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QUANTITATIVE DESCRIPTORS IN MYOPIC EYES

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Doctorando:

Noelia Martínez Albert

Directores:

Robert Montés Micó

Andrés Gené Sampedro

Inmaculada Bueno Gimeno

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QUANTITATIVE DESCRIPTORS IN MYOPIC EYES

Memoria presentada por

NOELIA MARTÍNEZ ALBERT

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DECLARACIÓN

Ninguna parte de este trabajo ha sido presentada para optar a ningún otro grado ni titulación, ni en esta ni en otra universidad o institución educativa o de investigación.

El Prof. Robert Montés Micó, Catedrático de la Universidad de Valencia, el Dr. Andrés Gené Sampedro, Profesor Titular de la Universidad de Valencia y la Dra. Inmaculada Bueno Gimeno, Profesora Contratado Doctor de la Universidad de Valencia

CERTIFICAN que la presente memoria "QUANTITATIVE DESCRIPTORS IN MYOPIC EYES" resume el trabajo de investigación llevado a cabo por Dª Noelia Martínez Albert, bajo su dirección y supervisión, y constituye su Tesis Doctoral para optar al Grado de Doctor en Optometría y Ciencias de la Visión.

Y para que así conste, y en cumplimiento de la legislación vigente, firman el presente certificado en Valencia, a octubre de dos mil veinte.

Fdo. Robert Montés Micó

Fdo. Andrés Gené Sampedro

Fdo. Inmaculada Bueno Gimeno

A mis padres,

Vicente y Amparo

A mi hermana y alma gemela,

Carolina

"I'm a greater believer in luck, and I find
the harder I work the more I have of it"

Thomas Jefferson

"Nothing in life is to be feared, it is only to be understood.
Now is the time to understand more, so that we may fear less."

Marie Curie

"You never change your life until you step out of your comfort zone;
change begins at the end of your comfort zone."

Roy T. Bennett

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RESUMEN

La miopía es uno de los trastornos refractivos más comunes, el cual ocurre cuando no hay armonía entre la potencia refractiva ocular y el crecimiento de la longitud del ojo. Debido a esta descompensación, la imagen de los objetos distantes resulta desenfocada. Los objetos distantes se enfocan por delante del plano de la retina, lo que resulta en la percepción borrosa de las imágenes. Las lentes correctoras de potencia negativa pueden proporcionar imágenes claras enfocadas en la fóvea a través de la divergencia de los rayos de luz incidentes. Aunque el error refractivo cambia desde el nacimiento hasta la edad adulta, los cambios más importantes ocurren durante la niñez cuando se desarrolla el ojo. El mecanismo de emetropización es el responsable de la compensación entre los cambios de los componentes oculares durante el desarrollo del ojo para guiar el error refractivo hacia la emetropía.

El crecimiento de los componentes oculares ha demostrado ser diferente entre aquellos que desarrollan miopía y aquellos que no. Los miopes en desarrollo han mostrado principalmente una mayor tasa de crecimiento de la profundidad de cámara vítrea (VCD) y longitud axial (AL). Los miopes parecen no ralentizar el crecimiento del ojo con la edad como lo hacen los emétropes en la fase tardía de crecimiento. La tasa de pérdida de potencia del cristalino también aumenta para compensar el crecimiento de la AL, aunque llega un momento en que el cristalino ya no puede mantener esta compensación. Además, la tasa de adelgazamiento del cristalino aumenta cuando se desarrolla la miopía. Y a pesar de la mayor potencia corneal en la miopía, su tasa de cambio no ha presentado diferencias significativas en comparación con los no miopes. Por tanto, el ojo miope sufre cambios oculares, incluso antes del inicio de la miopía, que lo distinguen del ojo emétrope. Los cambios refractivos ocurren junto con cambios oculares estructurales y funcionales en el ojo.

La prevalencia de la miopía está creciendo a nivel global y casi la mitad de la población mundial puede ser miope en 2050 y alrededor del 10% miope alto. La miopía ha alcanzado niveles epidémicos en los países desarrollados del este y sudeste de Asia. En estas regiones, la prevalencia ha ido aumentando con el tiempo y especialmente en edades más tempranas. Del mismo modo, Europa ha experimentado un aumento de la prevalencia de la miopía a lo largo de los años. Además, la prevalencia de la miopía ha demostrado ser mayor entre la población con una educación superior. Se cree que el tiempo dedicado a actividades de trabajo cercano tiene un papel en dicha asociación entre

la miopía y el nivel educativo alcanzado. De hecho, el tiempo dedicado al trabajo cercano y su intensidad, especialmente la lectura continua, han demostrado aumentar las probabilidades de miopía en niños.

De esta forma, los estudiantes universitarios constituyen un grupo de población joven expuesto a mucho trabajo cercano prolongado como consecuencia de las altas exigencias académicas. Esta población académica tiene un riesgo especial de desarrollo y progresión de la miopía durante sus estudios y, por lo tanto, se les debe prestar especial atención. El aumento de la prevalencia de la miopía entre los estudiantes universitarios durante las últimas décadas ha tenido un ritmo diferente según la región geográfica. Generalmente, la prevalencia de la miopía en aquellos con línea de ascenso europea es mucho menor que en el este y sudeste asiático. El pico de prevalencia de la miopía se sitúa en torno a los 25 y 29 años en la población europea.

La miopía se ha convertido en un problema de salud pública ya que en la actualidad es una de las causas de pérdida visual significativa. Esto se debe a sus complicaciones asociadas que la convierten en miopía patológica. La miopía ha mostrado ser un factor de riesgo para padecer algunas afecciones oculares como maculopatía miópica, desprendimiento de retina, glaucoma y cataratas. La miopía no corregida también puede afectar la calidad de vida a través de la alteración producida en la función visual. Adicionalmente, la miopía tiene un impacto económico, teniendo en cuenta el coste de los métodos de corrección así como el manejo de la miopía y sus complicaciones en los sistemas de salud.

La miopía puede desarrollarse e incluso seguir progresando en adultos jóvenes durante sus estudios universitarios. Sin embargo, el desarrollo y la progresión de la miopía en adultos jóvenes no se ha evaluado tan ampliamente como en niños o adolescentes hasta ahora. Por tanto, esta tesis se llevó a cabo ante la necesidad de realizar más investigaciones sobre la miopía en la población universitaria y con el fin de evaluar los cambios oculares producidos como consecuencia de la progresión de la miopía. Esta investigación tuvo como objetivo caracterizar el ojo miope mediante descriptores oculares cuantitativos, medidos con técnicas no invasivas, y analizar el cambio de los mismos con el tiempo en relación con la progresión de la miopía en una muestra de jóvenes universitarios. Además, también se pretendió determinar los descriptores

cuantitativos que mejor representan las características oculares de los ojos miopes y su progresión.

Se diseñó un estudio prospectivo longitudinal para evaluar a estudiantes universitarios miopes y emétropes con un seguimiento de un año. La metodología general del estudio se engloba en el Capítulo 4. El protocolo del estudio se realizó según los principios de la Declaración de Helsinki y fue aprobado por el Comité de Ética de la Universidad de Valencia. La población a evaluar estaba constituida por estudiantes caucásicos sanos de la Universidad de Valencia con una edad entre 18 y 35 años. Los criterios de exclusión fueron los siguientes: etnia no caucásica, equivalente esférico (SE) hipermetrópico > +1,00 D, patologías oculares, enfermedades sistémicas con efectos oculares, cirugía ocular previa o traumatismo ocular, medicación ocular actual, problemas de visión binocular, mala fijación o agudeza visual mayor a 0,1 logMAR con compensación refractiva.

La evaluación preliminar consistió en la anamnesis, estado del error de refractivo y examen con lámpara de hendidura para garantizar que todos los sujetos cumplían con los criterios de inclusión. Se completó un cuestionario en línea para cada participante como anamnesis con el fin de obtener información sobre: fecha de nacimiento, sexo, años de estudios universitarios, salud sistémica y ocular, alergias, tratamientos oculares, medicación actual, última revisión visual, síntomas visuales (visión borrosa , halos, etc.), error refractivo ya diagnosticado con su año de primera compensación, tipo de compensación utilizada y horas de uso, calidad de visión subjetiva (visión lejana y cercana) y horas de lectura al día. La última prescripción de gafas también se registró una vez verificada en un frontofocómetro automático.

En primer lugar, se obtuvo la refracción automática objetiva tomada con el L67 Auto Kerato Refractometer (Visionix Luneau, France) y se realizó un ajuste subjetivo. Se utilizó el método de miopización añadiendo potencia positiva a la refracción objetiva preliminar para controlar la acomodación de los sujetos. El criterio adoptado para el punto final de la refracción subjetiva fue el máximo positivo para lograr la máxima agudeza visual, mientras que el refinamiento del astigmatismo se realizó con la técnica de los cilindros cruzados. Todos los pacientes lograron una agudeza visual con corrección de lejos de al menos 0,1 en notación logMAR.

Posteriormente, el protocolo de medida se realizó de la siguiente manera: biometría ocular (IOLMaster 700; Carl Zeiss Meditec, Germany), topografía corneal (Visante Omni; Carl Zeiss Meditec, Germany), OCT de segmento anterior (Visante OCT; Carl Zeiss Meditec, Germany), aberrometría corneal y ocular (i.Profiler^{plus}; Carl Zeiss Meditec, Germany) y fotografía de fondo de ojo (CR-2 Plus; Canon, Tokyo). Generalmente, se pidió a los pacientes que colocaran la barbilla y la frente en el dispositivo y se les indicó que mantuvieran su visión en la luz de fijación durante el examen. También se les pidió que realizaran un parpadeo completo antes de cada escaneo para lograr una película lagrimal adecuada y mantener los ojos bien abiertos durante la adquisición de la medida. Solo se obtuvieron datos del ojo derecho debido a la similitud de las medidas para ambos ojos. A continuación, se dividió a los pacientes en grupos refractivos según la potencia de los meridianos principales. Los pacientes que tenían miopía en ambos meridianos y cuyo meridiano menos negativo era ≤-0,75 D se incluyeron en el grupo de miope. Por otro lado, el grupo emétrope estuvo formado por aquellos cuyo meridiano menos positivo fue > -0,75 D y el meridiano más positivo ≤ + 0,75 D.

Después de un año, los pacientes se sometieron a una visita de seguimiento. En esta segunda visita, se pidió a los pacientes que respondieran varias preguntas sobre cualquier cambio en la calidad de su visión, cualquier cambio de compensación refractiva (gafas/lentes de contacto), cualquier complicación ocular o medicación actual. A continuación, se realizaron las mismas medidas que en la primera visita siguiendo el mismo orden del protocolo, desde la refracción objetiva en adelante. El cambio de las variables medidas se obtuvo generalmente a través de la diferencia entre la visita de seguimiento y la visita inicial.

Las variables relativas al cuestionario y las variables refractivas de la muestra se analizaron en el Capítulo 5. En un primer momento se evaluó una muestra de 89 estudiantes universitarios, pero de ellos, se excluyeron 11 por no cumplir los criterios establecidos para la clasificación refractiva. Por lo tanto, se incluyeron en la investigación un total de 78 (50 mujeres y 28 hombres) con una edad media de 23,46 ± 4,51 años. Los grupos refractivos consistieron en 31 sujetos emétropes (21 mujeres y 10 hombres) y 47 sujetos miopes (29 mujeres y 18 hombres). La edad media fue 23,35 ± 3,97 y 23,53 ± 4,88 años para el grupo emétrope y miope, respectivamente. No hubo diferencias significativas de edad o sexo entre los grupos refractivos. Más tarde, se realizó el seguimiento en 65 de

los 78 sujetos iniciales (83,33%) después de 12,66 ± 1,17 meses. En consecuencia, los grupos refractivos después del seguimiento resultaron en 25 sujetos emétropes (17 mujeres y 8 hombres) y 40 sujetos miopes (25 mujeres y 15 hombres).

En la primera visita, la esfera y SE mostraron diferencias entre los grupos. Además, el cilindro refractivo resultó ser significativamente mayor en el grupo miope. La distribución de estudiantes pregrado y posgrado fue similar entre el grupo emétrope y miope, así como el total de años de estudios universitarios. Los estudiantes informaron que dedicaban principalmente entre 2 y 6 horas diarias a la lectura, y esto no fue diferente entre los grupos refractivos. Dentro del grupo miope, la edad promedio de inicio de la miopía fue de 11,72 ± 4,9 años, donde alrededor del 89% tuvo un inicio temprano (antes de los 16 años).

Después de un año, el SE experimentó un cambio significativo general de -0,10 ± 0,17 D en promedio, de -2,88 ± 3,45 D a -2,97 ± 3,52 D. No se encontró ningún cambio en el SE en 42 sujetos, 21 sujetos tuvieron un cambio en el SE por debajo de -0,50 D y los otros 2 sujetos tuvieron un cambio de -0,50 y -1,00 D, respectivamente. Eso significa que más de la mitad de la muestra, el 64,62%, permaneció estable mientras que el 33,84% tuvo un cambio de hasta -0,50 D. Considerando como clínicamente significativo un cambio del SE de al menos -0,25 D, solo alrededor del 25% de la muestra tuvo un cambio refractivo significativo. Concretamente, el SE sufrió un cambio tras el seguimiento en 17 miopes iniciales (42,5%) y 6 emétropes iniciales (24%), quedando estable el SE para el 57,5% de los miopes y el 76% de los emétropes. Además, dentro de los miopes con cambio, el 88,23% tuvo un cambio por debajo de -0,50 D y solo el 5% superó el cambio de -0,50 D. Mientras tanto, el total de emétropes con cambio lo tuvieron hasta -0,37 D, y estos cambios no llevaron a convertirlos en miopes en ningún caso. Por tanto, la variación del SE fue mayor en el grupo miope (-0,13 ± 0,20 D) que en el emétrope (-0,05 ± 0,09 D). El cambio de esfera con el tiempo resultó ser significativamente mayor en los miopes hacia valores más negativos, mientras que el cambio de astigmatismo fue similar entre los grupos.

Las diferencias biométricas entre emétropes y miopes se analizaron en el Capítulo 6. Los parámetros biométricos obtenidos mediante el dispositivo IOLMaster 700 fueron los siguientes: espesor corneal central (CCT) definido como la distancia entre el epitelio corneal y el endotelio, profundidad de cámara anterior (ACD) definido como la distancia

entre el endotelio y la superficie anterior del cristalino, espesor del cristalino (LT) definido como la distancia entre las superficies anterior y posterior del cristalino en su parte central y AL definida como la distancia entre el epitelio corneal y la fóvea. La longitud del segmento anterior (ASL) se calculó como la suma de CCT, ACD y LT para estimar posteriormente la VCD. La VCD representa la distancia entre la superficie posterior del cristalino y la retina, que se determinó restando la ASL de la AL.

El grupo miope manifestó una ACD más profunda, así como VCD y AL más largas. De hecho, SE correlacionó con una ACD más profunda y una VCD más larga. También hubo una tendencia de un LT ligeramente más delgado en el grupo miope, aunque no fue estadísticamente significativo. De hecho, VCD tuvo una relación positiva con una ACD más profunda y LT más delgado. Además, el ajuste cuadrático demostró que esta relación lineal no se mantenía en todo el rango de VCD. Por lo tanto, se observó que el aumento de ACD y la disminución de LT ocurrían hasta que la VCD era de alrededor 20 mm. Además, LT y ACD manifestaron una relación inversa, de forma que un LT más delgado estaba presente en los sujetos con una ACD más profunda. Nuestra muestra no presentó diferencias significativas en CCT debido a la miopía ni CCT se relacionó con el SE o VCD. La regresión múltiple indicó que el principal contribuyente al SE fue la VCD, que explicaba el 68,2% de su varianza. Mientras tanto, un SE más negativo y un LT más delgado dieron como resultado una VCD más larga, que representaba un 79,9% de la variabilidad de la VCD.

Los cambios biométricos longitudinales también se evaluaron junto con los cambios refractivos para determinar el efecto de estos en la progresión de la miopía. En toda la muestra, LT y VCD aumentaron significativamente mientras que ACD disminuyó, lo que resultó en un incremento de la AL. Los cambios de VCD fueron diferentes entre los grupos refractivos, donde los miopes exhibieron un mayor alargamiento de VCD que los emétropes. Estos resultados coincidieron con el mayor cambio de SE encontrado en el grupo miope. Mientras tanto, ACD y LT también cambiaron entre las visitas, aunque fueron similares para ambos grupos refractivos. El engrosamiento de LT observado no se relacionó con cambios refractivos, sino que fue un cambio más bien relacionado con la edad. Por consiguiente, la disminución de ACD fue una consecuencia directa del incremento de LT. El análisis de regresión múltiple determinó que el cambio de VCD era el único predictor significativo del cambio de SE (19,8% de varianza) de modo que una

mayor elongación de la VCD conducía a un cambio negativo mayor. Al mismo tiempo, el cambio de VCD fue el que más contribuyó a los cambios de AL (variación del 32,7%) seguido de los cambios de LT y ACD.

Los parámetros corneales se evaluaron en el Capítulo 7. Las medidas tomadas en la córnea mediante el dispositivo Visante Omni consistieron en su espesor, diámetro, curvatura, forma y elevación. EL espesor corneal (CT) se adquirió en las siguientes zonas corneales: de 0 a 2 mm; de 2 a 5 mm; de 5 a 7 mm y de 7 a 10 mm. El diámetro corneal, también conocido como la distancia blanco-blanco (WTW), se midió como la distancia horizontal entre los bordes del limbo corneal. Las variables de queratometría de K curva, K plana y astigmatismo se evaluaron en primer lugar en los 4,5 mm centrales. Posteriormente, se examinó la queratometría en la córnea central (0-3 mm), paracentral (3-6 mm) y periférica (6-9 mm). El análisis de la forma corneal se realizó con datos de excentricidad, asfericidad (Q) y factor de forma. También se incluyeron en el análisis medidas de excentricidad en diferentes orientaciones meridionales (0, 10, 15, 20, 25 y 30°). La elevación corneal se determinó mediante la esfera de mejor ajuste (BFS) y el ajuste tórico. Además, la relación entre la longitud axial y el radio corneal (AL/CR) se calculó como la proporción entre AL y CR, ambos expresados en mm.

No hubo diferencias para CT en ninguna zona corneal debido al error refractivo. Aunque WTW fue similar entre el grupo emétrope y miope, WTW aumentó con mayor VCD hasta alcanzar aproximadamente los 19 mm, pero posteriormente no mostró dependencia de la elongación ocular. El grupo miope exhibió mayor curvatura corneal que los emétropes, especialmente para el meridiano más curvo en la córnea central y paracentral. En efecto, se observó una asociación negativa del SE con K media y K curva. También se obtuvo un mayor astigmatismo corneal en ojos miopes en la córnea central, mientras que para la córnea paracentral no alcanzó la significancia. En la periferia corneal, el astigmatismo fue similar entre nuestros grupos refractivos debido al mayor incremento del astigmatismo de córnea paracentral a periférica en el grupo emétrope. Adicionalmente, los grupos refractivos en su mayoría no tuvieron diferencias en los parámetros de forma. Sin embargo, cuando la excentricidad se evaluó por meridianos, esta fue mayor para los miopes en los meridianos de 0 a 30°, lo que significa un mayor aplanamiento del centro a la periferia en estos meridianos. Es probable que estos

hallazgos se deban a que los miopes manifestaron mayor curvatura corneal y astigmatismo.

