquzzaman M. Changes of Corneal Biomechanics With

941   Keratoconus. Cornea. 2012 Aug;31(8):849–54.

942   135.   Urban B, Raczyńska D, Bakunowicz-Łazarczyk A, Raczyńska K, Krętowska M. Evaluation

943   of Corneal Endothelium in Children and Adolescents with Type 1 Diabetes Mellitus.

944   Mediators Inflamm. 2013;2013:1–6.

945   136.   Roszkowska AM, Tringali CG, Colosi P, Squeri CA, Ferreri G. Corneal endothelium

946   evaluation in type I and type II diabetes mellitus. Ophthalmologica. 1999;213(4):258–61.

947   137.   Lee JS, Oum BS, Choi HY, Lee JE, Cho BM. Differences in corneal thickness and corneal

948   endothelium related to duration in Diabetes. Eye. 2006 Mar 15;20(3):315–8.

949   138.   Gul A, Cinal A, Caglar C, Yasar T, Kilic A. Comparing biometry in normal eyes of children

950   with unilateral cataract/corneal disease to age-matched controls. Nepal J Ophthalmol. 2015

951   Jul 25;7(14):108–16.

952 139. Khan S, Ali M, Zaheer N. Comparison of pre-operative central corneal thickness in pediatric

953   cataract cases versus normal. J Coll Physicians Surg Pak. 2014 Aug;24(8):561–4.

954 140. Lin D, Chen J, Liu Z, Wu X, Long E, Luo L, et al. Prevalence of Corneal Astigmatism and

955   Anterior Segmental Biometry Characteristics Before Surgery in Chinese Congenital Cataract

956   Patients. Sci Rep. 2016 Feb 25;6:22092.

957 141. Burns RR, Bourne WM, Brubaker RF. Endothelial function in patients with cornea guttata.

958   Invest Ophthalmol Vis Sci. 1981 Jan;20(1):77–85.

959 142. Kopplin LJ, Przepyszny K, Schmotzer B, Rudo K, Babineau DC, Patel S V, et al.

960   Relationship of Fuchs Endothelial Corneal Dystrophy Severity to Central Corneal

961   Thickness. Arch Ophthalmol. 2012 Apr 1;130(4):433–9.

962 143. Ozdamar Y, Berker N, Ertugrul G, Gurlevik U, Karakaya J, Ozkan SS. Is there a change of

963   corneal thickness in uveitis with Behçet disease? Cornea. 2010 Nov;29(11):1265–7.

964 144. Wanichwecharungruang B, Laophulsuk V, Sopitanont S, Vanichvaranont S, Harncharoen K.

965   Central corneal thickness in the central retinal vein occlusion fellow eyes. J Med Assoc

966   Thai. 2010 Aug;93(8):943–9.

967 145. Zheng Y, Ge J, Huang G, Zhang J, Liu B, Hur Y-M, et al. Heritability of central corneal

968   thickness in Chinese: the Guangzhou Twin Eye Study. Invest Ophthalmol Vis Sci. 2008 Oct

969   1;49(10):4303–7.

970

971

972   **Titles and legends to figures:**

973

974   Figure 1. Factors influencing CCT

975

976   Figure 2. Factors influencing corneal topography and biomechanics. Figure presenting the factors

977   that influence corneal topography by dividing them in external factors, internal factors and corneal

978   factors. Corneal factors are directly related to the components of the corneal stroma. Biomechanical

979   properties of the cornea such as central corneal thickness and hysteresis, are in turn also dependent

980   on these components.

981

Ophthalmology Research Chair
School of Medicine and Health Sciences
Tecnologico de Monterrey
Monterrey, N.L., Mexico.
E-mail: jorge.valdez@itesm.mx

Andrew J Lotery, MD
Editor
Eye

March 28, 2017

Dear Dr. Lotery:

Please find enclosed the outline of a review article entitled "**Factors Influencing Central Corneal Thickness**" we are submitting for consideration of publication in the Journal *Eye*.

In this article we provide a review of the subject of central corneal thickness (CCT) from a stand point that covers all aspects related to it. These include the anatomical and physiological basis behind it, its impact in the field of biomechanics and corneal topography, the so called "normal" CCT values in different populations, the genetic implications surrounding it, and the different factors influencing it. To our knowledge there isn't an article in the literature that covers individually a similar spectrum of topics related to CCT.

We consider this manuscript is adequate for *Eye* given that it offers a comprehensive, updated revision of all the aspects related to CCT. We believe this article will be of interest to readers because of the broad clinical fields in which CCT is implicated; from its role as a risk factor for developing glaucoma, its impact in management of ocular hypertension and its importance in management of candidate patients for refractive surgery.

Following this letter, you will find the proposed outline we have considered in this review.

Thank you for your consideration.

Sincerely,

Jorge E. Valdez-García, MD

Outline:

1. Introduction
2. Cornea: physiology, structure and function. Figure 1 illustrates some of the factors influencing CCT and the ways in which they relate to thickness (genetics, age, UV radiation, and diseases).
3. Corneal Topography. Figure 2 summarizes the factors that influence corneal topography and biomechanics (external such as atmospheric pressure; internal, such as intraocular pressure, hysteresis, elasticity, and thickness)
4. Corneal Biomechanics.
5. Clinical significance of CCT values. Table 1 summarizes some of the main clinical implications of CCT (glaucoma, ocular hypertension, refrective surgery, among others).
6. "Normal" CCT values. Table 2 summarizes most of the populations studies conducted in this regard.
7. Genetic aspects of CCT. Discussion of the four main genes (*COL5A1*, *FOXO1*, *AVGR8*, and *ZNF469*) and several other gene single-nucleotide polymorphisms (SNPs) known to influence CCT. Table 3 summarizes the findings of the genes described, as well as some of the reports on additional Genome-wide association studies (GWAS) and SNPs that could be related to CCT.
8. Factors influencing CCT. Disussion of the role of age, UV radiation, altitude, chronic contact lens use, and disorders that impact over CCT.
9. Heritability. Breif discussion about the additive genetic effect over the variation of CCT.
10. Conclusion

BMC Ophthalmology
Safety and Efficacy of Myopic LASIK performed on Thin Corneas
--Manuscript Draft--