De acuerdo con las diferencias de curvatura, la BFS anterior fue más curvada para los miopes como resultado de la mayor elevación del meridiano curvo. La BFS posterior también fue más curvada en los miopes, aunque el ajuste del elipsoide tórico no reveló diferencias significativas. La VCD tuvo una relación dicotómica con la curvatura y elevación de la córnea, de modo que la elongación ocular llevó a la córnea a aplanarse hasta que la VCD alcanzaba los 19-19,5 mm, punto a partir del cual la córnea ya no podía compensar el alargamiento del ojo e incluso se curvaba. De esta forma, se observó mayor AL/CR en miopes que en emétropes, donde los miopes estaban mayormente por encima de 3.00 en esta proporción. En consecuencia, la regresión lineal múltiple demostró que el SE se predecía mejor cuando se incluía la curvatura corneal junto con la biometría ocular. Nuestra proporción AL/CR también fue mayor en los estudiantes con ACD más profunda y LT más delgado, características que se observaron principalmente en ojos miopes.

CT y WTW tuvieron muy pocos cambios después de un año y estos no se relacionaron con los cambios de SE ni AL. La curvatura del meridiano plano experimentó una disminución general en la córnea central, paracentral y periférica. Sin embargo, la reducción de la K plana en la córnea central y paracentral solo fue significativa dentro del grupo emétrope. Mientras tanto, el astigmatismo aumentó significativamente en la córnea periférica dentro del grupo emétrope. Estos cambios de curvatura no se relacionaron con los cambios del SE y tendieron a ser aún mayores para los emétropes. Esto indicó que, aparentemente, algunos estudiantes aún podían compensar la elongación ocular con el aplanamiento corneal, y por lo tanto, la emetropización podría permanecer en la edad adulta joven.

La muestra no experimentó cambios significativos en los parámetros de forma con el tiempo. Los cambios de forma se correlacionaron con los cambios de curvatura de la K curva en la córnea central y la K plana en la periferia. Por lo tanto, el cambio hacia una Q más negativa se correlacionó con el aumento de la K curva central o una menor reducción, mientras que con una mayor reducción de la K plana en la periferia. El incremento de la excentricidad fue significativo en la horizontal cuando se evaluó por meridianos. Los meridianos 0 y 10° se hicieron más prolatos y esto también se relacionó con cambios en la curvatura de la K curva central y de la K plana periférica. Estos meridianos fueron más

prolatos particularmente en el grupo emétrope ya que la disminución de la curvatura de la K plana mostró una tendencia no significativa a una mayor disminución en la córnea periférica en este grupo refractivo.

Los cambios longitudinales de BFS están alineados con los de curvatura. La BFS anterior experimentó un aplanamiento, que fue significativo dentro del grupo emétrope. Asimismo, la elevación del meridiano posterior curvo también tendió a disminuir su curvatura entre los emétropes. La relación AL/CR obtuvo un cambio diferente entre los grupos refractivos donde el grupo miope experimentó un aumento de 0.005 ± 0.019 mientras que el emétrope tuvo una reducción AL/CR de -0.004 ± 0.015. Pero los cambios de AL/CR no resultaron estar relacionados con los cambios de SE y, por lo tanto, esta proporción no se consideró útil para monitorizar o cuantificar la progresión de la miopía en adultos jóvenes.

En el Capítulo 8, se realizó la evaluación de las medidas de aberrometría. Las medidas del frente de onda corneal y ocular dieron lugar a la obtención de los polinomios de Zernike para un tamaño de pupila de 3 y 5 mm. El frente de onda interno se obtuvo posteriormente restando los coeficientes corneales a los coeficientes oculares. De este modo se analizaron los coeficientes de Zernike de segundo a séptimo orden para el frente de onda corneal, interno y ocular. La raíz cuadrática media (RMS) de las aberraciones de bajo orden (LOA) se calculó considerando los coeficientes de segundo orden, mientras que la RMS de las aberraciones de alto orden (HOA) representó todos los coeficientes de tercer a séptimo orden. La RMS también se calculó en cada orden superior por separado (3º, 4º, 5º, 6º y 7º). Además, se llevó a cabo el cálculo de la RMS para el astigmatismo de bajo orden (Z_2^{-2} y Z_2^2), astigmatismo de alto orden ($Z_4^{-2}, Z_4^2, Z_6^{-2}, Z_6^2$), aberración esférica ($Z_4^0$ y Z_6^0), aberración tipo coma (Z_3^{-1}, Z_3^1, Z_5^{-1}, Z_5^1, Z_7^{-1}, Z_7^1) y aberración tipo trébol (Z_3^{-3}, Z_3^3, Z_5^{-3}, Z_5^3, Z_7^{-3}, Z_7^3). Para evaluar la contribución del frente de onda interno en el ocular, se calculó el factor de compensación para los datos de aberrometría con un tamaño de pupila de 5 mm. El factor de compensación es igual a 1 cuando hay compensación total entre la óptica corneal e interna, mientras que toma el valor 0 cuando no hay compensación alguna. Los valores inferiores a 0 se obtienen cuando la óptica interna agrega aberraciones. Por último, valores superiores a 1 indican que la óptica interna ha sobrecompensado el frente de onda corneal, añadiendo aberraciones pero en sentido contrario.

El astigmatismo de bajo orden manifestó diferencias significativas asociadas con el error de refracción. Un astigmatismo a favor/en contra de la regla (WTR/ATR) Z_2^2 ocular y corneal más negativo se asoció con una esfera más miope. El astigmatismo interno WTR/ATR Z_2^2 fue significativamente mayor en miopes con un tamaño de pupila de 3 mm. Generalmente, la RMS del astigmatismo de bajo orden tendió a ser más alta en ojos miopes, particularmente significativo para el frente de onda ocular (3 y 5 mm). La compensación entre la RMS del astigmatismo de bajo orden corneal e interno terminó siendo más eficaz en los emétropes debido a la mejor compensación del astigmatismo WTR/ATR Z_2^2, que es el que más contribuye al astigmatismo corneal. El astigmatismo oblicuo Z_2^{-2} estuvo más compensado en ojos miopes porque estos tenían ligeramente más componente oblicuo en el frente de onda corneal.

Algunos coeficientes del astigmatismo de alto orden también manifestaron diferencias a pesar de que la RMS del astigmatismo de alto orden ocular resultó similar entre los grupos. El astigmatismo oblicuo secundario Z_4^{-2} y Z_6^{-2} mostró diferencias tanto en el frente de onda corneal como en el interno. El astigmatismo secundario WTR/ATR Z_4^2 interno también tendía a ser mayor en miopes con una pupila más pequeña (3 mm). Considerando la RMS del astigmatismo de alto orden ocular, la compensación entre el frente de onda corneal e interno fue bastante similar entre la emetropía y la miopía. Por otro lado, una aberración esférica más negativa Z_4^0 se relacionó significativamente con una esfera más miope o mayor VCD para el frente de onda interno y ocular (5 mm) a pesar de que no hubo diferencias significativas entre los grupos. Una aberración esférica Z_4^0 interna más negativa condujo a una mayor proporción de compensación parcial en ojos miopes para este coeficiente. Por tanto, la RMS de la aberración esférica ocular reveló valores más bajos en ojos miopes.

Entre las HOA, se encontraron otras diferencias para las aberraciones de coma y trébol, especialmente con pupilas de mayor tamaño (5 mm). Los coeficientes de coma del tercer orden (Z_3^{-1}, Z_3^1) estaban relacionados tanto con la esfera como con la VCD. El coma vertical Z_3^{-1} fue significativamente más positivo en los miopes para el frente de onda interno (3 y 5 mm) y también hubo esta tendencia en el frente de onda corneal. Mientras tanto, los sujetos emétropes tendían a exhibir valores negativos de coma vertical Z_3^{-1} corneal como interno, mostrando principalmente un aumento de este coeficiente en lugar de una compensación entre ellos. Aunque los ojos miopes tenían una mejor proporción de

infracompensación, el coma vertical Z_3^{-1} ocular seguía siendo más positivo en los ojos miopes. El coma horizontal Z_3^1 reveló valores significativamente menos negativos para el frente de onda corneal, mientras que valores menos positivos para el frente de onda interno (5 mm) en sujetos miopes en comparación con los emétropes. La compensación entre el frente de onda corneal e interno fue similar entre los grupos y el coma horizontal ocular Z_3^1 no fue diferente. Los coeficientes de coma secundario (Z_5^{-1}, Z_5^1) tendieron a ser aumentados por la óptica interna en la miopía, sin embargo, las diferencias de frente de onda (córnea, óptica interna, ocular) entre los grupos no fueron significativas. Por lo tanto, la RMS tipo coma no difirió significativamente, aunque los miopes tuvieron valores promedio ligeramente mayores.

El análisis de regresión múltiple manifestó que parte de la variabilidad del SE y la VCD se podía predecir incluyendo todos los coeficientes de Zernike, pero no resultó ningún modelo significativo que incluyera solo HOA. Las variables predictoras más importantes para SE fueron el desenfoque Z_2^0, el trébol Z_3^{-3}, la aberración esférica Z_4^0 y el coma horizontal Z_3^1. Mientras tanto, el desenfoque Z_2^0, la aberración esférica Z_4^0 y Z_6^0 fueron los más importantes para el modelo de la VCD.

Después del seguimiento, hubo un incremento general del desenfoque Z_2^0 ocular siendo un poco mayor en ojos miopes. Así, el aumento del desenfoque Z_2^0 se relacionó con el alargamiento de la VCD a lo largo del tiempo. Mientras que el astigmatismo WTR/ATR Z_2^2 ocular se mantuvo estable en el grupo emétrope, este aumentó negativamente en los miopes debido a la óptica interna. De hecho, el astigmatismo WTR/ATR Z_2^2 interno se asoció con el cambio negativo de la esfera refractiva. El astigmatismo oblicuo Z_2^{-2} manifestó cambios opuestos entre grupos, sin embargo, no se asoció con ningún cambio refractivo o biométrico. En cuanto a las HOA, los datos longitudinales demostraron que el trébol de tercer orden, coma de tercer orden y aberración esférica primaria fueron los coeficientes principales en presentar algunas diferencias entre el grupo emétrope y miope. Sin embargo, los cambios observados después de un año no fueron lo suficientemente diferentes como para obtener diferencias estadísticamente significativas entre grupos refractivos en la mayoría de los casos.

A pesar de algunas diferencias en el frente de onda corneal e interno, el trébol Z_3^{-3} ocular y el coma vertical Z_3^{-1} ocular cambiaron de manera similar en ambos grupos refractivos. Mientras tanto, el grupo miope tendió a aumentar positivamente el coma horizontal Z_3^1 y a reducir los valores positivos del trébol Z_3^3. Los cambios de algunos coeficientes de tercer orden también mostraron una asociación con el cambio refractivo miópico y/o la elongación de la VCD. Además, los ojos miopes sufrieron una leve reducción de la aberración esférica ocular Z_4^0 como consecuencia del mayor aumento negativo de la interna. No obstante, los cambios en la aberración esférica no se asociaron con los cambios refractivos ni biométricos. En términos generales, los cambios de aberraciones experimentados en nuestra muestra joven no se asociaron fuertemente con el cambio refractivo miópico o la elongación de la VCD. Por tanto, estos cambios pueden no ser el desencadenante de la progresión de la miopía sino más bien una consecuencia de ella.

De los resultados obtenidos en el presente estudio se pueden extraer varias conclusiones. Los ojos miopes mostraron diferencias en algunos de los descriptores cuantitativos evaluados al inicio del estudio. Para la biometría ocular, el grupo miope tuvo una ACD más profunda, una VCD más larga y el LT tendía a ser ligeramente más delgado. Además, la ACD más profunda y LT más delgado se asociaron con una VCD más larga, sin embargo, esta relación lineal no se mantuvo cuando el alargamiento de la VCD excedía los 20 mm. La curvatura, elevación y astigmatismo corneal también fueron mayores en los miopes. Tanto la curvatura como la elevación corneal mostraron un aplanamiento hasta que la VCD alcanzó los 19-19,5 mm, punto a partir del cual la córnea ya no podía compensar el alargamiento del ojo e incluso se curvaba. De esta forma, se observó mayor AL/CR en miopes que en emétropes, donde los miopes estaban generalmente por encima de 3,00 en esta proporción. Los emétropes obtuvieron una mejor compensación del astigmatismo WTR/ATR Z_2^2 por lo que los miopes manifestaron valores más negativos en el frente de onda ocular. Por el contrario, hubo una mayor proporción de compensación parcial en ojos miopes para la aberración esférica Z_4^0, lo que resultó en una RMS de la aberración esférica ocular menor. Además, el coma vertical ocular Z_3^{-1} fue más positivo en ojos miopes y se relacionó con una esfera más miope y una VCD más larga.

Tras el seguimiento, el error refractivo experimentó un cambio negativo en una parte de los estudiantes miopes iniciales, aunque fue pequeño, demostrando que la miopía puede seguir progresando durante esta etapa académica. Los miopes mostraron un mayor alargamiento de la VCD coincidiendo con su mayor incremento negativo del SE en comparación con los emétropes. La mayor disminución de la curvatura del meridiano plano en el grupo emétrope, que no estaba relaciona con el cambio del SE, podría indicar que el alargamiento axial todavía puede compensarse con el aplanamiento corneal en adultos jóvenes emétropes. La relación AL/CR no manifestó una relación con el cambio del SE y no se consideró útil para monitorizar o cuantificar la progresión de la miopía en adultos jóvenes. Como se esperaba, el desenfoque ocular Z_2^0 tuvo un mayor aumento en el grupo miope y se relacionó con el alargamiento de la VCD. El astigmatismo WTR/ATR Z_2^2 también aumentó negativamente en los miopes mientras que se mantuvo estable en los emétropes. Además, los ojos miopes tendían a aumentar positivamente el coma horizontal ocular Z_3^1 y a reducir los valores positivos del trébol ocular Z_3^3. La aberración esférica ocular Z_4^0 sufrió una leve reducción en el grupo miope pero esta no se relacionó con los cambios refractivos ni biométricos.

ABSTRACT

Myopia is one of the most common refractive disorders, which occurs when there is no harmony between ocular power and eye length growth. Because of this decompensation, the image of distant objects results to be out of focus. Distance objects are focused anteriorly to the retinal plane, resulting in a blurry perception of the visual images. Corrective lenses of negative power can provide clear images focused on the fovea through the divergence of the incident light rays. Even though the refractive error changes from birth to adulthood, the major changes occur during childhood when the eye develops. The emmetropization mechanism is responsible for the compensation between the changes of the ocular components during eye development to guide the refractive error towards emmetropia.

The growth of the ocular components has proved to be different between those who develop myopia and those who do not. Developing myopes mainly have shown an increased rate of growth of vitreous chamber depth (VCD) and axial length (AL). Myopes seem not to slow the eye growth with age as emmetropes do in the late growth phase. The crystalline lens power loss rates also increase in order to compensate for the AL growth albeit there comes some point when the lens can no longer maintain this compensation. Besides, the rate of lens thinning increases when myopia develops. And despite the greater corneal power in myopia, its change rate has not exhibited significant differences compared with those non-myopic. Therefore, myopic eye undergoes ocular changes, even before the myopia onset, which distinguish it from the emmetropic eye. The refractive changes occur along with structural and functional ocular changes in the eye.

The prevalence of myopia is globally growing and nearly half of the world's population may be myopic by 2050 and around 10% highly myopic. Myopia has reached epidemic levels in the developed countries of East and Southeast Asia. In these regions, the prevalence has been increasing over time and especially at younger ages. Alike, Europe has undergone an increment of myopia prevalence through the years. Further, myopia prevalence has demonstrated to be greater among the population with the highest education. The time spent in near work activities is thought to have a role in such association between myopia and the educational level achieved. Indeed, the time spent in near work and its intensity, especially continuous reading, have shown to increase the myopia odds in children.

In this way, the students at university constitute a young population group exposed to high prolonged near work as a result of the high academic demands. This academic population is at special risk of myopia development and progression during their studies and, therefore, attention should be payable to them. The increase of myopia prevalence among students at university over the last decades has different rate depending on the geographical region. Generally, myopia prevalence in European line of ascent is much lower than the one in East and Southeast Asia. The peak in myopia prevalence is around 25 and 29 years in the European population.

Myopia has become a public health issue since it is currently one of the causes of significant visual loss. This is due to its associated complications, which turn it in pathological myopia. Myopia has shown as a risk of suffering some ocular conditions such as myopic maculopathy, retinal detachment, glaucoma and cataracts. Uncorrected myopia can also affect the quality of life through the alteration of visual function produced. Furthermore, myopia has an economic impact, taking into account the cost of correction methods as well as myopia management and its complications in the health care systems.

Myopia can develop and even keep progressing in young adults during their university studies. However, myopia development and progression in young adults have not been assessed as widely as in children or teenagers up to now. Thus, this thesis was carried out given the need for more investigations about myopia in the university population in order to evaluate the eye changes produced as a result of myopia progression. The purpose of this research was to characterise the myopic eye by means of quantitative ocular descriptors, measured with non-invasive techniques, and to analyse the change of them over time in connection with myopia progression in a sample of young university students. Further, this research aimed to determine the quantitative descriptors that best represent the ocular features of myopic eyes and their progression.

A prospective longitudinal study was designed to evaluate myopic and emmetropic university students with a one-year follow-up. The general methodology of the study is included in Chapter 4. The study protocol was performed according to the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the University of Valencia. The population to evaluate consisted of Caucasian healthy students from the University of Valencia with an age between 18 and 35 years. The exclusion criteria were the following: non-Caucasian ethnicity, hyperopic spherical equivalent (SE) > +1.00 D,

ocular pathologies, systemic diseases with ocular effects, previous ocular surgery or ocular trauma, current ocular medication, binocular vision problems, poor fixation or visual acuity worse than 0.1 logMAR with refractive compensation.

The preliminary evaluation consisted of the anamnesis, refractive error status and slit-lamp examination to ensure every subject met the inclusion criteria. An online questionnaire was completed for each participant as anamnesis in order to obtain information about: birth date, gender, the yeas studying at university, systemic and ocular health, allergies, ocular treatments, current medication, last visual revision, visual symptoms (blur vision, halos, etc.), refractive error already diagnosed with its year of first compensation, type of compensation used and hours of use, subjective vision quality (distance and near vision) and hours spent reading per day. The latest spectacle prescription was also recorded once checked in an auto lensmeter.

Firstly, objective automatic refraction was taken with the L67 Auto Kerato Refractometer ((Visionix Luneau, France) followed by a subjective refinement. The fogging method was used adding positive power to the preliminary objective refraction to control the subjects' accommodation. The adopted criterion for the subjective refraction endpoint was the maximum plus to achieve the best visual acuity while the astigmatism refinement was done with the cross-cylinder technique. All patients achieved a visual acuity with distance correction of at least 0.1 in logMAR notation.