Manuscript Number:	BOPH-D-17-00219
Full Title:	Safety and Efficacy of Myopic LASIK performed on Thin Corneas
Article Type:	Research article
Section/Category:	Cataract and refractive surgery
Funding Information:	
Abstract:	Background: Thin corneas have been historically considered as corneas with biomechanical liability and therefore to have an increased risk for developing ectasia after LASIK surgery. However, recent evidence suggests that thin corneas (with normal topography) performance after ablative refractive surgery is as effective, safe and stable as in corneas with "normal" thickness. The purpose of this manuscript is to report on the visual outcomes and safety of myopic LASIK performed in patients with corneas with central thickness below average (<540µm) and normal topography. Methods: Retrospective cohort study at a private practice setting. Mexican Hispanic patients who underwent myopic LASIK between January 2014 and January 2015. Analysis of records, patients >18 years-old with previous normal topography, stable refraction, corrected visual acuity ≥ 20/20 (Snellen), central corneal thickness (CCT) < 540µm and at least 12 months follow up after surgery. Main outcome measures: Standard visual outcomes (efficacy, safety, refractive stability), percent tissue altered analysis. Results: A total of 51 patients (102 eyes) were included, 56% (n=57) were female. Mean age: 26.52 ± 8.06 (range 18-55 years), mean follow up: 13.9 ± 1.2 months. Preoperative CCT: 515.44 ± 17.87µm (range 452-540µm), mean refractive spherical equivalent (SEQ): -4.08 ± 2.17 D (range -0.75 to -9.75 D), mean refractive cylinder: -1.44 ± 1.29 D (range 0.00 to -6.00 D). Mean predictability of postoperative SEQ: -0.20 ± 0.40 D (range -1.25 to +1.25). Postoperative SEQ: ±0.50 D in 71%, ±1.00 D in 93% of the eyes. Postoperative uncorrected distance visual acuity: ≥20/20 in 78% and ≥20/25 in 95%. One line of CDVA was lost in 3% of the eyes, no eyes lost ≥2 lines. No ectasia cases were observed during follow-up. Conclusions: LASIK surgery in Mexican Hispanic patients with thinner than "normal" corneas (<540 µm) is safe, efficient and predictable at 1 year follow up for myopic refractive corrections with no evidence of postoperative keratectasia.
Corresponding Author:	Jorge E Valdez-Garcia, MD, MA Instituto Tecnologico y de Estudios Superiores de Monterrey Escuela de Medicina Ignacio A Santos MEXICO
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Instituto Tecnologico y de Estudios Superiores de Monterrey Escuela de Medicina Ignacio A Santos
Corresponding Author's Secondary Institution:	
First Author:	Jorge E Valdez-Garcia, MD, MA
First Author Secondary Information:	
Order of Authors:	Jorge E Valdez-Garcia, MD, MA
	Julio C Hernandez-Camarena, MD
	Denise Loya-García, MD
	Paloma Lopez-Montemayor, BN
	Jesus Merayo-Lloves, MD, PhD, MBA, DO

Order of Authors Secondary Information:	
Opposed Reviewers:	

ORIGINAL ARTICLE – CLINICAL SCIENCE

Safety and Efficacy of Myopic LASIK performed on Thin Corneas

Jorge E. Valdez-García MD, MA [1], Julio C. Hernandez-Camarena MD[1], Denise Loya-García MD[1], Paloma López-Montemayor BN[1], Jesús Merayo-Lloves MD, PhD, MBA, DO[2]

Affiliations:

[1] Ophthalmology and Visual Sciences Institute. School of Medicine, Tecnologico de Monterrey, Monterrey, Mexico.

[2] Instituto Universitario Fernández-Vega. Universidad de Oviedo. Fundación de Investigación Oftalmológica, Oviedo, Spain.

Corresponding author

Jorge E. Valdez-García, MD
Dean of the School of Medicine
Ophthalmology Associate Professor
Service of Cornea and Refractive Surgery
Ophthalmology and Visual Sciences Institute
School of Medicine of the Tecnologico de Monterrey
112 Batallon de San Patricio, 1st Floor East
San Pedro Garza García, Nuevo Leon, Mexico, 66278
+52(81) 88880550
Email: jorge.valdez@itesm.mx

Short running tittle: LASIK performed on Thin Corneas

Abstract

Background: Thin corneas have been historically considered as corneas with biomechanical liability and therefore to have an increased risk for developing ectasia after LASIK surgery. However, recent evidence suggests that thin corneas (with normal topography) performance after ablative refractive surgery is as effective, safe and stable as in corneas with "normal" thickness. The purpose of this manuscript is to report on the visual outcomes and safety of myopic LASIK performed in patients with corneas with central thickness below average (<540μm) and normal topography.

Methods: Retrospective cohort study at a private practice setting. Mexican Hispanic patients who underwent myopic LASIK between January 2014 and January 2015. Analysis of records, patients >18 years-old with previous normal topography, stable refraction, corrected visual acuity $\geq$ 20/20 (Snellen), central corneal thickness (CCT) < 540μm and at least 12 months follow up after surgery.

Main outcome measures: Standard visual outcomes (efficacy, safety, refractive stability), percent tissue altered analysis.

Results: A total of 51 patients (102 eyes) were included, 56% (n=57) were female. Mean age: 26.52 $\pm$ 8.06 (range 18-55 years), mean follow up: 13.9 $\pm$ 1.2 months. Preoperative CCT: 515.44 $\pm$ 17.87μm (range 452-540μm), mean refractive spherical equivalent (SEQ): -4.08 $\pm$ 2.17 D (range -0.75 to -9.75 D), mean refractive cylinder: -1.44 $\pm$ 1.29 D (range 0.00 to -6.00 D). Mean predictability of postoperative SEQ: -0.20 $\pm$ 0.40 D (range -1.25 to +1.25). Postoperative SEQ: $\pm$0.50 D in 71%, $\pm$1.00 D in 93% of the eyes. Postoperative uncorrected distance visual acuity: $\geq$20/20 in 78% and $\geq$20/25 in 95%. One line of CDVA was lost in 3% of the eyes, no eyes lost $\geq$2 lines. No ectasia cases were observed during follow-up.

Conclusions: LASIK surgery in Mexican Hispanic patients with thinner than "normal" corneas (<540 μm) is safe, efficient and predictable at 1 year follow up for myopic refractive corrections with no evidence of postoperative keratectasia.

Key words: LASIK, Central Corneal Thickness, thin corneas, post-LASIK ectasia

Background

Laser *in situ* keratomileusis has been the treatment of choice for correcting corneal refractive errors since its introduction in early 1990 [1,2]. Resulting in immediate high quality visual outcomes and having an excellent efficacy, predictability, stability and safety profiles, it's no wonder why LASIK surgery has become one of today's most popular elective procedures, with more than 28 million procedures performed worldwide [3,4]. As with any other surgical procedure, an increased frequency and widespread use is also associated with a grown incidence of complications.