Subsequently, the measurement protocol was performed as follows: ocular biometry (IOLMaster 700; Carl Zeiss Meditec, Germany), corneal topography (Visante Omni; Carl Zeiss Meditec, Germany), anterior segment OCT (Visante OCT; Carl Zeiss Meditec, Germany), corneal and ocular aberrometry (i.Profiler^{plus}; Carl Zeiss Meditec, Germany) and fundus photography (CR-2 Plus; Canon, Tokyo). Generally, patients were asked to place the chin and forehead in the device and instructed to focus their vision in the fixation light during the examination. They were also asked to perform a complete blink prior to each scan to achieve an appropriate tear film and to keep their eyes wide open during the measurement acquisition. Only data from the right eyes were obtained due to the similarity of the measurements for both eyes. Patients were then divided into refractive groups according to the power of the principal meridians. Patients who had myopia in both meridians and whose least negative meridian was ≤-0.75 D were included

in the myopic group. On the other hand, the emmetropic group was made up of those whose least positive meridian was > -0.75 D and most positive meridian ≤ +0.75 D.

After one year, patients underwent a follow-up visit. In this second visit, patients were asked to answer several questions regarding any change in their vision quality, any refractive compensation change (glasses/contact lens), any ocular complication or any current medication. Subsequently, the same measurements as in the baseline visit were performed following the same protocol order, from the objective refraction onwards. The change of the measured variables was generally obtained through the difference between follow-up and baseline visit.

The variables regarding the questionnaire and refractive variables of the sample were analysed in Chapter 5. At first, a sample of 89 university students was assessed but from them, 11 were excluded because they did not meet the criteria established for the refractive classification. Therefore, a total of 78 (50 females and 28 males) were enrolled in the research with a mean age of 23.46 ± 4.51 years. Refractive groups consisted of 31 emmetropic subjects (21 females and 10 males) and 47 myopic subjects (29 females and 18 males). The mean age was 23.35 ± 3.97 and 23.53 ± 4.88 years for the emmetropic and myopic group, respectively. There were no significant differences in age nor sex between refractive groups. Then, the follow-up was carried out in 65 of the 78 initial subjects (83.33%) after 12.66 ± 1.17 months. Consequently, the refractive groups after the follow-up resulted in 25 emmetropic subjects (17 females and 8 males) and 40 myopic subjects (25 females and 15 males).

In the baseline visit, the sphere and SE differed between groups. Moreover, the refractive cylinder resulted significantly greater in the myopic group. The distribution of undergraduate and postgraduate students was similar between the emmetropic and myopic group as well as the total of years studying at the university. The students informed to spend mostly between 2 and 6 hours per day on reading, and this was not different between refractive groups. Within the myopic group, the average age of myopia onset was 11.72 ± 4.9 years where around 89% had early-onset (before the 16 years).

After a year, the SE experienced a general significant shift of -0.10 ± 0.17 D on average, from -2.88 ± 3.45 D to -2.97 ± 3.52 D. No change of SE was found in 42 subjects, 21 subjects had an SE shift below -0.50 D and the other 2 subjects had -0.50 and -1.00 D

change, respectively. That means more than a half of the sample, 64.62%, remained stable while 33.84% had a change up to -0.50 D. Considering as clinically significant a SE shift of at least -0.25 D, only around 25% of the sample had significant refractive change. Concretely, the SE underwent a change after the follow-up in 17 initial myopes subjects (42.5%) and 6 initial emmetropic (24%) thus remaining the SE stable for 57.5% of myopes and 76% of the emmetropes. Further, within the changing myopes, 88.23% of them had a shift beneath a -0.50 D and only the 5% exceeded -0.50 D change. Meantime, the total of the changing emmetropes had a shift up to -0.37 D, and these changes did not lead them to become myopic in any case. Thus, the SE shift was greater in the myopic group (-0.13 ± 0.20 D) than in the emmetropic (-0.05 ± 0.09 D). The sphere change over time resulted to be significantly greater in myopes towards negative values while the astigmatism change was similar between groups.

The biometric differences between emmetropes and myopes were analysed in Chapter 6. The analysed biometric parameters obtained with IOLMaster 700 were the following: central corneal thickness (CCT) defined as the distance between corneal epithelium and endothelium, anterior chamber depth (ACD) defined as the distance between endothelium and anterior crystalline lens surface, lens thickness (LT) defined as the distance between anterior and posterior surfaces of the crystalline lens in its centre and AL defined as the distance between corneal epithelium and fovea. Anterior segment length (ASL) was calculated as the addition of CCT, ACD and LT to subsequently estimate the VCD. VCD represents the distance between the posterior crystalline lens surface and retina, which was determined by subtracting the ASL from the AL.

The myopic group manifested deeper ACD, as well as longer VCD and AL. Indeed, the SE correlated with deeper ACD and longer VCD. There was also a tendency of slightly thinner LT in the myopic group, though no statistically significant. In fact, the VCD had a positive relationship with deeper ACD and thinner LT. Further, the quadratic fit demonstrated that this linear relationship was not maintained across the entire VCD range. Thus, the ACD increase and LT decrease was seen to occur until the VCD was around 20 mm. Besides, LT and ACD manifested an inverse relationship so as thinner LT was present in subjects with deeper ACD. Our sample did not exhibit significant CCT differences because of myopia nor CCT was related to the SE or VCD. Multiple regression indicated that the main contributor to SE was the VCD, explaining 68.2% of its variance.

Meantime, more negative SE and thinner LT resulted in longer VCD, accounting for 79.9% VCD variability.

The longitudinal biometric changes were also assessed alongside the refractive changes in order to determine the effect of them in myopia progression. In the entire sample, the LT and VCD increased significantly while the ACD decreased, which turned out to an AL increment. The VCD changes differed between refractive groups, where myopes exhibited higher VCD elongation than emmetropes. These results agreed with the greater SE change found in the myopic group. Meanwhile, ACD and LT also changed between visits although these were similar for both refractive groups. The observed LT thickening was not related to the refractive changes but rather was an age-related change. Consistently, the ACD decrease was a direct consequence of the LT increment. Multiple regression analysis determined the VCD change was the only significant predictor of the SE change (19.8% variance) so that more VCD elongation conducted to a greater negative shift. At the same time, the VCD change was the most contributor to the AL changes (32.7% variance) followed by the changes of LT and ACD.

Corneal parameters were assessed in Chapter 7. The measurements taken on the cornea by the Visante Omni consisted of its thickness, diameter, curvature, shape and elevation. The corneal thickness (CT) was acquired in the following corneal zones: from 0 to 2 mm; from 2 to 5 mm; from 5 to 7 mm, and from 7 to 10mm. The corneal diameter, also known as white-to-white (WTW), was measured as the horizontal distance between the corneal limbus borders. The keratometry variables of steep K, flat K and astigmatism were firstly assessed in the central 4.5 mm. Then, keratometry was examined in the central (0-3 mm), paracentral (3-6 mm) and peripheral cornea (6-9 mm). The corneal shape analysis was carried out with data of eccentricity, asphericity (Q) and shape factor. Measurements of eccentricity at different meridional orientations (0, 10, 15, 20, 25 and 30°) were also included in the analysis. Corneal elevation was determined by means of the best-fit-sphere (BFS) and toric fit. Additionally, the axial length to corneal radius (AL/CR) ratio was calculated as the ratio between AL and CR both expressed in mm.

There were no differences for the CT in any corneal zone due to the refractive error. Although the WTW was similar between our emmetropic and myopic group, WTW increased with longer VCD until reaching about 19 mm but subsequently showed no dependency on the eye elongation. The myopic group exhibited greater corneal curvature

than emmetropes, especially for the steep meridian in central and paracentral cornea. Indeed, a negative association of the SE with the mean K and steep K was observed in our sample. Higher corneal astigmatism was also seen in myopic eyes in the central cornea while in paracentral corneal it did not reach the significance. In the periphery, astigmatism was similar between our refractive groups because of the greater increment of astigmatism from paracentral to peripheral cornea in the emmetropic group. Furthermore, refractive groups mostly had no difference in the shape parameters. However, when the eccentricity was assessed by meridians, it was greater for myopes in the meridians from 0 to 30° meaning more flattening from centre to periphery in these meridians. These findings are likely to occur as a result of the greater corneal curvature and astigmatism in myopes.

Consistent with the curvature differences, the anterior BFS was steeper for myopes due to the greater elevation of the steep meridian. Posterior BFS was also steeper in myopes although the toric ellipsoid fit did not reveal significant differences. The VCD had a dichotomous relationship with corneal curvature and elevation so that eye elongation led the cornea to flatten until the VCD reached 19-19.5 mm, point from which the cornea could no longer compensate the eye enlargement and it even steepened. Thus, greater AL/CR ratio was seen in myopes than in emmetropes, where myopes were mostly above 3.00 in this ratio. Accordingly, multiple linear regression proved that SE was better predicted when the corneal curvature was included with the ocular biometry. Moreover, the AL/CR ratio was higher in the students with deeper ACD and thinner LT, features seen mostly in myopic eyes.

The CT and WTW had very little changes after one year and these were not related to the SE nor AL changes. The curvature of the flat meridian experienced a general decrease in central, paracentral and peripheral cornea. However, the reduction of flat K in the central and paracentral cornea was only significant within the emmetropic group. Meantime, astigmatism increased significantly within the emmetropic group in the peripheral cornea. These curvature changes did not associate with the SE changes and tended to be even greater for emmetropes. This indicated that apparently some students still may compensate the eye elongation with the corneal flattening and, therefore, the emmetropization could remain in young adulthood.

The sample did not experience significant changes in the shape parameters with time. The shape changes were correlated to the curvature changes of the steep K in the central cornea and the flat K in the periphery. Thereby, the change to more negative Q correlated to the increase of the central steep K or less reduction, while more reduction of flat K in the periphery. The eccentricity increment was significant in the horizontal when assessed by meridians. The meridians 0 and 10° became more prolate and it was also related to the changes in the curvature of the central steep K and the peripheral flat K. These meridians were more prolate particularly in the emmetropic group since the curvature decrease of flat K showed a non-significant tendency of greater decrease in the peripheral cornea in this refractive group.

The longitudinal changes of BFS are aligned with the curvature ones. Anterior BFS experienced a flattening, which was significant within the emmetropic group. Likewise, the elevation of the posterior steep meridian also tended to decrease its curvature within the emmetropes. The AL/CR ratio obtained different change among the refractive groups where the myopic group experienced an increase of 0.005 ± 0.019 whereas the emmetropic had an AL/CR reduction of -0.004 ± 0.015. Nonetheless, the AL/CR ratio changes did not result to be related to the SE changes and, therefore, this ratio was not considered useful to monitor or quantify myopia progression in young adults.

In Chapter 8, the evaluation of the aberrometry measurements was performed. Corneal and ocular wavefront measures yielded to the obtaining of Zernike polynomials for a 3 and 5 mm pupil size. Then, the internal wavefront was obtained subtracting the corneal coefficients from the ocular coefficients. So that Zernike coefficients from second to seventh-order were analysed for corneal, internal and ocular wavefront. Low order aberrations root mean square (LOA RMS) was computed considering second-order coefficients while the high order aberrations root mean square (HOA RMS) accounted for all the coefficients from third to seventh-order. The RMS was also calculated in each high order separately (3rd, 4th, 5th, 6th and 7th). Moreover, the calculation of the RMS for low order astigmatism (Z_2^{-2} and Z_2^2), high order astigmatism ($Z_4^{-2}, Z_4^2, Z_6^{-2}, Z_6^2$), spherical aberration (Z_4^0 and Z_6^0), coma-like aberration (Z_3^{-1}, Z_3^1, Z_5^{-1}, Z_5^1, Z_7^{-1}, Z_7^1), and trefoil-like aberration (Z_3^{-3}, Z_3^3, Z_5^{-3}, Z_5^3, Z_7^{-3}, Z_7^3) was carried out. In order to assess the contribution of the internal wavefront to the ocular, the compensation factor was calculated for the aberrometry data with 5 mm pupil size. The compensation factor is equal to 1 when there

is total compensation between corneal and internal optics whereas it takes the value 0 when there is no compensation at all. Values below 0 are obtained when the internal optics aggregated aberrations. Finally, values above 1 indicate that the internal optics have overcompensated the corneal wavefront, adding aberrations but in the opposite direction.

Low order astigmatism manifested significant differences associated with the refractive error. More negative corneal and ocular with-the rule/against-the rule (WTR/ATR) astigmatism Z_2^2 was associated with more myopic sphere. Internal WTR/ATR astigmatism Z_2^2 was significantly greater in myopes with 3 mm pupil size. Generally, low order astigmatism RMS tended to be higher in myopic eyes particularly significant for the ocular wavefront (3 and 5 mm). Compensation between corneal and internal low order astigmatism RMS ended up being more effective in emmetropes because the better compensation of WTR/ATR astigmatism Z_2^2, which is the most contributor to corneal astigmatism. Oblique astigmatism Z_2^{-2} was more compensated in myopic eyes because they tended to have a slightly more oblique component in corneal wavefront.

Some high order astigmatism coefficients also manifested differences even though high order ocular astigmatism RMS resulted similar among groups. Secondary oblique astigmatism Z_4^{-2} and Z_6^{-2} differed for both corneal and internal wavefront. Internal secondary WTR/ATR astigmatism Z_4^2 also tended to be greater in myopes with smaller pupil size (3 mm). Considering the total high order astigmatism RMS, compensation between corneal and internal wavefront was quite similar between emmetropia and myopia. On the other side, more negative spherical aberration Z_4^0 was significantly related to more myopic sphere or longer VCD for internal and ocular wavefront (5 mm) despite the non-significant differences between groups. The more negative internal spherical aberration Z_4^0 led to more proportion of partial compensation in myopic eyes for this coefficient. Thereby, ocular spherical aberration RMS revealed lower values in myopic eyes.

Other HOA differences were found for coma and trefoil aberrations, especially with larger pupil size (5 mm). Third-order coma coefficients (Z_3^{-1}, Z_3^1) were related to both sphere and VCD. Vertical coma Z_3^{-1} was significantly more positive in myopes for internal wavefront (3 and 5 mm) and there was also this tendency in corneal wavefront. Meanwhile, emmetropic subjects tended to exhibit negative values of both corneal and

internal vertical coma Z_3^{-1}, showing mostly an augmentation of this coefficient rather than compensation. Although myopic eyes had better proportion of undercompensdation, ocular vertical coma Z_3^{-1} still remained more positive in myopic eyes. Horizontal coma Z_3^1 revealed significantly less negative values for corneal wavefront while less positive values for internal wavefront (5 mm) in myopic subjects compared to emmetropes. Compensation between corneal and internal wavefront was similar among groups and ocular horizontal coma Z_3^1 did not differ. Secondary coma coefficients (Z_5^{-1}, Z_5^1) tended to be augmented by the internal optics in myopia, however, the wavefront differences (cornea, internal optics, ocular) between groups were not significant. Thus, coma-like RMS did not result to differ significantly, though myopes had slightly greater average values.

The multiple regression analysis manifested that the SE and VCD were predicted including all Zernike coefficients but no significant model resulted including only HOA. The most important predictors for SE were defocus Z_2^0, trefoil Z_3^{-3}, spherical aberration Z_4^0 and horizontal coma Z_3^1. Meantime, the defocus Z_2^0 as well as the spherical aberration Z_4^0 and Z_6^0 were the most important coefficients for the VCD model.

After the follow-up, there were was a general increment of ocular defocus Z_2^0 being a bit greater in myopic eyes. Thus, the defocus Z_2^0 increase was related to the VCD elongation over time. While ocular WTR/ATR astigmatism Z_2^2 was stable in the emmetropic group, it increased negatively in myopes because of the internal optics. Indeed, internal WTR/ATR astigmatism Z_2^2 was associated with the negative change of the refractive sphere. Oblique astigmatism Z_2^{-2} manifested opposed changes between groups, however, it was not associated with any refractive or biometric change. Regarding the HOA, the longitudinal data demonstrated that third-order trefoil, third-order coma and primary spherical aberration were the main coefficients that have some differences between the emmetropic and myopic group. However, the changes observed after one year were not different enough to obtain statistically differences between refractive groups in most of the cases.

Despite some differences in corneal and internal wavefront, ocular trefoil Z_3^{-3} and vertical coma Z_3^{-1} changed similarly in both refractive groups. Meantime, the myopic group tended to increase positively horizontal coma Z_3^1 and reduce the positive values of trefoil Z_3^3. The changes of some third-order coefficients also showed an association with the

myopic shift or/and the VCD enlargement. Besides, myopic eyes underwent a slight reduction of ocular spherical aberration Z_4^0 as a result of the greater negative increase of the internal one. Nonetheless, the changes in spherical aberration were not associated with the refractive nor biometric changes. Broadly, the aberration changes experienced in our young sample were not strongly associated with the myopic shift or VCD elongation. Therefore, these changes may not be the trigger of myopic progression but rather a consequence of it.

From the results obtained in the present study, several conclusions can be extracted. Myopic eyes exhibited differences in some of the quantitative descriptors evaluated at baseline. For ocular biometry, the myopic group had deeper ACD, longer VCD and tended to have slightly thinner LT. Further, deeper ACD and thinner LT associated with longer VCD, however, this linear relationship was not maintained when the VCD elongation exceeded 20 mm. Corneal curvature, elevation and astigmatism were greater in myopes. Both corneal curvature and elevation showed to flatten until the VCD reached 19-19.5 mm, point from which the cornea could no longer compensate the eye enlargement and it even steepened. Therefore, higher AL/CR was seen in myopes than in emmetropes, where myopes were mostly above 3.00 in this ratio. Emmetropes obtained better compensation of the WTR/ATR astigmatism Z_2^2 so that myopic manifested more negative values in the ocular wavefront. In contrast, there was more proportion of partial compensation in myopic eyes for spherical aberration Z_4^0, resulting in lower ocular spherical aberration RMS. Besides, ocular vertical coma Z_3^{-1} was more positive in myopic eyes and was related to more myopic sphere and longer VCD.

After the follow-up, the refractive error experienced a negative shift in some part of the initial myopic students, though small, demonstrating that myopia may keep progressing during this academic stage. Myopic students showed higher VCD elongation agreeing with their greater negative SE shift compared to the emmetropes. The larger decrease of the flat meridian curvature in the emmetropic group, which was not related to the SE change, may indicate that axial elongation still may be compensated by corneal flattening in young emmetropic adults. AL/CR ratio did not manifest a relationship with the SE shift and was not considered useful to monitor or quantify myopia progression in young adults. As expected, ocular defocus Z_2^0 had a greater increase in the myopic group and was related to the VCD elongation. WTR/ATR astigmatism Z_2^2 also increased

negatively in myopes whereas it remained stable in emmetropes. Moreover, myopic eyes tended to increase positively the ocular horizontal coma Z_3^1 and reduce the positive values of ocular trefoil Z_3^3. Ocular spherical aberration Z_4^0 underwent a slight reduction in the myopic group but this was not related with the refractive nor biometric changes.

ACRONYMS

°	Degrees
µm	Microns
ACD	Anterior Chamber Depth
AL	Axial Length
AL/CR	Axial Length to Corneal Radius ratio
ANOVA	Analysis of Variance
AQD	Anterior Aqueous Depth
ASL	Anterior Segment Lenght
AS-OCT	Anterior Segment Optical Coherence Tomography
ATR	Against-The-Rule
BFS	Best-Fit-Sphere
CCT	Central Corneal Thickness
CF	Compensation Factor
CI	Confidence Interval
CoR	Coefficient of Repeatability
CoV	Coefficient of Variation
CR	Corneal Radius
CT	Corneal Thickness
D	Diopters
FAF	Fundus Auto Fluorescence
HOA	High order aberrations
ICC	Intraclass Correlation Coefficient
IMI	International Myopia Institute
K	Keratometry
LCD	Liquid-Crystal Display
LE	Left Eye
LED	Light-Emitting Diode
LoA	Limits of Agreement
LOA	Low Order Aberrations
logMAR	Logarithm of the Minimum Angle of Resolution

LT	Lens Thickness
MANOVA	Multivariate Analysis of Variance
mm	Millimetres
OCT	Optical Coherence Tomography
Q	Asphericity
R^2	Coefficient of determination
RE	Right Eye
RMS	Root Mean Square
SD	Standard Deviation
SE	Spherical equivalent
SF	Shape Factor
SS-OCT	Swept-Source Optical Coherence Tomography
S_w	Within-subject Standard Deviation
Sβ	Standardised regression coefficient
VCD	Vitreous Chamber Depth
VIF	Variance Inflation Factor
WTR	With-The-Rule
WTW	White-To-White
β	Non-standardised coefficient

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CHAPTER 1. INTRODUCTION

1.1 Myopia definition

Myopia is one of the most common refractive disorders, which occurs when there is no harmony between ocular power and eye length growth. The term emmetropization refers to the mechanism that regulates this compensation of the ocular elements during eye growth (Mutti et al., 2005). During this process, eyes usually become myopic when the power of the cornea and crystalline lens cannot compensate the eye elongation. The enlargement is mainly produced in the posterior ocular segment, which is the vitreous chamber depth (VCD) (Jones et al., 2005; Wong et al., 2010). Because of this decompensation, the image of distant objects results to be out of focus. Distance objects are focused anteriorly to the retinal plane (Figure 1.1 A), resulting in a blurry perception of the visual images. Corrective lenses of negative power can provide clear images focused on the fovea through the divergence of the incident light rays (Figure 1.1 B).

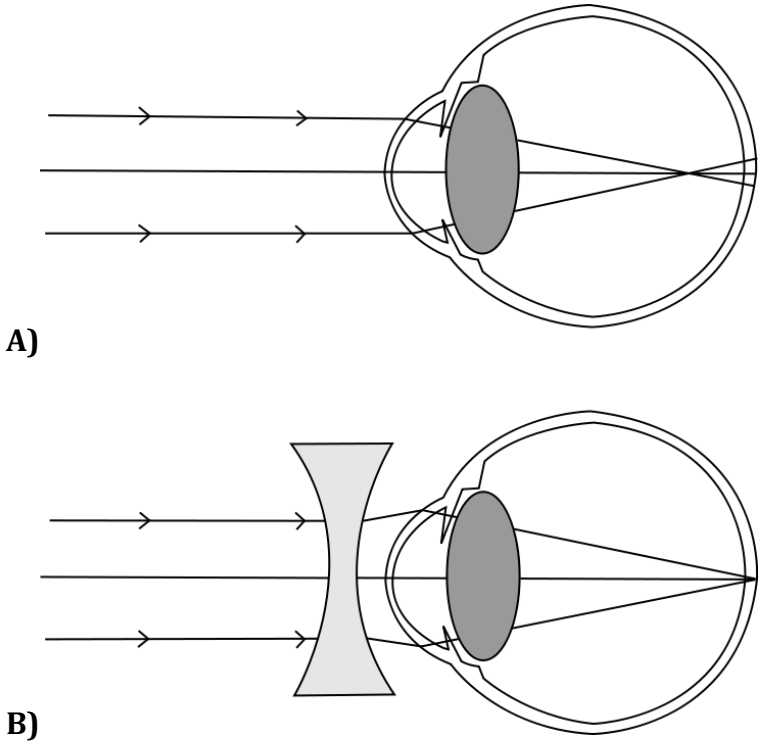

Figure 1.1. A) Schematic myopic eye and B) myopic eye corrected with a negative lens.

1.2 Myopia classification

Through the years, myopia has been defined and classified in a wide variety of ways: rate of progression, anatomical features, refractive components relation, pathology

associated, refractive degree and age of onset. Donders (1864) divided myopia on the basis of the progression rate into three groups. *Stationary myopia* refers to the low myopic degrees (up to -2.00 D) without progression. When myopia has progression, it was considered as *temporarily progressive myopia,* and *permanently progressive myopia* when this progression leads to reach myopia above -6.00 D. In accordance with the anatomical structure originating this refractive error, Emsley (1955) defined axial and refractive myopia. *Axial myopia* is attributed to the axial elongation while refractive myopia to the excessive power of the cornea and/or crystalline lens. Further, *refractive myopia* was categorized depending on whether the increased power is caused by the refractive index, curvature or decreased ACD. Sorsby (1957) described myopia in terms of the relation between refractive components. The refractions up to -4.00 in which the refraction components were quite coordinated and on the other hand, the refractions above -4.00 D produced by an AL beyond the normal range.

Duke-Elder (1948) and Curtin (1985) differentiated simple myopia from pathological myopia. *Pathological myopia* considered the degenerative changes that occur in the posterior segment with myopia. Myopia degree, as well as the age of onset, was considered by Goldschmidt (1968) to introduce the categories of low myopia, late myopia and high myopia. *Low myopia* describes the most frequent type that progresses slowly whereas *high myopia* reaches high degrees with degenerative changes associated with an early onset. *Late-onset myopia* was the one developed after growth development. Then, Grosvenor (1987) proposed a classification into 4 groups based on the age of onset: *congenital myopia, youth-onset myopia, early adult-onset myopia and late adult-onset myopia*. Nowadays, myopia classification is still based on some of the above criteria. The most common classification in research is the one based on the myopia degree although the classification by structural features, age of onset and pathology associated are usually applied as well.

1.2.1 Structural features

Myopia can be qualitatively divided between refractive and axial myopia. Refractive myopia applies to the cases in which the power of the cornea and/or crystalline lens is higher than the needed for the AL. Conversely, axial myopia happens in eyes with a longer AL than the expected according to the ocular power (Meng et al., 2011). As optical refraction is the result of the link between ocular power and length, both elements are of

relevance in numerous eyes and their monitorization is advised to assess myopia progression (Flitcroft et al., 2019).

1.2.2 Degree

Quantification and objectivity are generally the advantages of this classification, although thresholds used to define myopia and high myopia among scientific studies are quite varied. In epidemiological studies, myopia has been mostly described using the SE cut-off value of -0.50 D (Holden et al., 2016). However, values of -0.75 D (Kleinstein, Jones and Hullett, 2003; Onal et al., 2007) or -1.00 D (Lithander, 1999; Kempen et al., 2004; Younan et al., 2002) have also been used. High myopia has been defined with the SE refraction as greater than -5.00 D (Saw et al., 2008; Pan et al., 2011) or -6.00 D (Younan et al., 2002) as well as on the basis of an AL higher than 26 mm (Flores-Moreno et al., 2013). Other studies (Baird, Schäche and Dirani, 2010; Bueno-Gimeno et al., 2014) have further categorized myopia into low myopia up to -3.00 D, moderate myopia from -3.00 to -6.00 D and high myopia with values above -6.00 D. Meantime, Vitale, Sperduto and Ferris (2009) considered moderate myopia within the range from -2.00 D to -7.90 D and -7.90 D or more as severe myopia.

In 2015, the World Health Organization report introduced refractive thresholds for the terms low myopia (≤ -0.50 D) and high myopia (≤ -5.00 D) and does not recommend the use of AL to divide by myopia degree (World Health Organization and Brien Holden Institute, 2015). Recently, one of the reports of the IMI has proposed modifications for the definitions and thresholds of myopia (Flitcroft et al., 2019). Their standardisation is required so as to unify them between studies and, therefore, to achieve evidence-based and consistent approaches for myopia management. First of all, the IMI report (Flitcroft et al., 2019) recommends to treat myopia as a negative value and to use the comparison mathematical symbols to express the quantitative classification, which has also been adopted in throughout this document. Then, the standardised classification suggested to describe de myopia degree is the following:

- Low myopia: the SE refractive error of an eye is ≤ -0.50 D and > -6.00 D when ocular accommodation is relaxed.
- High myopia: the SE refractive error of an eye is ≤ -6.00 D when ocular accommodation is relaxed.

The choice of both thresholds for low and high myopia is based on its majority use in researches up to now, albeit thresholds should be adapted to the research purpose. Thus, more negative thresholds for low myopia may be considered when non-cycloplegic techniques are used and especially in younger subjects, such as -0.75 D.

1.2.3 Age of onset

The classification introduced by Grosvenor (1987) is still in use at the present time and consists of the following groups:

- Congenital myopia: myopia that remains throughout the infancy and early school ages. This myopia tends to persist through life.
- Youth-onset myopia: myopia that appears between the school-age of 6 years and the adolescence.
- Early adult-onset myopia: myopia that occurs between 20 and 40 years.
- Late adult-onset: myopia that emerges after 40 years and is usually due to the incipient nuclear cataracts.

Other authors have assumed a classification into two main groups: early-onset myopia or school myopia and late-onset myopia, where late-onset myopia is considered after 15 years of age (McBrien and Millodot, 1987; Bullimore, Gilmartin and Royston, 1992). The value of the classification by age on onset has been questioned since it is not known for sure if the biological process subjacent myopia in childhood is different from the one in young adults (Flitcroft et al., 2019). Besides, the age of onset has been proved to be different between ethnic groups (Rudnicka et al., 2016).

1.2.4 Pathology associated

High myopia and greater AL are related with complications in the posterior ocular segment (Morgan, Ohno-Matsui and Saw, 2012). During myopia progression, the excessive elongation of the eye leads to thinning of the retina, choroid and sclera because of chorioretinal stretching. The complications resulted from this process usually are posterior staphyloma, chorioretinal atrophy, maculopathy, choroidal neovascularization, vitreomacular traction and retinal detachment (Cho, Shin and Yu, 2016).

Pathological myopia has been classified through cut-off values based on the refractive error, -5.00, -6.00. -8.00 or -10.00 D (Saw et al., 2005a) as well as AL above 25.5

or 26.5 mm (Silva, 2012). But not all eyes with high myopia end up developing pathological myopia (Morgan, Ohno-Matsui and Saw, 2012). In fact, several studies have demonstrated that some pathological signs also extend to myopia > -5.00 D (Vongphanit, Mitchell and Wang, 2002; Liu et al., 2010; Gao et al., 2011) and AL < 26.5 mm (Wang et al., 2016a), although with less prevalence. Besides, structural complications of pathological myopia have shown an age dependency (Lai et al., 2006; Hayashi et al., 2010; Liu et al., 2010; Gao et al., 2011).

The standardised definition for pathologic myopia proposed by the IMI report (Flitcroft et al., 2019) is as follows: "excessive axial elongation associated with myopia that leads to structural changes in the posterior segment of the eye (including posterior staphyloma, myopic maculopathy, and high myopia-associated optic neuropathy) and that can lead to loss of best-corrected visual acuity". Lately, the Meta-Analysis for Pathologic Myopia Study Group (Ohno-Matsui et al., 2015) has developed a photographic classification for myopic maculopathy. This classification allows grading the myopic maculopathy from the fundus signs observed.

1.3 Myopia prevalence

Myopia has reached epidemic levels in the developed countries of East and Southeast Asia. In these regions, the prevalence has been increasing over time and especially at younger ages. Increased incidence has been reported in populations from 6 years of age (Fan et al., 2011; Ma et al., 2016) and the prevalence has reached values between 80-90% in teenagers (Lin et al., 2004; Quek et al., 2004). Alike, Europe has undergone an increment of myopia prevalence through the years (Williams et al., 2015a). Prevalence increases in European children from 7-8 years of age (Czepita, Żejmo and Mojsa, 2006) and the reported prevalence ranges from 17 to 36% in teenagers with European ancestry (Villarreal et al., 2000; Vitale et al., 2009; Pärssinen, 2011; McCullough, O'Donoghue and Saunders, 2016).

Generally, myopia prevalence in children and teenagers with European line of ascent is much lower than the one in East and Southeast Asia (Morgan et al., 2018; French et al., 2013a). Regions with greater expansion of urbanization and higher education have shown an earlier increase in both Europe (Pärssinen, 2011; Williams et al., 2015a; Morgan and Rose, 2013) and Asia (Wong et al., 2002; Morgan and Rose, 2013).

Thus, myopia prevalence is only between 5-10% for young adults in the less developed regions because of the lower educational evolution (Morgan et al., 2018).

Furthermore, high myopia has also increased as a result of the increased myopia prevalence in younger people as well as the rates of progression (Lin et al., 2004; McCullough, O'Donoghue and Saunders, 2016). Asians also seem to have higher rates of myopia progression than Europeans (Donovan et al., 2012). In Spain, Alvarez-Peregrina et al. (2019) have recently reported an increment of high myopia from 1.7% to 3.6% in children between 5 and 7 years during one year. Previous studies (Iribarren, Cortinez and Chiappe, 2009; Chua et al., 2016) have demonstrated that the later age of onset is, the lower risk to progress to high myopia since an earlier age allows myopia more time to progress.

1.4 Impact of myopia

The prevalence of myopia is globally growing and nearly half of the world's population may be myopic by 2050 and around 10% highly myopic (Holden et al., 2016). Myopia has become a public health issue since it is currently one of the causes of significant visual loss (Bourne et al., 2013). This is due to its associated complications, which turn it in pathological myopia. Myopic maculopathy has been reported to be the main blindness cause in Japan (Iwase et al., 2006) and China (Wu et al., 2011a; Tang et al., 2015). Fricke et al. (2012) have estimated the myopic maculopathy prevalence at 0.57% of the global population by 2050 if actions are no taken to manage the development and progression of myopia. Myopia has also shown as a risk of suffering some ocular conditions such as retinal detachment (Flitcroft, 2012; Chen, Lian and Wei, 2015), glaucoma (Marcus et al., 2011; Hsu, Chen and Lin, 2015) and cataracts (Leske et al., 2002; Mukesh et al., 2006; Wong et al., 2003). Uncorrected myopia can also affect the quality of life through the alteration of visual function produced (Lamoureux et al., 2009; Kandel et al., 2017). Furthermore, myopia has an economic impact, taking into account the cost of correction methods as well as myopia management and its complications in the health care systems (Fricke et al., 2012; Zheng et al., 2013).

1.5 Aetiology of myopia

1.5.1 Refractive development

1.5.1.1 Emmetropization

Refractive error changes from birth to adulthood, however, the major changes occur during childhood when the eye develops. The emmetropization mechanism is responsible for the compensation between the changes of the ocular components during eye development to guide the refractive error towards emmetropia (Wallman and Winawer, 2004). This mechanism is evidenced in the leptokurtic distribution of the refractive error in adults where there is a higher frequency of emmetropic subjects or near emmetropia (Brown, Koretz and Bron, 1999; Ojaimi et al., 2005). While on the contrary, the ocular components such as corneal and crystalline lens power, ACD or AL follow a normal distribution (Brown, Koretz and Bron, 1999; Ojaimi et al., 2005). The ametropia presence in adulthood is considered the result of the failure of emmetropization or emmetropia maintenance.

Newborns usually are not emmetropic and manifest variable hyperopic refractive error which has a normal distribution (Figure 1.2 A) (Wood, Hodi and Morgan, 1995; Mayer et al., 2001). During the first year of life, the refractive error and its variable distribution decrease as a result of rapid eye growth (Pennie et al., 2001; Mayer et al., 2001; Mutti et al., 2005). The refractive error evolves thus to a leptokurtic distribution with a positive skew (Figure 1.2 B) because of a high proportion of hyperopes (Ojaimi et al., 2005).

After the early rapid phase, the emmetropization still goes on but with a slower rate in order to maintain emmetropia (Jones et al., 2005). The leptokurtic refractive distribution changes from a positive to a negative skew in most of the populations as a result of an increase in myopia prevalence (Flitcroft, 2014). The increase of myopia prevalence is manifested from 7-8 years, especially in Asians (Edwards, 1999; Lin et al., 2004; Kleinstein, 2012). This late slow phase is characterised by the continuation of the AL elongation as well as the power reduction of the crystalline lens and its thinning (Mutti et al., 1998; Zadnik et al., 2003; Ip et al., 2007a; Iribarren et al., 2012). Conversely, corneal power has demonstrated to be relatively stable in the later phase (Zadnik et al., 2003;

Mutti et al., 2005; Ip et al., 2007a). The study of Ip et al. (2007a) demonstrated that AL still is the most contributor in determining the refraction at ages between 6 and 12 years in both East Asians and European Caucasians.

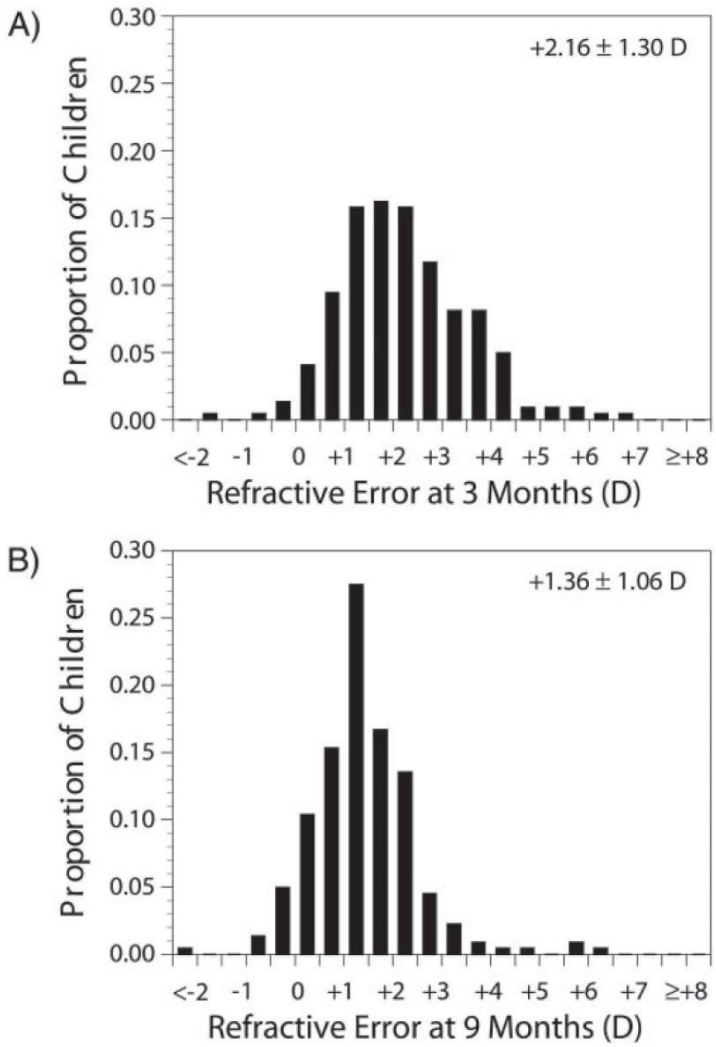

Figure 1.2. Refractive distribution of children at (A) 3 months and (B) 9 months of age. Taken from Mutti et al. (2005).