Although effective methods to treat most of the complications related to LASIK have emerged (either with eye drops or with surgical correction) [5,6] post-LASIK ectasia is one of the most feared complications since its treatment often involves extensive management strategies that go from intrastromal corneal rings [7] and crosslinking [8] to keratoplasty [9].

Specific risk factors for developing corneal ectasia after LASIK have been identified and they include deep ablation, residual stromal bed thickness lower than 300μm, abnormal topography and central corneal thickness (CCT) less than 500μm [10–12]. Randleman et al. also considered factors as young age and high refractive correction to develop an Ectasia Risk Score System (ERSS) with the objective to assess the preoperative risk for developing ectasia after LASIK [13]. Recently, the role of the percent tissue altered (PTA) has been emphasized by Santhiago et al. as a robust risk indicator for developing ectasia after LASIK in eyes with normal topography [14].

Either directly (ERSS) or indirectly (PTA), thin corneas have been considered as corneas with biomechanical liability and therefore to have an increased risk for developing ectasia after ablative surgery [13,14]. However, recent evidence shows not only that thin corneas (<500μm) have not an increased risk for ectasia but that LASIK is as effective, safe and stable as in corneas with 500μm or greater [15,16]. In this study we assessed the visual outcomes and safety of myopic LASIK performed in patients with corneas with central thickness below average <540 μm and normal topography.

Methods

104 A retrospective analysis was performed on the records of Hispanic patients who underwent myopic LASIK

105 between January 2014 and January 2015, at the Zambrano-Hellion Medical Center, Tec de Monterrey

106 (Monterrey, México). The analysis followed the tenets of the Declaration of Helsinki, informed consent was

107 obtained from all patients after details of the surgical procedure were explained. Inclusion criteria for the

108 initial treatment were: age over 18 years; stable refraction with spherical component up to -8.50D, a

109 cylindrical component between up to -6.50D; corrected visual acuity $\geq$ 20/20 (Snellen visual acuity chart) a

110 central corneal thickness (CCT) < 540μm and at least 12 months follow up. We defined a cornea thinner than

111 "normal" as corneas <540 μm accordingly to the reported values (statistical mean and mode) in our

112 population [26]. Patients with LASIK surgery general contraindications as autoimmune diseases, diabetes,

113 pregnancy, and ocular diseases including glaucoma, cataract, retinal diseases, and dry eye were excluded.

114 Preoperative examination included uncorrected distance visual acuity (UDVA), corrected distance visual

115 acuity (CDVA), manifest refraction, cyclopegic refraction, intraocular pressure measurement (Goldmann

116 applanation tonometer), ultrasonic pachymetry (Accutome AccuPach V, Malvern, PA, USA), corneal

117 topography (Orbscan IIz, Bausch and Lomb, Rochester, NY, USA) and slit lamp examination. The CCT was

118 obtained using ultrasonic pachymetry (Accutome 4sight pachymeter module; Accutome, Inc., Malvern, PA,

119 USA). Briefly, the cornea was anesthetized with topical 1% tetracaine and the patient was asked to adopt a

120 face up position on the examination chair and solicited to fixate a target on the ceiling. The pachymeter probe

121 was brought in contact with the cornea centrally and perpendicularly over the visual axis. CCT was recorded

122 as the average of 9 consecutive acquisitions. This process was repeated for every individual CCT

123 measurement.

124 Postoperative protocol consisted on moxifloxacin 0.5% ophthalmic solution (Vigamoxi ®, Alcon

125 Laboratories, Fort Worth TX, US) every 6 hours for 7 days and fluorometholone 0.1 opthalmic suspension

126 (Flumetol, Sophia ®, Jalisco, Mexico) in dose reduction for 2 weeks. Postoperative visits included UDVA,

127 CDVA, manifest refraction, corneal topography, Goldmann tonometry, slit lamp biomicroscopy and Visante

128 AS-OCT (Carl Zeiss Meditec Inc, Version 3.0, Dublin, CA, US) on postoperative week 1 to measure the

129 thickness of the corneal flap.

130 LASIK procedures were performed by the same surgeon using a Technolas-217 Excimer workstation

131 (Technolas Perfect Vision GmbH, München, Germany) using the standard technique. Briefly, under topical

132 anesthesia with tetracaine chlorhidrate 0.5% (Ponti ofteno, Sophia ®, Jalisco, México), the cornea was

133 marked with gentian violet and a superior hinge was performed using a Hansatome XP Microkeratome

134 (Bausch & Lomb, Rochester, NY). When indicated both eyes were operated the same day, with the refractive

135 target to emmetropia. A 6.0 mm optical zone and a 120 microns flap with a superior hinge and average

136 diameter of 9.5 mm (an 8.5 mm diameter ring was used in eyes with mean keratometry > 45D) was used in

137 every case. Zyoptix Tissue Saving-2 ablation profile was used to ensure a residual stromal bed $\geq$ 300μm.

138 Standard visual outcomes and percent tissue altered (PTA) analysis were obtained. The preoperative and

139 postoperative data were compared using Student's t test. Statistical analysis was implemented with the SPSS

140 software (version 20.0, IBM Inc., NY, USA) for Windows, a p value <0.05 was considered statistically

141 significant. Visual acuity was measured using Snellen´s visual acuity chart and then converted to LogMAR

142 for statistical analysis.

143

144 **Results**

145 A total of 51 patients (102 eyes) were included in the study, 56% (n=57) were female. The mean age was

146 26.52 $\pm$ 8.06 (range 18 to 55 years) with a mean follow up of 15.9 $\pm$ 1.2 months. Preoperatively, CCT was

147 515.44 $\pm$ 17.87μm (range 452-539μm), the mean refractive spherical equivalent (MRSE) was -4.06 $\pm$ 1.85 D

148 (range -0.75 to -9.75 D) with a mean refractive cylinder of -1.44 $\pm$ 1.29 D (range 0.00 to -5.75 D). On

149 postoperative week 1, the mean central thickness of the corneal flap was (128.66 $\pm$ 17.09μm). The analysis of

150 PTA showed a mean value of 0.35 $\pm$ 0.04 (range 0.22 to 0.44). Figure 1 shows the Standard Graphs for

151 Reporting Refractive Surgery.

152 The mean predictability of postoperative SEQ was -0.20 $\pm$ 0.40 D (range -1.25 to +1.25) at the end of the

153 follow up. Postoperative SEQ was $\pm$0.50 D in 71% and $\pm$1.00 D in 93% of the eyes. Preoperative CDVA was

154 20/20 or better in 93% of the eyes. Postoperative uncorrected distance visual acuity was 20/20 or better in

155 78% and 20/25 or better 95%. One line of CDVA was lost in 3% of eyes and none of the eyes lost more than

156 2 lines of CDVA. Over the follow up (from postoperative month 3 to postoperative month 12), only 4% of the

157 eyes changed >0.50D. A strong squared correlation (R^2=0.981) was observed between attempted and

158 achieved SEQ correction. Table 1 shows the changes in visual and refractive outcomes before and after the

159 lasik procedure. Intraoperative complications consisted on epithelial defect in 3 cases (3% of total) and flap

160 striae that required flap re-lifting in 1 eye (1%). No ectasia cases were observed during follow-up.