1.5.1.2 Myopia development

The growth of the ocular components has proved to be different between those who develop myopia and those who do not (Jones et al., 2005; Wong et al., 2010). Meanwhile, the growth pattern for emmetropizing hyperopes and persistent hyperopes has evidenced many similarities with that of emmetropes (Jones et al., 2005; Wong et al., 2010). Thereby, hyperopia does appear to be due to the initial eye size in the

early development stage rather than a difference in the eye growth rate during infancy (Jones et al., 2005).

Developing myopes mainly have shown an increased rate of growth of VCD and AL (Jones et al., 2005; Garner et al., 2006; Wong et al., 2010). Myopes seem not to slow the eye growth with age as emmetropes do in the late growth phase. The crystalline lens power loss rates also increase in order to compensate for the AL growth albeit there comes some point when the lens can no longer maintain this compensation (Garner et al., 2006; Mutti et al., 2012; Iribarren et al., 2012; Rozema et al., 2019). Besides, the rate of lens thinning increases when myopia develops (Garner et al., 2006; Mutti et al., 2012; Rozema et al., 2019). And despite the greater corneal power in myopia, its change rate has not exhibited significant differences compared with those non-myopic (Jones et al., 2005; Garner et al., 2006; Wong et al., 2010). Figure 1.3 depicts the growth curves by Jones et al. (2005).

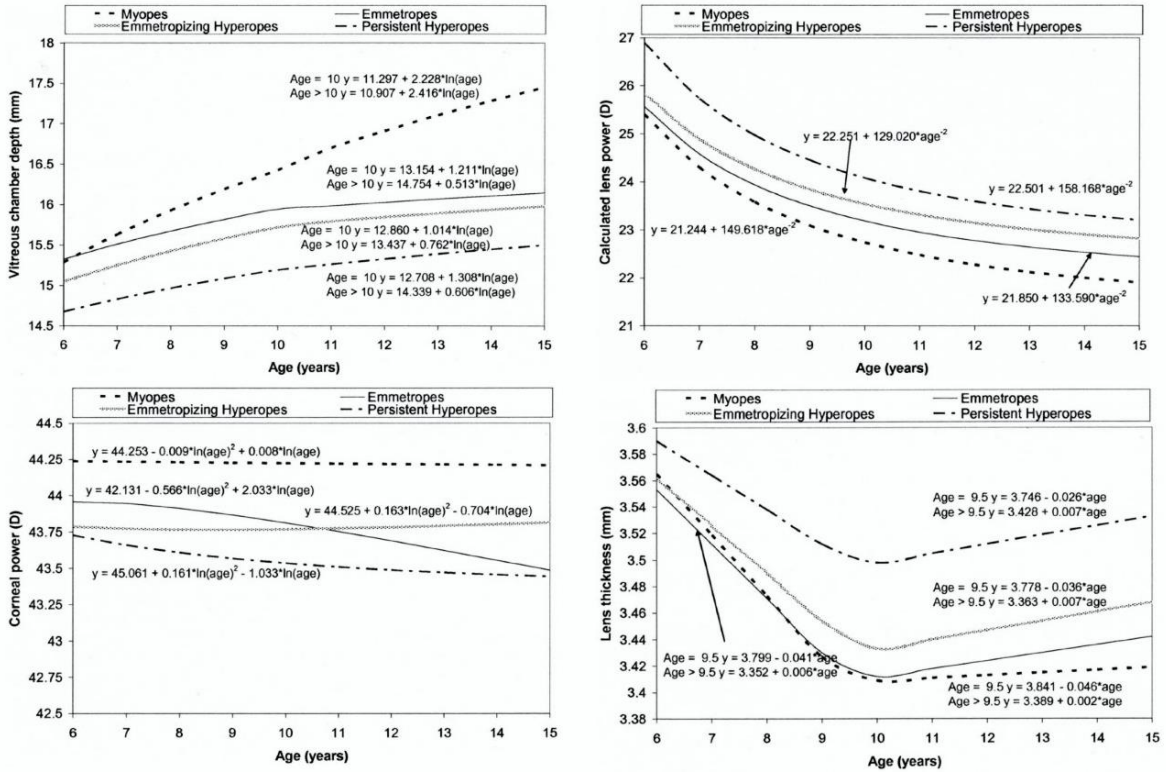

Figure 1.3. Growth curves for VCD, lens power, corneal power and LT for different refractive groups. Adapted from Jones et al. (2005).

Changes in refractive error and AL become greater compared to emmetropic children between 2 to 4 years before myopia onset (Mutti et al., 2007; Xiang, He and Morgan, 2012). Thus, children developing myopia manifest less hyperopia up to 4 years before myopia onset in contrast to those who remain emmetropic (Mutti et al., 2007; Xiang, He and Morgan, 2012). The change rate of both refractive error and AL slows the year after the myopia onset even though it is still higher than in emmetropia (Mutti et al., 2007; Xiang, He and Morgan, 2012; Rozema et al., 2019). Crystalline lens power loss and thinning slow down around one year before the myopia onset whereas the rate remains stable for emmetropic children (Mutti et al., 2012; Iribarren et al., 2012; Rozema et al., 2019). Given that corneal power experiences little changes during the late growth phase, refractive development is the result of both crystalline lens and AL changes. Therefore, the interruption of the balance between axial elongation and power lens loss may lead to myopia development (Mutti et al., 2012; Rozema et al., 2019). Figure 1.4 depicts these changes according to the age of onset.

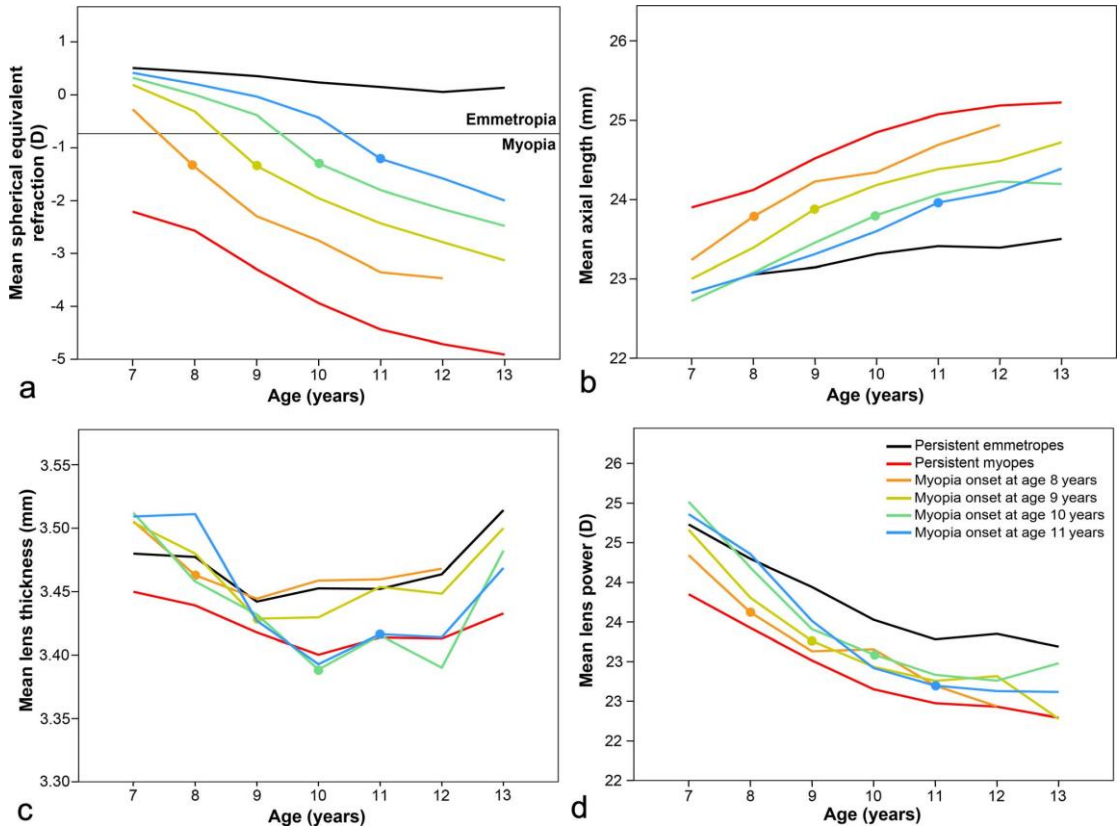

Figure 1.4. Changes in SE, AL, LT and lens power according to the age for different myopia age onset. Taken from Rozema et al. (2019).

1.5.2 Risk factors

Myopia is complex in aetiology as both genetic and environmental factors are involved in its development and progression as well as the gene-environment interaction may have an important role.

1.5.2.1 Genetic factors

The genetic contribution has been evidenced by familiar and genome-wide association studies. Previous studies have already shown children who have myopic parents are highly likely to become myopic compared with those who do not (Saw et al., 2001a; Mutti et al., 2002; Saw et al., 2006; Ip et al., 2007b). Ip et al. (2007b) reported that myopia prevalence increases in children with the number of myopic parents from 14.9% for one myopic parent to 43.6% for two myopic parents. Similarly, Jones et al., (2007) informed that two myopic parents raised the risk of having myopia 5.07 times and one parent raised it 2.08 times. Nonetheless, the relation of refractive error between children and parents may be partially due to families share the environment in addition to genes. Studies in monozygotic twins have provided a better understanding of the myopia heritability as they have the same genes and shared a similar environment. The findings of these studies have exhibited that monozygotic twins have more similar refractive error and ocular components than dizygotic (Lyhne et al., 2001; Dirani et al., 2006; Klein et al., 2009; Zhu et al., 2008).

Recently, one genome-wide association meta-analysis has established 161 independent loci for refractive error (Tedja et al., 2018). Genome-wide association studies have pointed out the myopia polygenicity even though the current findings only account for up to 10% of the refractive error (Kiefer et al., 2013; Verhoeven et al., 2013a; Tedja et al., 2018). Additionally, there is evidence of the environmental influence in the phenotypic variation. The gene-environment interaction for refractive error has been assessed to look if the response of the different genotypes might be different in the same environment. That is to say, whether some genotypes are more susceptible to changes than others in the same environment. Studies in adults have evidenced the educational level influences the genetic risk of myopia developing (Wojciechowski et al., 2013; Verhoeven et al., 2013b; Fan et al., 2016).

There are numerous syndromes in which high myopia is related to, such as Marfan, Knobloch or congenital stationary night blindness, although these myopia forms are only present in a few per cent of the population. These syndromes are linked to genetic mutations affecting the connective tissue (Biggin et al., 2003; Menzel et al., 2004; Pusch et al., 2000). Alike, non-syndromic high myopia has been associated with some chromosomal locations and candidate genes (Naiglin et al., 2002; Paluru et al., 2003; Lam et al., 2003). However, these findings cannot explain all cases in either inherited syndromic and non-syndromic high myopia.

1.5.2.2 Environmental factors

The rise of myopia prevalence particularly in some regions does not seem to be due to only the genetic heritage, being that genes cannot change in such a rapid way. Actually, populations with the same ethnic background have exhibited different myopia prevalence depending on the environment they live in (Ip et al., 2008a; Uzma et al., 2009; Zhang et al., 2010).

1.5.2.2.1 Education and near work

The educational level has a strong correlation with myopia prevalence, which agrees with the fact that myopia progresses during the school years. Higher education level has been associated with higher myopia prevalence throughout different populations (Shimizu et al., 2003; Mirshahi et al., 2014; Williams et al., 2015a). Besides, both years and intensity of study should be taken into account to evaluate the effect of the education on myopia. Indeed, higher school performance (Mutti et al., 2002; Saw et al., 2007) and intelligence quotient (Saw et al., 2004; Saw et al., 2006) have shown to be related with myopia. Aligned with that, attending extra tuition classes increase the risk of myopia incidence in children (Saw et al., 2001b; Morgan and Rose, 2013; Ku et al., 2019). Thereby, the study styles, which involves near work activities, might have an influence on myopia development (Bez et al., 2019).

Near work might be considered as involved in such a correlation between education and myopia. Several studies have acquired an association of near work with both myopia development and progression in children (Saw et al., 2002; French et al., 2013b; Guo et al., 2016; Lin et al., 2016; Hsu et al., 2017; Ip et al., 2008b). This association was stronger in younger children in two studies and, therefore, with

earlier onset (Saw et al., 2002; French et al., 2013b). Guo et al. (2016) found that both shorter distance and longer time spent for near work increase the risk of myopia in children. A 22-year follow-up (Pärssinen and Kauppinen, 2018) in schoolchildren obtained an association of adulthood high myopia with more time spent on reading and close work. Contrary, other authors have reported no correlation between near work and myopia incidence (Saw et al., 2006; Jones et al., 2007; Guggenheim et al., 2012) nor its progression (Saw et al., 2000; Jones-Jordan et al., 2012). Meanwhile, Jones-Jordan et al. (2011) did not find evidence of the relationship of the near work in the myopia development since the visual activity became different once the myopia onset. A recent meta-analysis stated that each dioptre-hour of near work per week lead to a 2% increased odds of having myopia (Huang, Chang and Wu, 2015).

Other authors have found a relationship between reading and myopia rather than with near work per se (Saw et al., 2002; Williams et al., 2008; Ip et al., 2008b; Li et al., 2015a). Besides, the Sydney myopia study (Ip et al., 2008b) reported the continuous reading (>30 min) and closer reading distance (<30 cm) to increase the odds of having myopia 1.5 and 2.5, respectively. This showed up the relevance of the near work intensity as a risk factor. Faster myopic progression has been linked with shorter reading distance (<25 cm) (Hsu et al., 2017) and more time of near work (Lin et al., 2016) in children. Scheiman et al. (2013) suggested a relationship between the near work activity and the myopia stabilisation. Concretely, each additional hour of near work per week would decrease the odds of myopia stabilisation by 2% at 15 years old.

Traditionally, the greater accommodation in use has been thought to be the link between near work and myopia. Myopic children have exhibited significantly less accommodative response than emmetropic (Gwiazda et al., 1993; Gwiazda, Thorn and Held, 2005). Other authors reported higher variability of the accommodative response in myopes. (Harb, Thorn and Troilo, 2006; Langaas et al., 2008). Nevertheless, animal studies have elucidated that even when accommodation is inactive, the eye growth remains working (Schaeffel et al., 1990; Wildsoet, 2003; Choh et al., 2006). Likewise, the findings of animal models have arisen the hypothesis that the hyperopic defocus produced as a result of accommodative lag may influence on myopia development (Hung, Crawford and Smith, 1995; Troilo, Quinn and Baker, 2007). Greater accommodative lag in myopic children has been found in some studies (Gwiazda et al., 1993; Rosenfield, Desai

and Portello, 2002; Nakatsuka et al., 2003). Mutti et al. (2006) reported that increased lag of accommodation is observed the year after myopia onset. However, longitudinal studies reported no correlation between accommodative lag and myopia progression (Weizhong et al., 2008; Berntsen et al., 2011; Koomson et al., 2016).

1.5.2.2.2 Time outdoors and light exposure

At first, some studies associated less time in sports activity as a risk factor for myopia (Mutti et al., 2002, Jones et al., 2007). Further studies obtained lower myopia was associated with higher time spent outdoors rather than the time of sports practice (Rose et al., 2008a; Ip et al., 2008b; Wu et al., 2010; Guggenheim et al., 2012; Jones-Jordan et al., 2012; French et al., 2013b; Wu et al., 2013). This fact suggests a greater time spent outdoors might protect from myopia development. Instead, a few authors informed of no influence by outdoor activity on myopia development (Saw et al., 2006; Lu et al., 2009; Low et al., 2010).

The Avon Longitudinal Study of Parents and Children (Shah et al., 2017) reported the additional time spent outdoors in children between 3 and 9 years reduced the myopia incidence at the age of 10 and 15 years. Besides, the longitudinal study of Pärssinen and Kauppinen (2018) obtained a lower time of outdoor activities was associated with adulthood high myopia. The Guangzhou Outdoor Activity Longitudinal Trial (He et al., 2015a), which was a randomized clinical trial performed in children aged 6-7 years, obtained a reduction of myopia incidence from 39.5% to 30.4% when a 40 min daily class of outdoor activity was added during 3 years. Similarly, the ROCT711 program trial in Taiwan (Wu et al., 2018), another randomized clinical trial, found a 17% decrease of myopia incidence in children, aged 6-7 years, who spent outdoor time up to 11 hours per week during 1 year.

Regarding myopia progression, former studies indicated no relationship of outdoors activity with myopia progression (Jones-Jordan et al., 2012; Oner et al., 2016) nor myopia stabilization (Scheiman et al., 2013). The Anyang Childhood Eye Study (Li et al., 2015b) disclosed a slower elongation rate was related to outdoor activity only in those children who were non-myopic at the study baseline. To all appearances, outdoor activity has shown to be a key factor in reducing the myopia incidence but not in slowing its progression. Indeed, a meta-analysis (Xiong et al., 2017) has recently reported the

effect of protection on both myopia incidence and prevalence but not on myopia progression. However, a 23-year follow-up study (Pärssinen, Kauppinen and Viljanen, 2014a) found slower myopic progression rate among myopic who spent more than 3 hours a day on outdoor activities. In the North India Myopia Study (Saxena et al., 2017) it has also been obtained that an outdoor activity higher than 2 hours might be protective for myopia progression. Conformed with this, the randomized trial of Wu et al. (2018) obtained a reduction of myopia progression of 30% in 1 year by doing outdoors activity of up to 11 hours per week. For now, further studies are needed to support the possible inhibition of myopia progression due to outdoor activity.

Several theories have emerged to explain the biological mechanism underlying the protective effect of outdoor activity, among which are the increase of light exposure, dopamine release, vitamin D or the increased depth of field (French et al., 2013c). According to the light intensity hypothesis referred by Rose et al. (2008a), slower axial elongation associated with greater daily light exposure in the study of Read, Collins and Vincent (2015). This last study reported that brighter light intensities above 3000 lux are required for greater influence on eye growth slowdown. In the same line, the ROCT711 program trial (Wu et al., 2018) stated that the protection against myopia could be achieved with short periods of high light intensity or otherwise long periods of moderate light intensity. The light-dopamine theory proposes that higher light intensity mediate the release of the dopamine retinal transmitter (French et al., 2013c), which have demonstrated a role in the axial growth regulation (Feldkaemper and Schaeffel, 2013). Alike, vitamin D theory supports the ultraviolet light stimulates the vitamin D production, which has a relationship in axial growth and myopic pathogenesis (Mutti and Marks, 2011; Tideman et al., 2016). Finally, the increased depth of focus theory is also related to light since the depth of focus is known to increase with the pupil constriction and, therefore, it would lead to a decrease in the retinal image blur. (French et al., 2013c).