161

162 **Discussion**

163 Post LASIK ectasia is rare, but even with a prevalence rate of 0.02% to 0.6% it remains as one of the most

164 feared complications in refractive surgery [17,18]. Risk factors for developing this condition have been

165 previously identified [12,14], amongst them thin corneas (<500μm) have been historically considered as

166 corneas with biomechanical frailty and therefore as corneas predisposed to develop ectasia [19, 20]. Evidence

167 shows that factors as race [21,22], age and gender [22,23] altitude [24] and UV light exposure [25] may

168 influence CCT, hence different "normal" corneal thickness have been stablished among various research

169 groups. In a meta-analysis conducted by Doughty et al. [23] an average CCT of 536 ± 29 μm was stablished

170 for normal healthy eyes. In a Hispanic population, our group observed a mean CCT of 545.69 ± 36.88 μm

171 (mode of 540 μm) in healthy corneas of Hispanic patients [26]. In this study we evaluate the visual outcome,

172 safety and predictability of LASIK performed on a large cohort of corneas thinner than "normal", defining the

173 latter as corneas <540 μm accordingly to the reported values (statistical mean and mode) in our population, at

174 a 12 month follow up.

175 Against the old paradigm that thin corneas have a biomechanical liability, recent evidence has shown not only

176 the absence of keratectasia during follow up but also no difference in visual outcomes, safety and

177 predictability when LASIK is performed on thin corneas with normal topography when compared with

178 preoperative corneas with average or normal thickness. Tomita et al, assessed the 6 year-follow up outcomes

179 of thin-flap LASIK in eyes with thin corneas (CCT<500 μm) but normal topography and compared them with

180 the outcomes of LASIK performed on corneas with CCT 500 μm or greater [16] They observed no difference

181 in visual, refractive and topographic outcomes at long-term between both groups. At their last follow-up 83%

182 of the eyes in the thin cornea group achieved a UDVA of 20/20 or better, 63% were stable or gained lines of

183 CDVA and had refractive stability with a MRSE change of -0.17 ± 0.42 D over time [16]. Similarly, we

184   observed 78% of the patients with UDVA ≥20/20, 97% of the eyes were stable or gained lines of CDVA at

185   the last follow up and a refractive stability with a MRSE change of -0.20 ± 0.40 over time. Likewise, we

186   observed a non-significant difference on visual and refractive outcomes when comparing 6 month follow-up

187   with the final follow up (Table 1), suggesting visual an refractive stability.

188   Caster et al, performed a retrospective analysis of 109 eyes with preoperative central corneal thickness of ≤

189   500 μm and otherwise normal topography that underwent LASIK, having a postoperative follow up of at least

190   12 months [15]. As in Tomita et al [16], and the present study, refractive stability was observed during the

191   follow up period with no incidence of postoperative keratectasia. Previously, Binder et al. examined a

192   database of 9700 eyes that underwent myopic lasik and he found 117 eyes with corneal pachymetry <500

193   microns and a follow up of at least 2 years with no report of corneal ectasia [17]. Kymionis et al, also showed

194   the results of 124 eyes with thin corneas less than 500 microns that underwent excimer laser cornea refractive

195   surgery (either PRK or LASIK) observing a good predictability (mean predictability of 0.08 ± 0.40 D for PRK

196   group, 0.14 ± 0.55D for the LASIK group) and no ectasia during the follow-up (1 year) [27].

197   Corneal thickness has been considered as an inherent sign of structural stability, hence different authors have

198   included thin corneas as a risk factor to develop postoperative keratectasia after excimer laser corneal

199   refractive surgery [13,17,27–30]. However, the question if thin corneas should be considered as "weak"

200   corneas and therefore as an independent risk for post-LASIK ectasia is yet in dispute. Recent evidence,

201   including the present study, has failed to categorize thinner than normal corneas as independent risk for

202   developing keratectasia after LASIK or PRK, since not only thin corneas perform as efficiently and safely

203   than normal thickness corneas after refractive surgery but they have not showed a trend over time to evolve in

204   to ectasia. Focusing on a flap thickness tailored to the initial corneal thickness and to the amount of ablation

205   has been a more important issue on the debate, since the evidence from the work of Santhiago et al [14], have

206   shown that the percent of tissue altered ≥40% (obtained from the quotient of the sum of flap thickness and

207   ablation depth over the central corneal thickness) was a more robust indicator that other individual variables

208   (included CCT <510μm) for the development of corneal ectasia after LASIK in eyes with normal topography.

209   In our series a mean PTA of 0.35 ± 0.04 was achieved and although the recommendation in these patients is

210   to create flaps of precise thickness using the femtosecond laser, we observed an acceptable flap thickness

211   using a mechanical microkeratome (postoperative flap thickness 128.66 ± 17.09μm).

212 A weakness of this study is its retrospective nature and the limited follow up to 13 months. However it is a

213 large retrospective cohort of patients eyes with thinner than "normal" corneas and normal topography that

214 underwent LASIK and along with previous studies of Caster [15] (109 eyes), Kymionis [27] (56 eyes with

215 LASIK and 68 with PRK), Binder [11] (107 eyes) and Tomita [16] (291 eyes, case control) it contributes with

216 evidence arguing against thin corneas as an independent risk factor for keratectasia after ablative corneal

217 surgery. A control group with normal corneas for our population (≥540μm) could also potentially enhance

218 the power of the study by eliminating of isolating confounding variables and bias.

219

Conclusions

221 In conclusion, we observed that LASIK surgery in patients with corneas thinner than "normal" (<540μm) is

222 safe, efficient and predictable at 1 year follow up for myopic refractive corrections with no evidence of

223 postoperative keratectasia. Evidence in this and similar works suggest that LASIK surgery in eyes with

224 preoperative thinner than normal cornea and normal topography may not be a risk factor if a fair residual

225 stromal bed (at least 300 μm) and a PTA <40% is ensured. Longer follow up and larger cohorts of patients

226 are needed to support and reinforce the proposition that thinner than normal corneas perform as efficiently

227 and safely than normal thickness corneas after excimer refractive surgery.