1.5.2.2.3 Urban environment

The residence in an urban or rural environment is also considered as a risk factor. Epidemiology studies have shown that between populations with similar genetic ancestry the lower prevalence is found in those who have grown up in rural environments (Saw et al., 2001c; Dandona et al., 2002; He et al., 2007; Uzma et al., 2009; Gao et al., 2012).

Significant differences in myopia progression have also been obtained in some studies (He, Zheng and Xiang, 2009; Shih et al., 2010).

These differences may be attributable to educational and socioeconomic levels, which tend to be higher in the urban environment and also involve the near work and time outdoors at the same time. However, the population density has exhibited an association with greater myopia prevalence regardless of the time outdoors and the near work in Australian and Chinese children (Ip et al., 2008a; Zhang et al., 2010). Higher population density was related to longer AL and more negative refractive error in two studies in children (Guo et al., 2013; Choi et al., 2017). Recently, Read et al. (2018) acquired different outdoor light exposure between children from two urban locations in Australia and Singapore, respectively. Likewise, children of Chinese ethnicity grown up in Singapore have demonstrated to have differences in the outdoor time activity compared to those in Sydney (Rose et al., 2008b). More studies are required to establish the mechanism that lies behind these associations.

1.5.3 Animal models

The research in animals has helped to better knowledge about the emmetropization process and the development of refractive errors together with the ocular changes which go along with them. Despite the differences across the range of species, findings from animal studies have consistently demonstrated the eye growth is guided by visual feedback (Schaeffel and Feldkaemper, 2015). Besides, this has also allowed breakthroughs on the optical interventions for myopia management.

1.5.3.1 Form-deprivation myopia

Form-deprivation myopia refers to the experiments that the retinal image is degraded. Traditionally, eyelids suture or corneal opacification were the ways to achieve the vision deprivation (Sherman, Norton and Casagrande, 1977; Wiesel and Raviola, 1979). Later studies started to impose on the eye translucent diffusers (Smith III and Hung, 1999; Howlett and McFadden, 2006; Ashby, Ohlendorf and Schaeffel, 2009; Tkatchenko, Shen and Tkatchenko, 2010). These studies have extensively demonstrated that depriving retina to form vision promotes axial myopia. This myopia is considered as an open-loop condition because the eye growth is not well regulated due to the visual feedback absence (Schaeffel and Howland, 1991). That is to say, the absence of visual

stimulation makes impossible the eye to detect if the refractive error is emmetropia, hyperopia or myopia, which leads the eye to elongate in an unregulated way (Chakraborty et al., 2019).

Form-deprivation myopia occurs due to vitreous chamber elongation along with choroid and sclera thinning (Figure 1.5) (Howlett and McFadden, 2006; Wallman et al., 1995; Wildsoet and Wallman, 1995). Moreover, the more contrast reduction of the retinal image, the more grade of axial elongation (Smith and Hung, 2000; Bowrey et al., 2015). This eye response has shown a decrease with age in several animal species, though (Wallman et al., 1995; Troilo, Nickla and Wildsoet, 2000). Generally, a reduction of the induced myopia occurs when the translucent diffusers are removed by means of the deceleration of eye growth (Wallman et al., 1995; Wildsoet and Wallman, 1995; Howlett and McFadden, 2006). However, the recovery depends on the magnitude as well as the age at the end of the experiment since the eye ability to response decreases with age (Qiao-Grider et al., 2004).

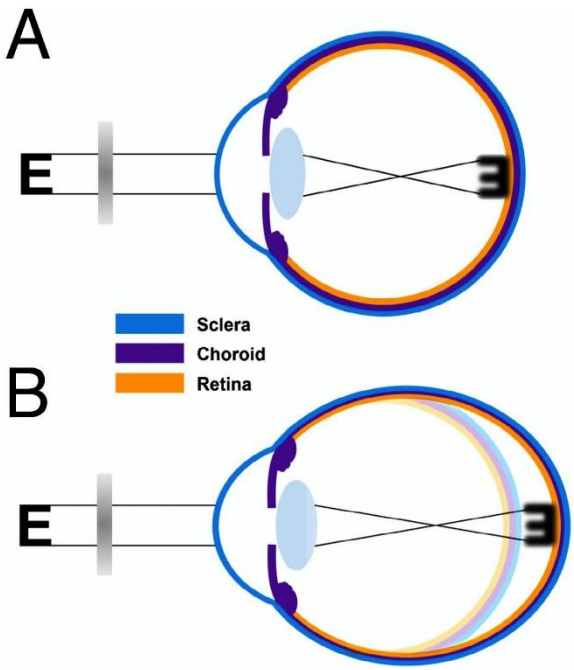

Figure 1.5. Form-deprivation myopia. A) The diffusers produce a blurry retinal image. B) The eye response to the visual absence feedback through scleral thinning and axial elongation. Taken from Chakraborty et al. (2019).

1.5.3.2 Lens-imposed defocus

The greater understanding of the eye grown regulation has been provided by the experimental studies in animals which have looked at the ocular response against imposed defocus. The eye response seen in animals consists on ocular growth changes in an attempt to compensate the defocus (Wallman et al., 1995; Smith III and Hung, 1999; Norton, Siegwart and Amedo, 2006; Howlett and McFadden, 2009; Tkatchenko, Shen and Tkatchenko, 2010). Positive lenses induce myopic defocus which produces the axial elongation to slow down and the choroid to thicken and, therefore, a hyperopic shift occurs (Figure 1.6 A). On the contrary, negative lenses induce hyperopic defocus which promote faster axial elongation and choroid thinning leading to a myopic shift (Figure 1.6 B). The lens-imposed defocus is considered as a closed-loop condition because the eye elongates until the induced defocus is compensated (Schaeffel and Howland, 1991; Chakraborty et al., 2019).

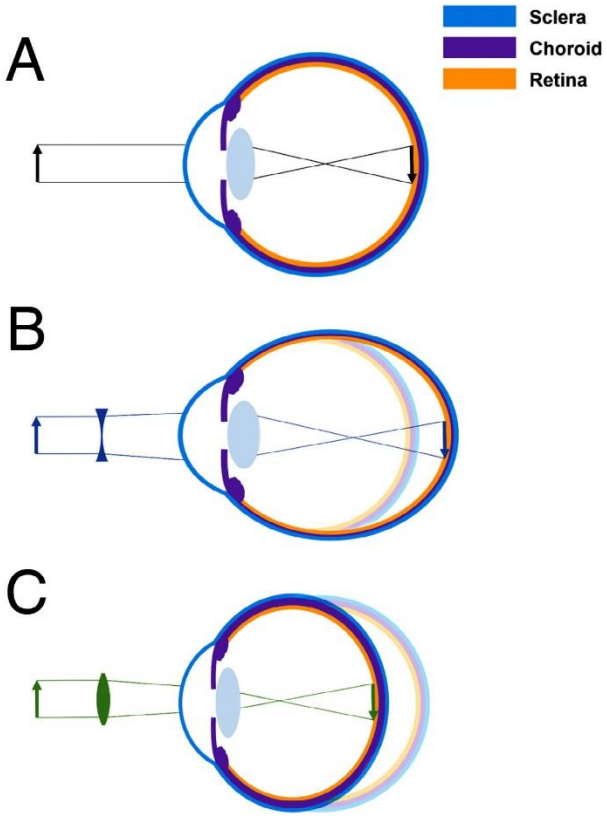

Figure 1.6. Refractive error induced with imposed lenses. A) Normal eye. B) Hyperopic defocus with negative lenses. C) Myopic defocus with positive lenses. Taken from Chakraborty et al. (2019).

The findings of animal studies have evidenced the mechanism for axial growth regulation is able to detect the defocus sign and respond in the correct direction. In this case, the degree of the eye growth response is associated with the degree of lens power imposed (Graham and Judge, 1999; Howlett and McFadden, 2009) and this also declines with age (Wildsoet and Wallman, 1995). All animal species have evidenced to reverse the changes in both AL and choroidal thickness when the imposed defocus is removed. (Wallman et al., 1995; Wildsoet and Wallman, 1995). Strikingly, the chick eyes have shown to develop hyperopia when they are exposed to alternating myopic and hyperopic defocus (Winawer and Wallman, 2002; Winawer et al., 2005). This hyperopic shift has even been observed when chicks were exposed to brief periods of myopic defocus after daily wear of negative lenses (Zhu, Winawer and Wallman, 2003). These findings have pointed out that the control mechanism of the eye growth has greater sensitivity to myopic defocus than to hyperopic defocus. Further, it has been hypothesised the visual system may use separated response mechanisms to compensate hyperopic and myopic defocus (Zhu, 2013). Recently, studies in humans have also reported bidirectional changes, albeit small and short-term, in choroidal thickness and AL after being exposed to myopic and hyperopic defocus (Chakraborty, Read and Collins, 2012; Chakraborty, Read and Collins, 2013; Wang et al., 2016b; Moderiano et al., 2019).

1.6 Myopia and ocular features

Myopic eye undergoes ocular changes, even before the myopia onset, which distinguish it from the emmetropic eye. Refractive changes occur along with structural and functional ocular changes in the eye. The main ocular structures are depicted in Figure 1.7.

1.6.1 Refractive features

Developing myopic eyes have demonstrated to have less hyperopia than the age-matched emmetropic up to 4 years before the onset of myopia (Mutti et al., 2007; Xiang, He and Morgan, 2012). Zadnik et al. (2015) suggested refractive thresholds according to the children's age to consider them at risk of developing myopia as follows: ≤ +0.75 D at age of 6, ≤ +0.50 D at 7-8 years, ≤ +0.25 D at 9-10 years and emmetropia at 11 years of age.

From myopia onset, myopic refractive error progresses at a certain rate. One study in European children (Hyman et al., 2005) reported the myopia progression rate decreased from -0.51 D to -0.36 D after 3 years of follow-up. When the progression was analysed by age groups, the progression rate resulted to be greater for the younger group (6-7 years) compared to the older (11 years). In Singaporean children, the 3-year follow-up study by Saw et al. (2005b) found a progression rate of -2.40 D at 7 years, -1.97 D at 8 years and -1.71 D at 9 years. One meta-analysis (Donovan et al., 2012) also reported a decreased rate of myopia progression age in Asian children from around -1.12 to -0.50 D/year at 7 and 12 years of age, respectively.

Several studies have supported that the younger age of myopia onset is, the faster its progression (Khandekar, Kurup and Mohammed, 2007; Gwiazda et al., 2007; Price et al., 2013; Chua et al., 2016). Studies performed in Chinese children informed the myopic progression rate ranged between -0.35 to -0.68 D/y (Zhao et al., 2002; Fan et al., 2004a; Zhou et al., 2016). In Taiwan, Hsu et al. (2017) and Wu et al. (2018) reported a rate of -0.42 D/y and -0.79 D/y, respectively. One study in Australian children (12 and 17 years) obtained a similar myopia progression for those with European Caucasian and East Asian ethnic background (French et al., 2013a). They also found greater progression rate for the younger cohort (-0.41D) than the older (-0.31D). Smaller rates of myopic progression have been reported in Caucasian children of 6-7 years (-0.23 D) and 12-13 years (-0.10 D) in a 6-year follow-up study (McCullough, O'Donoghue and Saunders, 2016).

Prevalence among university students tend to be lower in Caucasian, between 22-50%, (Kinge and Midelfart, 1994; Kinge and Midelfart, 1999; Fledelius, 2000; Jorge, Almeida and Parafita, 2007; Onal et al., 2007) compared to Asiatic, between 70-90% (Lin et al., 1996; Woo et al., 2004; Wang et al., 2017; Wei et al., 2018; Huang et al., 2019). Norwegian university students (mean age 20.6 ± 1.2 years) had a mean refractive change of -0.50 ± 0.45 D after a 3-year follow-up (Kinge et al., 1999). Other 3-year longitudinal study (Jorge, Almeida and Parafita, 2007) acquired a mean refractive change of -0.30 D in Portuguese university students and where the 22% showed changes ≤ -0.5 D and only 2.5% had a change ≤ -1.00 D Then, Jorge, Braga and Queirós (2016) reported the myopia prevalence changed from 23.4 to 41.3% after 12 years among Portuguese university students. The mean refractive change after 1 year was -0.17 D for medical students in Turkey (Onal et al., 2007).

Regarding the astigmatic refractive error, myopic subjects have exhibited greater astigmatism than emmetropic in previous studies (Leung, Lam and Kee, 2013; Manny et al., 2016). Some authors have suggested the astigmatism is associated with myopia development and progression in children (Gwiazda et al., 2000; Fan et al., 2004b). The longitudinal study of Pärssinen, Kauppinen and Viljanen (2014b) reported that the amount and prevalence of refractive astigmatism increased in myopic subjects after a 23-year follow-up. Besides, a greater myopic refractive error has been associated with higher refractive astigmatism in both children (Fan et al., 2004b; Shih et al., 2004; Pärssinen, Kauppinen and Viljanen, 2014b) and young adults (Farbrother, Welsby and Guggenheim, 2004; Heidary et al., 2005). Recently, a study in a Chinese sample of 12-year-old (Li et al., 2018) obtained mean refractive astigmatism of 0.49 D for low myopia (-3 D$<$SE≤ -0.5 D), 0.71 D for moderate myopia (-6.0 D$<$SE≤ -3.0 D) and 1.30 D for high myopia (SE≤ -6 D). As seen, current scientific evidence does not explain the exact role of refractive astigmatism on myopia and, therefore, additional research will be needed to clarify if astigmatism rises when myopia progresses or if it does before the myopia onset.

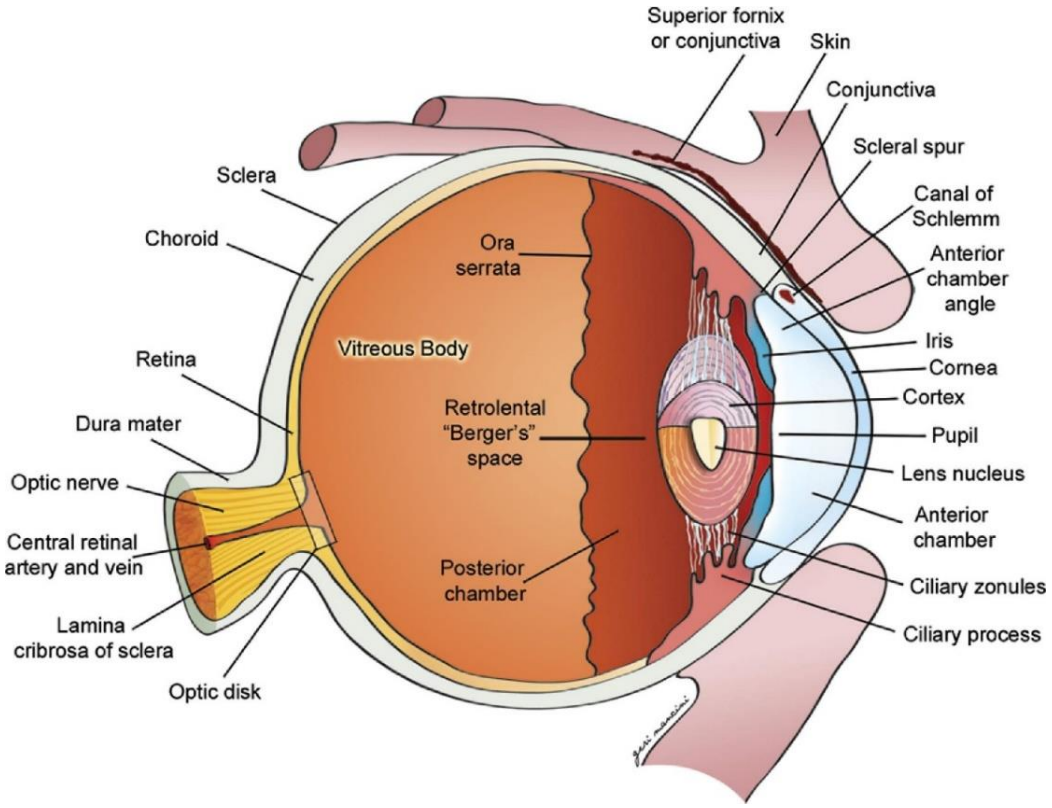

Figure 1.7. Structural parts of the ocular globe. Taken from Malhotra et al. (2011).

1.6.2 Cornea

1.6.2.1 Curvature

Many studies have shown the cornea has a relationship with myopia development and progression. Some studies have reported steeper cornea in myopic children (Li et al., 2016; Hashemi et al., 2018a) and adults (Grosvenor and Scott, 1991; Goss et al., 1997; Bullimore et al., 2006; González Blanco, Sainz Fernández and Muñoz Sanz, 2008; AlMahmoud et al., 2011; O'Donnell, Hartwig and Radhakrishnan, 2011). Contrary, other studies (Chang et al., 2001; Bao et al., 2010; Zhang et al., 2015; Jonas et al., 2016a) reported flatter corneal curvature with longer AL, however, only Bao et al. (2010) found this in myopic eyes. Scott and Grosvenor (1993) noticed that myopic eyes had steeper corneal curvature than emmetropic even though, in general, longer eyes showed flatter cornea regardless of the refractive error. Other study (Llorente et al., 2004) obtained a trend towards steeper corneal radius in myopes although it did not result to be significant.

In a study with Spanish university students (mean age 20.32±2.82 years), the corneal radius was even smaller in moderate myopes (≤ -3.00 D) (González Blanco, Sainz Fernández and Muñoz Sanz, 2008). They also obtained that corneal radius was related with AL rather than with the myopic refractive error directly, and this correlation tended to be lower in moderate myopia (r = 0.45) than in low myopia (r = 0.59). The correlation between corneal curvature and AL was not present in extremely long eyes in the study by Hoffmann and Hütz (2010). Alike, other study (AlMahmoud et al., 2011) observed the slope between SE and Km was significant when the refractive error range was -3.5 D ≤ SE ≤ 2.5 D. These findings might be explained according to the stretching theory by van Alphen (1961), as a reduction, or even loss, of corneal compensation to the axial elongation. That is to say, the cornea may steepen when the AL reaches a certain value because the cornea can no longer compensate the eye elongation.

Goss and Jackson (1995) observed in children between 4 and 14 years that corneal power increased in those who became myopic compared with those remaining emmetropic after a 3-year period. However, several studies informed no significant changes in corneal curvature in children (Horner et al., 2000; Saw, 2005; Davis et al., 2005; Breslin, O'Donoghue and Saunders, 2013) and young adults (Kinge et al., 1999; Jorge, Almeida and Parafita, 2007; Onal et al., 2007) with myopia progression. A 14-year follow-

up study in children between 6-12 years old obtained only significantly corneal flattening in the flattest meridian, which pointed out an increase WTR corneal astigmatism (Scheiman et al., 2016). This agrees with former studies (Fan et al., 2004b; Tong et al., 2004a; Leung, Lam and Kee, 2013) that have found higher levels of WTR astigmatism with myopia progression. AlMahmoud et al. (2011) found that keratometric astigmatism increased in myopes with greater corneal power.