228

Declarations

246 **References**

247 1. Varley GA, Huang D, Rapuano CJ, Schallhorn S, Boxer Wachler BS, Sugar A. LASIK for hyperopia,

248 hyperopic astigmatism, and mixed astigmatism: a report by the American Academy of

249 Ophthalmology. Ophthalmology. 2004;111(8):1604–17.

250 2. Sutton G, Lawless M, Hodge C. Laser in situ keratomileusis in 2012: a review. Clin Exp Optom.

251 2014;97(1):18–29.

252 3. Hammond SD, Puri AK, Ambati BK. Quality of vision and patient satisfaction after LASIK. Curr

253 Opin Ophthalmol. 2004;15(4):328–32.

254 4. Reinstein DZ, Archer TJ, Gobbe M. The History of LASIK. J Refract Surg. 2012;28(4):291–8.

255 5. Gil-Cazorla R, Teus M a., De Benito-Llopis L, Mikropoulos DG. Femtosecond laser vs mechanical

256 microkeratome for hyperopic laser in situ keratomileusis. Am J Ophthalmol. 2011;152(1):16–21.

257 6. Kashani S, Rajan M, Gartry D. Wavefront-guided retreatment after primary wavefront-guided laser in

258 situ keratomileusis in myopes and hyperopes: long-term follow-up. Am J Ophthalmol.

259 2009;147(3):417–423.

260 7. Moshirfar M, Fenzl CR, Meyer JJ, Neuffer MC, Espandar L, Mifflin MD. Simultaneous and

261 sequential implantation of intacs and verisyse phakic intraocular lens for refractive improvement in

262 keratectasia. Cornea. 2011;30(2):158–63.

263 8. Marino GK, Torricelli AAM, Giacomin N, Santhiago MR, Espindola R, Netto M V. Accelerated

264 Corneal Collagen Cross-linking for Postoperative LASIK Ectasia: Two-Year Outcomes. J Refract

265 Surg. 2015;31(6):380–4.

266 9. Salouti R, Nowroozzadeh MH, Makateb P, Zamani M, Ghoreyshi M, Melles GRJ. Deep anterior

267 lamellar keratoplasty for keratectasia after laser in situ keratomileusis. J Cataract Refract Surg.

268 2014;40(12):2011–8.

269 10. Kim TH, Lee D, Lee H Il. The safety of 250 microm residual stromal bed in preventing keratectasia

270 after laser in situ keratomileusis (LASIK). J Korean Med Sci. 2007;22(1):142–5.

271   11.   Binder PS. Ectasia after laser in situ keratomileusis. J Cataract Refract Surg. 2003;29(12):2419–29.

272   12.   Randleman JB, Russell B, Ward M, Thompson KP, Stulting RD. Risk factors and prognosis for

273   corneal ectasia after LASIK. Ophthalmology. 2003 Feb;110(2):267–75.

274   13.   Randleman JB, Woodward M, Lynn MJ, Stulting RD. Risk assessment for ectasia after corneal

275   refractive surgery. Ophthalmology. 2008;115(1):37–50.

276   14.   Santhiago MR, Smadja D, Gomes BF, Mello GR, Monteiro MLR, Wilson SE, et al. Association

277   between the percent tissue altered and post-laser in situ keratomileusis ectasia in eyes with normal

278   preoperative topography. Am J Ophthalmol. 2014;158(1):87–95.e1.

279   15.   Caster AI, Friess DW, Potvin RJ. Absence of keratectasia after LASIK in eyes with preoperative

280   central corneal thickness of 450 to 500 microns. J Refract Surg. 2007;23(8):782–8.

281   16.   Tomita M, Watabe M, Mita M, Waring GO. Long-term observation and evaluation of femtosecond

282   laser-assisted thin-flap laser in situ keratomileusis in eyes with thin corneas but normal topography. J

283   Cataract Refract Surg. 2014;40(2):239–50.

284   17.   Binder PS. Analysis of ectasia after laser in situ keratomileusis: risk factors. J Cataract Refract Surg.

285   2007;33(9):1530–8.

286   18.   Chen MC, Lee N, Bourla N, Hamilton DR. Corneal biomechanical measurements before and after

287   laser in situ keratomileusis. J Cataract Refract Surg. 2008;34(11):1886–91.

288   19.   Amoils SP, Deist MB, Gous P, Amoils PM. Iatrogenic keratectasia after laser in situ keratomileusis

289   for less than -4.0 to -7.0 diopters of myopia. J Cataract Refract Surg. 2000;26(7):967–77.

290   20.   Binder PS, Trattler WB. Evaluation of a risk factor scoring system for corneal ectasia after LASIK in

291   eyes with normal topography. J Refract Surg. 2010;26(4):241–50.

292   21.   Francis BA, Varma R, Chopra V, Lai M-Y, Shtir C, Azen SP. Intraocular pressure, central corneal

293   thickness, and prevalence of open-angle glaucoma: the Los Angeles Latino Eye Study. Am J

294   Ophthalmol. 2008;146(5):741–6.

295   22.   Aghaian E, Choe JE, Lin S, Stamper RL. Central corneal thickness of Caucasians, Chinese,

296   Hispanics, Filipinos, African Americans, and Japanese in a glaucoma clinic. Ophthalmology.

297   2004;111(12):2211–9.

298   23.   Doughty MJ, Zaman ML. Human corneal thickness and its impact on intraocular pressure measures: a

299   review and meta-analysis approach. Surv Ophthalmol. 2000;44(5):367–408.

300   24.   Morris DS, Somner JEA, Scott KM, McCormick IJC, Aspinall P, Dhillon B. Corneal thickness at

301   high altitude. Cornea. 2007;26(3):308–11.

302   25.   Riley M V, Susan S, Peters MI, Schwartz CA. The effects of UV-B irradiation on the corneal

303   endothelium. Curr Eye Res. 1987;6(8):1021–33.

304   26.   Valdez-García JE, Hernandez-Camarena JC, Lozano-Ramírez JF, Zavala J, Loya-García D, Merayo-

305   Lloves J. Correlation of age, corneal curvature and spherical equivalent with central corneal thickness.

306   Re Mex Oftlamol. 2016; doi: 10.1016/j.mexoft.2016.05.005

307   27.   Kymionis GD, Bouzoukis D, Diakonis V, Tsiklis N, Gkenos E, Pallikaris AI, et al. Long-term results

308   of thin corneas after refractive laser surgery. Am J Ophthalmol. 2007;144(2):181–5.