1.6.2.2 Corneal shape

Myopic eyes showed less flattening in the peripheral cornea with greater myopia degree and axial elongation in the study of Carney, Mainstone and Henderson (1997). Some studies (Budak et al., 1999; Horner et al., 2000; Davis et al., 2005) agree in reporting the corneal asphericity is more positive (less prolate shape) in myopic eyes. The longitudinal study by Horner et al. (2000) observed a decrease in the peripheral flattening rate of the cornea. They reported a 0.2 shift in Q for those that myopia progressed by 4.00 D or more. Whereas some authors (Llorente et al., 2004; Zhang et al., 2011; Leung, Lam and Kee, 2013) have found more negative Q (prolate shape) in myopia. Other authors (Nieto-Bona, Lorente-Velázquez and Móntes-Micó, 2008; Yazdani et al., 2016) reported no relationship between corneal Q and refractive error.

1.6.2.3 Corneal thickness

Regarding CT, results from former studies are also controversial. Most of the studies agree that CCT is not related to the myopia degree (Tong et al., 2004b; Pedersen, Hjortdal and Ehlers, 2005; Fam et al., 2006; Al-Mezaine et al., 2008; O'Donnell, Hartwig and Radhakrishnan, 2011; Ortiz et al., 2014; Hashmani et al., 2017). However, some authors have reported higher myopia is associated with either thicker CCT (Kunert et al., 2003; Wang, Dong and Wu, 2015; Mimouni et al., 2017; Kato et al., 2019) or thinner CCT (Chang et al., 2001; Uçakhan et al., 2008; AlMahmoud et al., 2011) although these correlations are weak. Uçakhan et al., 2008 acquired thinner CT in high myopes but not only on the central cornea since lower corneal volume was also obtained at different zones. Another study in Koreans (Kim et al., 2016) acquired that corneal epithelial thickness did not differ with myopia severity whereas the corneal stromal thickness did, being thinner in high myopia.

In the study of AlMahmoud et al. (2011), despite finding a relationship between SE and CCT, it was not present when myopes and hyperopes were evaluated separately. Contrary to Kim et al. (2016), there were no significant differences in any corneal layer associated with myopia in the study of Pekel et al. (2015). In general, previous studies have shown no significant association between CCT and AL (Shimmyo and Orloff, 2005; Oliveira et al., 2006; Tomais et al., 2008; Chen et al., 2009). However, Chung and Park (2016) did obtain CCT had a positive relationship with AL within the high myopic group (< -6.00 D). Alike, myopes with an AL > 28.5 mm showed thicker CCT compared to those with an AL between 24.5 and 26.5 mm in a recent study (Khokhar et al., 2017).

1.6.2.4 Corneal diameter

In most measuring methods, the corneal diameter is also referred to as WTW distance. The corneal diameter was not significantly different between refractive groups in two studies (Cosar and Sener, 2003; O'Donnell, Hartwig and Radhakrishnan, 2011) despite obtaining a positive relationship between corneal diameter with SE (Cosar and Sener, 2003) or with AL (O'Donnell, Hartwig and Radhakrishnan, 2011). Other studies have informed of lower corneal with higher myopic degree in adults with wide age range (Zha et al., 2012; Martin, Ortiz and Rio-Cristobal, 2013). In the study of Zha et al., 2012, the corneal diameter was significantly lower in median myopes (between -3.00 and -6.00 D) and high myopes (≤-6.00 D) compared to emmetropic and low myopic group (between -0.50 and -3.00 D). Meanwhile, similar values were obtained between median and high myopes as well as between emmetropic and low myopes. Differences in corneal diameter between myopic groups were found when high (<-6 D) and extremely myopes (<-12 D) were compared to low myopes (>-6 D), where high and extremely myopes showed lower corneal diameter (Martin, Ortiz and Rio-Cristobal, 2013). Instead, another study (Khokhar et al., 2017) reported significant higher WTW in myopic subjects with AL > 28.5 mm. In children between 4-18 years, larger corneal diameter was also associated with longer AL when it was ≤ 24.5 mm but above this value the corneal diameter showed to be independent of AL (Jiang et al., 2016).

1.6.3 Anterior chamber depth

Several studies informed a negative association between myopic refractive error and ACD in both children (Ojaimi et al., 2005; Li et al., 2016; Dogan et al., 2019) and adults (Hosny et al., 2000; Logan et al., 2005; Uçakhan et al., 2008; Hashemi et al., 2018b) whereas others (Rabsilber et al., 2003; González Blanco, Sainz Fernández and Muñoz Sanz, 2008) did not obtain such association. Studies in children (Jones et al., 2005; Garner et al., 2006; Wong et al., 2010) have reported that eyes developing myopia exhibit greater rate of ACD deepening. Deeper ACD had also a negative relationship with the refractive error in young adults (Mallen et al., 2005; Bullimore et al., 2006; Kato et al., 2019). Deeper ACD was found in high myopes (≤ -6.00D) compared with emmetropes and lower myopes (Uçakhan et al., 2008) while another study (Xie et al., 2009) showed similar ACD values when comparing between low, moderate and high myopia.

ACD was found to be greater between youth-onset myopes and emmetropes but it was not significant for early-adult onset myopes (Grosvenor and Scott, 1991). Longer AL was also found to be related to deeper ACD (Hosny et al., 2000; Rabsilber et al., 2003; O'Donnell, Hartwig and Radhakrishnan, 2011; Chung and Park, 2014). Two authors (Hosny et al., 2000; Chung and Park, 2016) have demonstrated that the positive relationship between ACD and AL is not maintained in high myopia when AL exceeds a certain value, from which the ACD does not keep increasing. These studies have reported the AL inflexion point to be between 26 and 27 mm (Hosny et al., 2000; Chung and Park, 2014). Contrary, one recent study in myopes (Khokhar et al., 2017) did not obtain a significant correlation between ACD and AL.

Longitudinal studies in young adults have shown little ACD change with myopia progression (Lin et al., 1996; Kinge et al., 1999; Jorge, Almeida and Parafita, 2007). Further, the ACD longitudinal changes have not differed between youth-onset and early adult-onset myopia (Grosvenor and Scott, 1993) nor between adult-onset myopes and emmetropes (McBrien and Adams, 1997). Another study (Onal et al., 2007) acquired a slightly significant decrease in ACD after a 1-year period in a sample including myopic, emmetropic and hyperopic young adults.

1.6.4 Crystalline lens

Numerous studies have reported lower crystalline LT and power in myopic children (Zadnik et al., 1995; Shih, Chiang and Lin, 2009; Iribarren et al., 2012; Li et al., 2016; Gwiazda et al., 2016). Besides, the crystalline lens has shown to have higher thinning rate and power loss in children developing myopia (Jones et al., 2005; Garner et al., 2006; Wong et al., 2010; Iribarren et al., 2012; Rozema et al., 2019). Iribarren et al., (2012) found the lens power was lower in the newly developed myopes when they were still emmetropic compared to those who remained emmetropic. Myopic Singaporean children exhibited a lens power 1D lower than emmetropic (Rozema et al., 2019). The growth model by Garner et al. (2006) suggested that the LT might be even thicker at first in developing myopic eyes but with higher thinning rate.

The maximum lens thinning was found to occur at 9 years in emmetropia whereas it was at 10 years for myopia in a study with Singaporean children (Wong et al., 2010). Mutti et al. (2012) reported the lens thinning and power loss to slow down 1 year before or in the myopia onset year. The early thinning stage has demonstrated to be followed by a late thickening in several studies in children (Jones et al., 2005; Wong et al., 2010; Rozema et al., 2019). Myopia progression was not related to the change rate in LT after a 3-year period in children (Saw, 2005). Alike, one 11-year follow-up study (Gwiazda et al., 2016) in myopic children obtained the same lens thinning pattern either myopia progressed or not. The ACD increment in myopia has been suggested to be attributable to lens thinning (Shih, Chiang and Lin, 2009).

Studies in adults have also reported lower crystalline LT and power with myopia (Mallen et al., 2005; O'Donnell, Hartwig and Radhakrishnan, 2011; Muralidharan et al., 2019). Instead, other authors did not obtain significant differences between myopic and emmetropic eyes in LT (González Blanco, Sainz Fernández and Muñoz Sanz, 2008; Xie et al., 2009; Richdale et al., 2016). There were also no differences in LT according to the age of myopia onset (Grosvenor and Scott, 1991; González Blanco, Sainz Fernández and Muñoz Sanz, 2008). Greater lens equatorial diameter has been related with more myopic refractive error (Richdale et al., 2016) and longer AL (Muralidharan et al., 2019) but with constant lens volume (Muralidharan et al., 2019), suggesting the lens stretching and equatorial expansion in myopia seem to be produced because of lens remodelling. Longitudinal studies in adults have revealed no change in LT (Lin et al., 1996; Onal et al.,

2007) or a slight thickening (Grosvenor and Scott, 1993; Kinge et al., 1999; Jorge, Almeida and Parafita, 2007) with myopic error progression. The increase in LT is likely to occur because of the age changes (O'Donnell, Hartwig and Radhakrishnan, 2011).

1.6.5 Ciliary muscle

Ciliary muscle is a structural part of the ciliary body, which is responsible for the accommodation process among others. Recent research has demonstrated differences in ciliary muscle thickness according to the refractive error. In myopic children, the anterior region of the ciliary muscle has shown to be thinner (Pucker et al., 2013) while the posterior region thicker (Bailey, Sinnott and Mutti, 2008; Pucker et al., 2013). Adults with unilateral high myopia have exhibited thicker ciliary body in the most myopic eye compared to the fellow one (Muftuoglu, Hosal and Zilelioglu, 2008) whereas moderate and low anisometropias have not shown differences (Kuchem et al., 2013). In general, eyes with greater AL had a longer ciliary muscle (Sheppard and Davies, 2010; Okamoto et al., 2017; Fernández-Vigo et al., 2019). One study found a correlation between AL and the ciliary muscle maximum thickness (Muftuoglu, Hosal and Zilelioglu, 2008) while other authors did not (Sheppard and Davies, 2010; Lewis et al., 2012; Jeon et al., 2012).

Buckhurst et al., (2013) obtained that both temporal and nasal ciliary muscle thickness at 1 and 2 mm from scleral spur associated positively with AL in non-myopic adults while this relationship was not present in myopic. Recently, Wagner, Zrenner and Strasser (2019) analysed the differences in the ciliary muscle morphology between emmetropes and myopes adults by means of ciliary muscle thickness profiles. The results of this study showed the myopic group had thicker ciliary muscle in the region from 1.4 mm to 4.5 mm from scleral spur while up to 1.4 mm was thinner compared to emmetropes. Indeed, two studies have already suggested more myopic and longer eyes tended to have a thinner portion of apical fibres although the portion of longitudinal fibres portion was thicker in children (Pucker et al., 2013) and adults (Kuchem et al., 2013).

During accommodation, one study reported less movement of the ciliary muscle in eyes with longer AL and higher myopic error (Jeon et al., 2012). Contrary, another study found larger movement in myopes since they had the ciliary apex more posteriorly and its position shift with accommodation was also larger in comparison with emmetropes (Wagner, Zrenner and Strasser, 2019). In this study, myopic eyes generally showed lower

thickness change with accommodation even though myopes showed an increase of ciliary thickness from 3 to 4 D of accommodative stimuli while for emmetropic it remained constant. Moreover, prolonged near work produced ciliary muscle thinning (up to 2 mm from scleral spur) for both myopes and emmetropes but only resulted in a myopic shift for distance vision for myopic eyes (Wagner et al., 2019).

1.6.6 Axial length and vitreous chamber depth

The AL comprises the full longitude of the ocular globe, from the cornea to the retina. Longer AL has been widely seen in myopic eyes in comparison to emmetropic (Llorente et al., 2004; González Blanco, Sainz Fernández and Muñoz Sanz, 2008; O'Donnell, Hartwig and Radhakrishnan, 2011; Li et al., 2016) although lower myopia degrees may exhibit ALs within the emmetropic range. The rate of axial elongation has shown to be faster in children developing myopia (Jones et al., 2005; Garner et al., 2006; Wong et al., 2010; Rozema et al., 2019) with the fastest rate change during the year before myopia (Mutti et al., 2007). Thus, longer AL was seen up to 3 years before myopia onset in children who became myopic (Mutti et al., 2007). Axial eye elongation is also responsible for late-onset myopia (McBrien and Adams, 1997; Grosvenor and Scott, 1991) and progressing high myopia in adults (Fledelius and Goldschmidt, 2009; Saka et al., 2010).

The axial elongation has been demonstrated to occur as a result of the changes in the VCD (Jiang and Woessner, 1996; Tong et al., 2002; Garner et al., 2006; Wong et al., 2010). Many studies have proved the VCD elongation occur with myopia progression in both children (Gwiazda et al., 2003; Fan et al., 2004c; Saw et al., 2005b) and adults (Grosvenor and Scott, 1993; McBrien and Adams, 1997; Kinge et al., 1999; Onal et al., 2007; Jorge, Almeida and Parafita, 2007). Thereby, myopic eyes have shown deeper vitreous chamber in several studies (Goss et al., 1997; Mallen et al., 2005; Xie et al., 2009). The vitreous chamber has resulted as one of the main contributors to refractive error such that the higher myopia is, the greater VCD (Tong et al., 2002; Mallen et al., 2005; Xie et al., 2009; Kato et al., 2019). Indeed, Garner et al., (2004) obtained the increase in VCD as a predictor of myopia, showing 75% of sensitivity and 44% of specificity. Besides, one study in young adults found myopic eyes had less oblate vitreous chamber shape than emmetropic, which could be approximated to a sphere (Gilmartin, Nagra and Logan, 2013).

1.6.7 Axial length to corneal radius ratio

The AL/CR ratio was first suggested to be used as a predictor of myopia by Grosvenor (1988). In general, higher AL/CR has been seen in eyes which become myopic compared to the emmetropic (Goss and Jackson, 1995; Llorente et al., 2004; González Blanco, Sainz Fernández and Muñoz Sanz, 2008). An AL/CR higher than three in emmetropic eyes is usually considered as a risk factor for myopia development (Grosvenor, 1988; Grosvenor and Scott, 1994; Goss and Jackson, 1995). Larger AL/CR ratio in an emmetropic eye indicates that the crystalline lens power loss may have compensated the axial elongation (Grosvenor and Scott, 1994) given that corneal curvature experiences very little changes from late emmetropization phase onwards. And once the crystalline lens power loss reached its limit, myopia would appear. With the cut-off of AL/CR > 3, two studies (Goss and Jackson, 1995; Zadnik et al., 1999) have reported that it presents a sensitivity between 69-88% and a specificity between 57-67% as a myopia predictor.

AL/CR ratio has demonstrated stronger correlation with the refractive error than AL or CR alone in both children (He et al., 2015b; Foo et al., 2016; Scheiman et al., 2016) and adults (Llorente et al., 2004; Mallen et al., 2005; González Blanco, Sainz Fernández and Muñoz Sanz, 2008; Hashemi et al., 2013). Further, the relationship between AL/CR ratio with SE was different between low and high myopia (Jong et al., 2018). Indeed, high myopia showed higher AL/CR ratio than low myopia in former studies (He et al., 2015b; Jong et al., 2018). AL/CR ratio explained between 40-66% of the refractive error variance in children (He et al., 2015b; Jong et al., 2018). The longitudinal COMET study (Scheiman et al., 2016) obtained an increase of AL/CR ratio from 3.15 to 3.31 along with myopia progression after 14-year follow-up. However, the association between AL/CR and SE progression has not resulted to be significant (Scheiman et al., 2016; Jong et al., 2018). Therefore, AL/CR ratio seems to be useful to determine the risk of developing myopia as well as the myopia degree but not to monitor myopia progression.

1.6.8 Fundoscopic changes

Larger optic disc diameter, greater disc area and cup to disc ratio have been seen in myopic eyes (Jonas, Gusek and Naumann, 1988; Jonas, 2005; Wu et al., 2011b). Increased disc size and area were related to longer AL and more myopic error in studies

with children (Huynh et al., 2006; Jung, Baek and Kim, 2013). The optic disc has found to have a more oval shape in myopic eyes (Tong et al., 2004c). One study found that 66.2% of the subjects with tilted disks were myopic while myopia was only present in the 12.4% among those with normal disk (Vongphanit, Mitchell and Wang, 2002). The tilted disk has been associated with longer AL and more myopic refractive error in several studies (Tay et al., 2005; Lim et al., 2008; Samarawickrama et al., 2011). Greater astigmatism was also associated with a tilted disk in some studies (Vongphanit, Mitchell and Wang, 2002; Bozkurt et al., 2002; Samarawickrama et al., 2011). A longitudinal study (Kim et al., 2012) reported progressive tilting of the optic nerve with a myopic refractive shift in children, demonstrating the tilted disc in an acquired feature in myopic eyes. Alike, children with tilted disc had more myopia progression in the study by Park, Park and Oh (2013).

Peripapillary atrophy, present in the region around the optic disc, is commonly found in myopic eyes (Vianna et al., 2016). This atrophy can be divided into: the area where Bruch's membrane is intact (beta zone) and the area with the absence of Bruch's membrane (gamma zone) (Jonas et al., 2012). Both longer AL and tilted disks have correlated with increased gamma zone (Jonas et al., 2016b; Guo et al., 2018a). The distance between the fovea and the optic disc is increased with higher AL (Jonas et al., 2015a; Guo et al., 2018a) due to an enlargement of the gamma zone. The longitudinal study of Guo et al. (2018b) obtained longer disc-fovea distance with greater axial elongation after 5-year follow-up. Moreover, the optic disc-fovea angle had a relationship with astigmatism but not with the refractive error (Jonas et al., 2015b). Generally, high axial myopia increases the incidence of fundus complications among those are the posterior staphyloma or myopic maculopathy (Ohno-Matsui et al., 2016).

1.6.9 Accommodation

The accommodation is the process through which the eye power changes to focus objects in near distance. Accommodation occurs due to changes in the shape, thickness and refractive index of the crystalline lens (Dubbelman, Van der Heijde and Weeber, 2005). Characteristics of the accommodative function have shown to differ according to refractive error throughout studies.

1.6.9.1 Accommodation amplitude

The amplitude of accommodation is the maximum accommodative response of the eye in order to focus objects in near distances. Some studies have reported greater amplitude of accommodation in myopes than emmetropes (McBrien and Millodot, 1986a; Kuriakose et al., 2005). McBrien and Millodot (1986a) obtained even higher accommodation amplitude in late-onset myopes than those with early-onset. Meanwhile, other studies acquired lower accommodation amplitude in myopes (Fong, 1997) or did not find differences between refractive groups (Fisher, Ciufreda and Levine, 1987). The mean accommodative range was also lower for myopes (4.7 D) compared with emmetropes (7.5 D) when using negative lenses in the study of Gwiazda et al. (1995).