309   28.   Randleman JB, Woodward M, Lynn MJ, Stulting RD. Risk assessment for ectasia after corneal

310   refractive surgery. Ophthalmology. 2008;115(1):37–50.

311   29.   Twa MD, Nichols JJ, Joslin CE, Kollbaum PS, Edrington TB, Bullimore MA, et al. Characteristics of

312   corneal ectasia after LASIK for myopia. Cornea. 2004;23(5):447–57.

313   30.   Tabbara KF KA. Risk factors for corneal ectasia after LASIK. Ophthalmology. 2006;113(9):1618–22.

314

315

316

317

318

319 **TABLES**

320

TABLE 1

Visual and Refractive Outcomes Before and After Myopic LASIK in Thin Corneas

Parameter	UDVA (LogMAR)[a]	CDVA (LogMAR)[a]	SEQ (D)[a]	Keratometry (D)[a]
Preoperative	0.84 ± 0.45	0.00 ± .05	-4.06 ± 1.85	-1.44 ± 1.29
6 months FwUp	0.00 ± .08	0.00 ± .04	-0.17 ± 0.41	-0.47 ± 0.40
End point FwUp	0.00 ± .05	0.00 ± .02	-0.20± 0.40	-0.36 ± 0.39
P value[b]	<.001	<.001	<.001	<.001
P value[c]	.78	.81	.13	.08

321 UDVA = uncorrected distance visual acuity; CDVA = corrected distance visual acuity; D = diopters;

322 FwUp= Follow Up; LogMAR= Logarithm of the Minimum Angle of Resolution; [a] Values reported as

323 mean ± standard deviation; [b] Mean comparison between preoperative and 6 months follow up; [c]

324 Mean comparison between 6 months follow-up and end point follow-up.

325

326

327

328 **Legends**

329

330 **Figure 1.** Nine standard graphs for reporting refractive surgery showing the visual

331 and refractive outcomes for 102 myopic eyes treated with Hansatome XP

332 Microkeratome (Bausch & Lomb, Rochester, NY) and Technolas-217 Excimer

333 workstation (Technolas Perfect Vision GmbH, München, Germany), using Zyoptix

334 Tissue Saving-2 ablation. UDVA= uncorrected distance visual acuity; CDVA=

335 corrected distance visual acuity; D = diopters; Postop = postoperative; Preop =

336 preoperative; SEQ = spherical equivalent refraction; TIA = target-induced

337 astigmatism; SIA = surgically induced astigmatism.
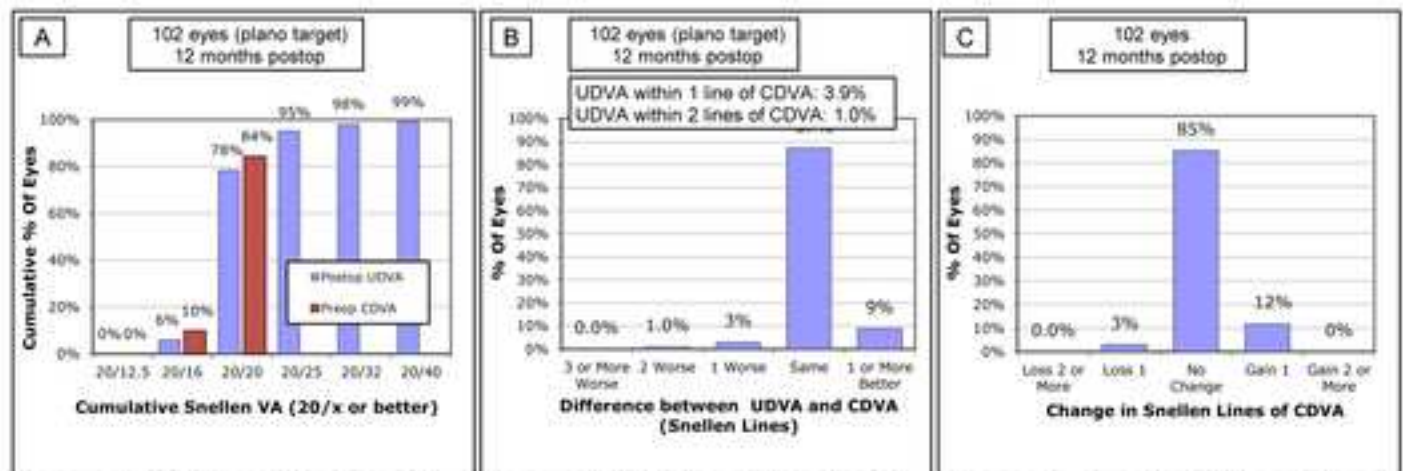
Table

TABLES

TABLE 1

Visual and Refractive Outcomes Before and After Myopic LASIK in Thin Corneas

Parameter	UDVA (LogMAR) [a]	CDVA (LogMAR) [a]	SEQ (D) [a]	Keratometry (D) [a]
Preoperative	0.84 ± 0.45	0.00 ± .05	-4.06 ± 1.85	-1.44 ± 1.29
6 months FwUp	0.00 ± .08	0.00 ± .04	-0.17 ± 0.41	-0.47 ± 0.40
End point FwUp	0.00 ± .05	0.00 ± .02	-0.20± 0.40	-0.36 ± 0.39
P value[b]	<.001	<.001	<.001	<.001
P value[c]	.78	.81	.13	.08

UDVA = uncorrected distance visual acuity; CDVA = corrected distance visual acuity; D = diopters;

FwUp= Follow Up; LogMAR= Logarithm of the Minimum Angle of Resolution; [a] Values reported as

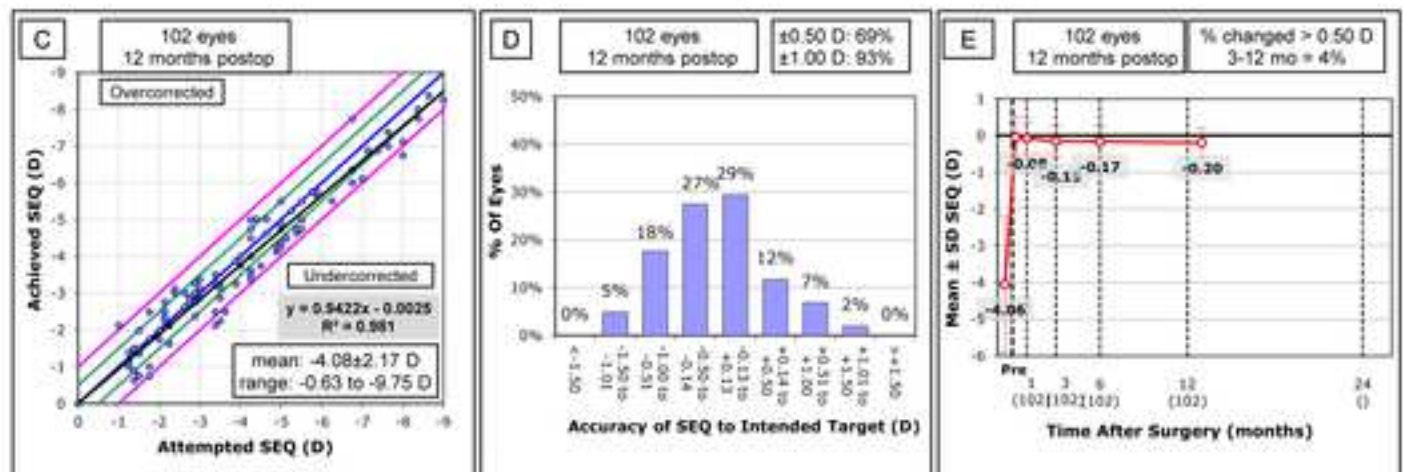mean ± standard deviation; [b] Mean comparison between preoperative and 6 months follow up; [c]

Mean comparison between 6 months follow-up and end point follow-up.

A — Uncorrected Distance Visual Acuity

B — Uncorrected Distance Visual Acuity vs. Corrected Distance Visual Acuity
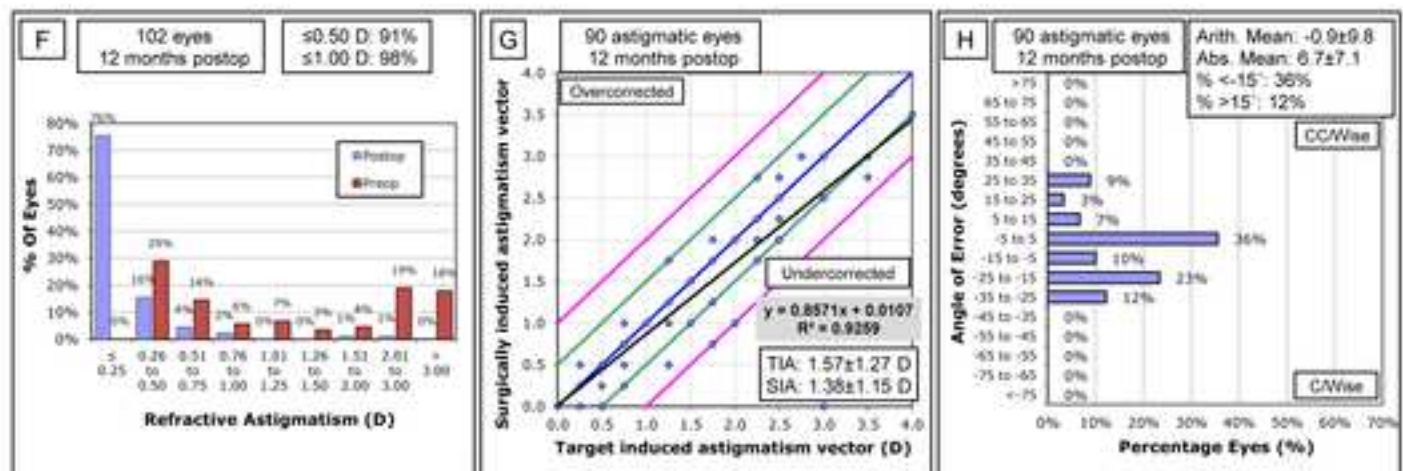
C — Change in Corrected Distance Visual Acuity

C — Spherical Equivalent Refraction Attempted vs Achieved

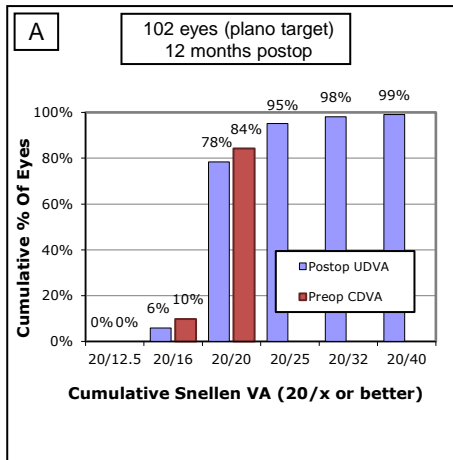**D** — Spherical Equivalent Refraction Accuracy

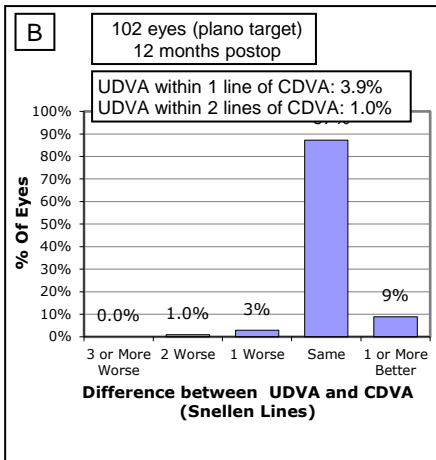**E** — Spherical Equivalent Refraction Stability

F — Refractive Astigmatism

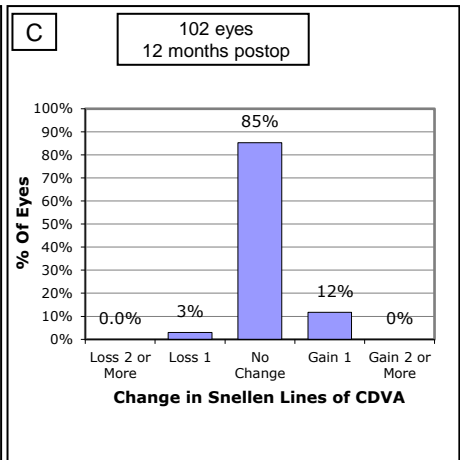**G** — Target Induced Astigmatism vs Surgically Induced Astigmatism
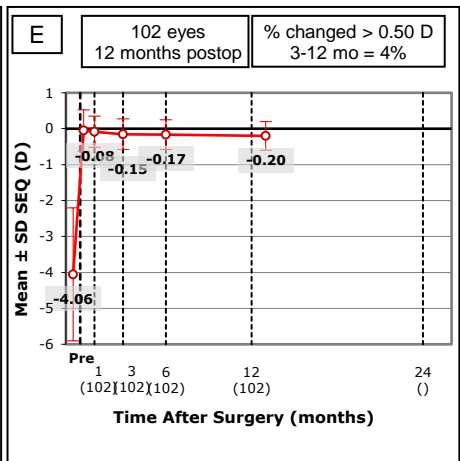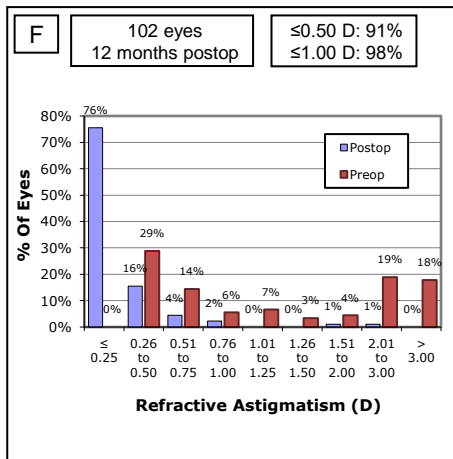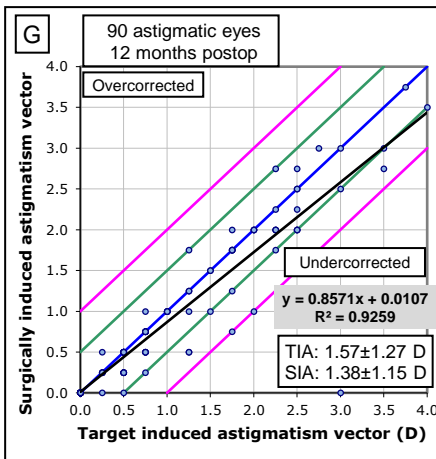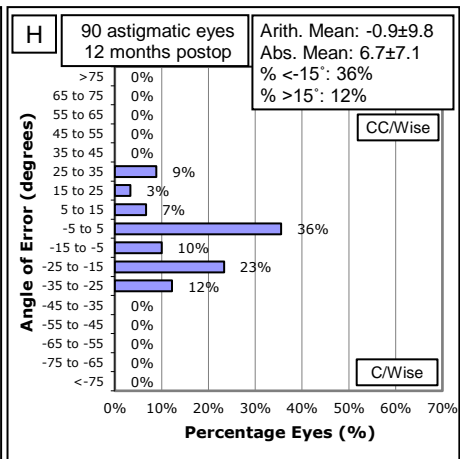
H — Refractive Astigmatism Angle of Error

A — 102 eyes (plano target) 12 months postop

Cumulative % Of Eyes

0% 0% | 6% 10% | 78% 84% | 95% | 98% | 99%

Postop UDVA
Preop CDVA

Cumulative Snellen VA (20/x or better)
20/12.5 20/16 20/20 20/25 20/32 20/40

Uncorrected Distance Visual Acuity

B — 102 eyes (plano target) 12 months postop

UDVA within 1 line of CDVA: 3.9%
UDVA within 2 lines of CDVA: 1.0%

% Of Eyes

0.0% | 1.0% | 3% | Same | 9%

3 or More Worse | 2 Worse | 1 Worse | Same | 1 or More Better

Difference between UDVA and CDVA (Snellen Lines)

Uncorrected Distance Visual Acuity vs. Corrected Distance Visual Acuity

C — 102 eyes 12 months postop

% Of Eyes

0.0% | 3% | 85% | 12% | 0%

Loss 2 or More | Loss 1 | No Change | Gain 1 | Gain 2 or More

Change in Snellen Lines of CDVA

Change in Corrected Distance Visual Acuity

C — 102 eyes 12 months postop

Overcorrected
Undercorrected

$y = 0.9422x - 0.0025$
$R^2 = 0.981$

mean: -4.08±2.17 D
range: -0.63 to -9.75 D

Achieved SEQ (D)
Attempted SEQ (D)

Spherical Equivalent Refraction Attempted vs Achieved

D — 102 eyes 12 months postop | ±0.50 D: 69% | ±1.00 D: 93%

% Of Eyes

0% | 5% | 18% | 27% | 29% | 12% | 7% | 2% | 0%

<-1.50 | -1.50 to -1.01 | -1.00 to -0.51 | -0.50 to -0.14 | -0.13 to +0.13 | +0.14 to +0.50 | +0.51 to +1.00 | +1.01 to +1.50 | >+1.50

Accuracy of SEQ to Intended Target (D)

Spherical Equivalent Refraction Accuracy

E — 102 eyes 12 months postop | % changed > 0.50 D 3-12 mo = 4%

Mean ± SD SEQ (D)

-0.08 | -0.15 | -0.17 | -0.20 | -4.06

Pre | 1 (102) | 3 (102) | 6 (102) | 12 (102) | 24 ()

Time After Surgery (months)

Spherical Equivalent Refraction Stability

F — 102 eyes 12 months postop | ≤0.50 D: 91% | ≤1.00 D: 98%

% Of Eyes

Postop
Preop

76% | 0% | 16% 29% | 4% 14% | 2% 6% | 7% 0% | 3% 1% | 4% 1% | 19% 0% | 18%

≤ 0.25 | 0.26 to 0.50 | 0.51 to 0.75 | 0.76 to 1.00 | 1.01 to 1.25 | 1.26 to 1.50 | 1.51 to 2.00 | 2.01 to 3.00 | > 3.00

Refractive Astigmatism (D)

Refractive Astigmatism

G — 90 astigmatic eyes 12 months postop

Overcorrected
Undercorrected

$y = 0.8571x + 0.0107$
$R^2 = 0.9259$

TIA: 1.57±1.27 D
SIA: 1.38±1.15 D

Surgically induced astigmatism vector
Target induced astigmatism vector (D)

Target Induced Astigmatism vs Surgically Induced Astigmatism

H — 90 astigmatic eyes 12 months postop

Arith. Mean: -0.9±9.8
Abs. Mean: 6.7±7.1
% <-15°: 36%
% >15°: 12%

CC/Wise
C/Wise

Angle of Error (degrees)

>75 0%
65 to 75 0%
55 to 65 0%
45 to 55 0%
35 to 45 0%
25 to 35 9%
15 to 25 3%
5 to 15 7%
-5 to 5 36%
-15 to -5 10%
-25 to -15 23%
-35 to -25 12%
-45 to -35 0%
-55 to -45 0%
-65 to -55 0%
-75 to -65 0%
<-75 0%

Percentage Eyes (%)

Refractive Astigmatism Angle of Error