1.6.9.2 Accommodative response and lag

Accommodative response error is usually referred as lag of accommodation and results from the difference between the accommodative demand and response. Lower accommodative response has been found in myopic children and adults (McBrien and Millodot, 1986b; Gwiazda et al., 1993; Chen et al., 2019). Accommodation in progressing myopic children was worse whereas it improved in those whom myopia was stabilized in the study of Gwiazda et al. (1995). The difference in accommodative response between myopic and emmetropic children has had even greater using negative lenses in some studies (Gwiazda et al., 1993; Abbott, Schmid and Strang, 1998; Yeo, Kang and Tang, 2006), which mean the blur cues are less effective than the proximity cues with myopia. Indeed, myopes have shown less sensitivity to detect blur presence than emmetropes previously (Rosenfield and Abraham-Cohen, 1999). Nonetheless, one study in young adults could not demonstrate differences in accommodative response between myopes and emmetropes (Harb, Thorn and Troilo, 2006).

Reduced accommodation responses have led to observe larger lags in myopic children (Abbott, Schmid and Strang, 1998; Nakatsuka et al., 2005; He et al., 2005; Chen et al., 2019). Nakatsuka et al. (2003) failed to demonstrate differences in accommodative lag between emmetropic and myopic adults. In fact, one recent study (Chen et al., 2019) reported significant differences in accommodative lag between myopic and non-myopic schoolchildren while myopic adults did not differ significantly from those without myopia. Progressing myopes have shown higher accommodative lag than stable myopes

in some studies (Abbott, Schmid and Strang, 1998; Gwiazda et al., 1995). As reported by Gwiazda, Thorn and Held (2005), children could have increased the accommodative lag up to 2 years before myopia onset. Conversely, Mutti et al., (2006) only found the increased lag after the myopia onset, stating thus it might occur as a consequence of myopia rather than be a cause. The results from subsequent studies are controversial to determine whether accommodative lag has a role in myopia progression or not. Contrary to the conventional hypothesis that the larger lag would lead to faster myopic progression, lower lags were obtained in adults with progressing myopia while larger lags in those with stable myopic error (Rosenfield, Desai and Portello, 2002). Some authors exhibited the accommodative lag changes were not related with myopia progression or changes in AL, though (Weizhong et al., 2008; Berntsen et al., 2011; Koomson et al., 2016). Meanwhile, other authors did report an association between increased accommodative lag and myopia progression (Allen and O'Leary, 2006; Price et al., 2013).

1.6.9.3 Accommodation variability

Variability of accommodation arises from the quantification of the standard deviation and microfluctuations of the accommodative response. Despite obtaining similar accommodative responses in myopes and emmetropes, myopic eyes tended to have greater variability response in the study by Harb, Thorn and Troilo, (2006). Further, higher fluctuation of the accommodative response has found in late-onset myopic adults (Day et al., 2006) and early onset myopic children (Langaas et al., 2008). One longitudinal study (Langaas and Riddell, 2012) found the decreased accommodation stability as a weak predictor of myopia progression. Thereby, accommodation variability seems to be affected when myopia is progressing and then stabilises (Day et al., 2006; Langaas et al., 2008; Langaas and Riddell, 2012). The greater variability of accommodative response has been hypothesized to be due to the deficient blur sensitivity and increased depth of focus in myopes (Harb, Thorn and Troilo, 2006; Day et al., 2006). Interestingly, in the study by Vera-Diaz et al. (2004), myopic eyes showed an increase in the accommodative response after a period adaptation to blur whereas it remained stable in emmetropic eyes. The accommodation improvement in myopes might be an adaptation of the accommodative system to long-term blur exposition.

1.6.10 Aberrations

Ocular aberrations are defined as the coefficients to quantify how the exiting wavefront of the eye differs from the ideal wavefront, which is free of aberrations and only limited by diffraction. Aberrations usually are divided into low and high-order. The latter are those remaining once both spherical and astigmatic refractive error are corrected. HOA are thought to have a role in myopia development since the quality of the retinal image (Liang and Williams, 1997) as well as accommodation (Li et al., 2011) are affected by them.

Myopic children have exhibited higher HOA RMS than emmetropes (He et al., 2002) and hyperopes (Kirwan, O'Keefe and Soeldner, 2006) while other authors informed no differences between refractive groups (Carkeet et al., 2002; Li et al., 2012; Little et al., 2014). Previous studies revealed the primary spherical aberration tend to took more negative values with myopia (Carkeet et al., 2002; Papamastorakis et al., 2015). Another study (Little et al., 2014) found the spherical aberration was related to AL rather than the refractive error, where longer eyes had less positive values of spherical aberration RMS. Besides, faster myopic progression (≤ -0.50 D) was associated with greater RMS of HOA, coma and third-order aberrations in Chinese schoolchildren (Zhang et al., 2013).

In adults, greater levels of HOA RMS have been also acquired in myopes compared to emmetropes (He et al., 2002; Buehren, Collins and Carney, 2005; Yazar et al., 2014; Kasahara et al., 2016). RMS of HOA has shown to increase with the myopia degree in young adults (Paquin, Hamam and Simonet, 2002). Other authors (Cheng et al., 2003; Kwan, Yip and Yap, 2009) have not obtained differences in HOA according to the refractive error. As seen in children, more negative spherical aberration correlated with higher myopia in adults (Kwan, Yip and Yap, 2009; Hartwig and Atchison, 2012; Yazar et al., 2014). Moreover, one study obtained higher coma-like aberrations with myopia (Paquin, Hamam and Simonet, 2002). Controversial results have been obtained for fourth-order aberrations with myopia, where some authors found lower values (Collins, Wildsoet and Atchison, 1995; Kwan, Yip and Yap, 2009) and others higher values (He et al., 2002; Yazar et al., 2014).

A few studies have been carried out to assess the aberration changes alongside refraction over time. In the longitudinal study by Philip et al. (2014), emmetropic children

who underwent a myopic shift ≤ -0.5 D had less RMS of coma and third-order aberrations compared to those who remained emmetropic. The myopic shift was accompanied by an increase of the RMS of third-order and coma in the same study (Philip et al., 2014). These findings were confirmed in a later study (Philip et al., 2018) for the emmetropic children with myopic shift but not for those already myopic at baseline. Spherical aberration and fourth-order RMS experienced a decrease with myopia progression for both emmetropic and myopic children at baseline (Philip et al., 2014; Philip et al., 2018). Furthermore, increased HOA RMS, negative oblique trefoil and more positive spherical aberration and vertical trefoil were associated with less axial eye growth in a 2-year follow-up in children (Lau et al., 2018). Meanwhile, Hiraoka et al., (2017) asserted the corneal HOA RMS was the more predictive for myopia progression and axial elongation than ocular HOA RMS in Japanese schoolchildren.

CHAPTER 2. STUDY RATIONALE

Myopia prevalence has demonstrated to be greater among the population with the highest education (Shimizu et al., 2003; Mirshahi et al., 2014; Williams et al., 2015a). Some studies have shown that higher school performance (Mutti et al., 2002; Saw et al., 2007) and intelligence quotient (Saw et al., 2004; Saw et al., 2006) are related with myopia. But the time spent in near work activities is thought to have a role in such association between myopia and the educational level achieved (Mutti et al., 2002). The time spent in near work and its intensity, especially continuous reading, have shown to increase the myopia odds in children (Ip et al., 2008b). The students at university constitute a young population group exposed to high prolonged near work as a result of the high academic demands. This academic population is at special risk of myopia development and progression during their studies and, therefore, attention should be payable to them. Indeed, a previous meta-analysis (Williams et al., 2015b) showed the peak in myopia prevalence was between 25 and 29 years in the European population.

Several studies demonstrate the increase of myopia prevalence among students at university over the last decades, though at a different rate depending on the geographical region. After 12 years, the myopia prevalence has been reported to change from 23 to 43% in Portuguese students (Jorge, Braga and Queirós, 2016) while from 93 to 96% in Taiwanese students (Wang et al., 2008). The myopia prevalence rate reached in some areas of East Asia, exceeding 90%, is especially striking (Woo et al., 2004; Sun et al., 2012). And the particular rise of high myopia (up to 20-30%) in this population implies a public health issue of concern due to the complications may occur (Woo et al., 2004; Sun et al., 2012). Former longitudinal studies (Lin et al., 1996; Kinge and Midelfart, 1999; Jorge, Almeida and Parafita, 2007) have already pointed out myopia can develop and even keep progressing in young adults during their university studies. However, myopia development and progression in young adult population have not been assessed as widely as in children or teenagers. Thus, there is a need for more investigations to be carried out about myopia in university population in order to evaluate the eye changes produced as a result of myopia progression as well as the risk factors that may trigger the adult-onset of myopia.

CHAPTER 3. AIMS AND OBJECTIVES

3.1 Main purpose

This research aims to characterise the myopic eyes by means of quantitative ocular descriptors, measured with non-invasive techniques, and to analyse the change of them over time in connection with myopia progression in a sample of young university students.

3.2 Secondary objectives

The main purpose will be achieved through the following specific objectives:

1. Evaluate the differences in anterior and posterior ocular biometry, corneal topography and aberrometry between myopic and emmetropic eyes.

2. Assess the one-year longitudinal changes of the quantitative descriptors in myopic versus emmetropic eyes and the relation of them to myopia progression.

3. Determine the quantitative descriptors that best represent the ocular features of myopic eyes and their progression.

CHAPTER 4. GENERAL METHODOLOGY

4.1 Study design and ethical considerations

A prospective longitudinal study was designed to evaluate myopic and emmetropic university students with a one-year follow-up. The study protocol was performed according to the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the University of Valencia. A document was written up to provide information about the study purposes, type of devices, measurement process and data treatment so as to obtain the informed consent. Additionally, an online questionnaire was designed to perform a brief anamnesis previously to the measurement protocol.

4.2 Patient recruitment and criteria

The population to evaluate consisted of students from the University of Valencia and the recruited volunteers were selected according to the inclusion and exclusion criteria detailed below.

4.2.1 Inclusion criteria

- Aged from 18 to 35 years
- Caucasian ethnicity
- SE < +1.00 D
- Visual acuity with refractive compensation equal to 0.1 logMAR or better
- Be willing to perform the one-year follow-up

4.2.2 Exclusion criteria

- Younger than 18 or older than 35 years
- Non-Caucasian ethnicity
- Hyperopia: SE ≥ +1.00 D
- Ocular pathologies
- Systemic diseases with ocular effects
- Previous ocular surgery or ocular trauma
- Current ocular medication
- Binocular vision problems
- Poor fixation
- Visual acuity with refractive compensation worse than 0.1 logMAR

4.3 Measurements and devices

This section describes the technical and operating information of the devices used for data collection. All devices are non-invasive and usually employed in optometric clinical practice. The repeatability of two of the devices used was evaluated prior to the start of this study (APPENDIX A and APPENDIX B).

4.3.1 Objective refraction

The measurements of objective refraction were performed using the L67 ARK Auto Refractor and Keratometer (Visionix Luneau, France; Figure 4.1). This device has a Shack-Hartmann sensor and the autorefraction is based on wavefront analysis. The minimum pupil diameter to acquire measurements is 2.0 mm. The sphere and cylinder power results can be obtained with 0.12 or 0.25 D steps while the astigmatism orientation has 1-degree steps.

Figure 4.1. L67 ARK Auto Refractor and Keratometer.

4.3.2 Subjective refraction and visual acuity

Subjective refraction was carried out with the VT-10 manual phoropter (Topcon, Japan; Figure 4.2 left). The CC-100 chart system (Topcon, Japan; Figure 4.2 right) is a high resolution 22'' LED LCD monitor used to display the visual acuity test, which was obtained in LogMAR notation. LogMAR charts have the same number of optotypes per line and a

logarithmic letter-size progression, allowing more precise visual acuity quantification (Lovie-Kitchin, 2015).

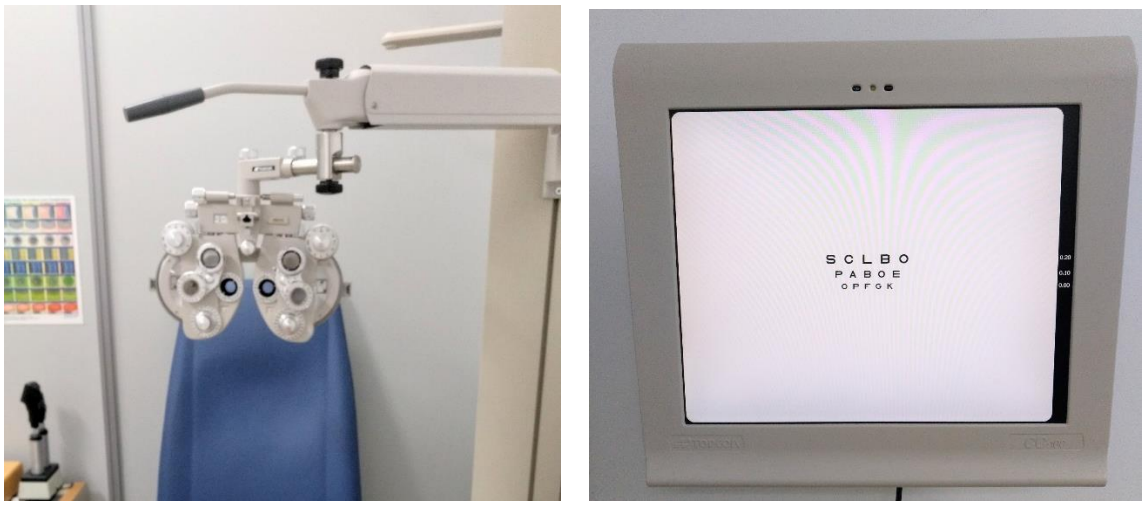

Figure 4.2. VT-10 phoropter (left side) and CC-100 chart (right side).

4.3.3 Ocular biometry

Biometry of the whole eye was obtained with the IOLMaster 700 device (Carl Zeiss Meditec, Germany). The IOLMaster 700 (Figure 4.3) is a non-invasive optical biometer based on SS-OCT technology to obtain ocular biometric measurements. It allows a 44 mm scan and a resolution in the tissue of 22 µm. The speed of the length measurement system allows acquisition of full-eye length tomograms at 2000 A-scans/s. Six consecutive measurements are acquired in one capture process, which takes around 3.5 s per eye, and then the average values are presented. In each capture, the biometric distances of CCT, ACD, LT, and AL are shown automatically. Besides, measures of keratometry are also taken through a telecentric technique using a refractive index of 1.3375, and WTW distance. WTW is measured through a high-contrast picture (using a LED light of 590 nm) to detect later the boundary between the paler sclera and the darker iris at either side.

After the measurement process, the scan of the entire eye is displayed so that the observer can check the eye geometry (Figure 4.4). The fovea scan is also shown to check the correct patient's fixation during the measurement (Figure 4.4). Good fixation is obtained when the depression is in the centre of the scan, which is the foveal pit, meaning the patient has fixated well during the measurement. If the foveal pit cannot be recognized that means the patient has not fixated well and the measurement should be repeated.

Additionally, the SS-OCT calculates the SD of the measurements and warns the operator if the measurement quality is low when the SD is less than a pre-set threshold by the manufacturer (Figure 4.4). The repeatability of the parameters obtained by IOLMaster 700 is enclosed in APPENDIX A.

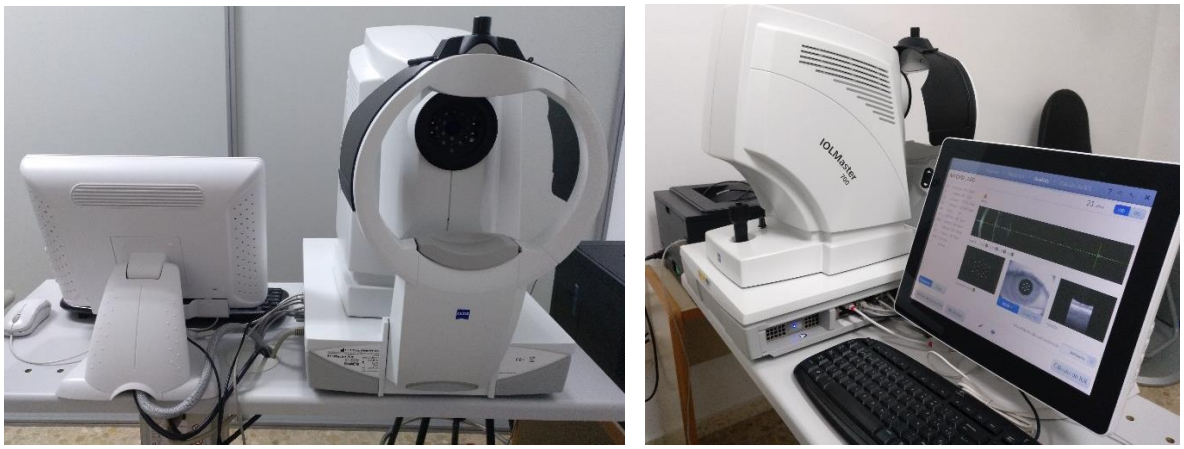

Figure 4.3. IOLMaster 700 biometer.

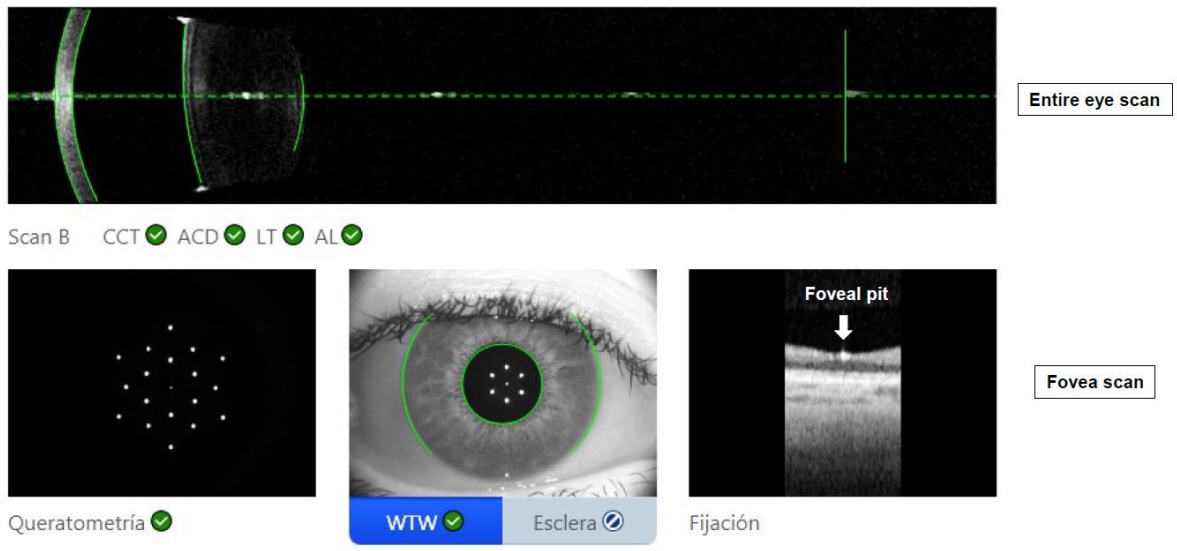

Figure 4.4. IOLMaster 700 scans: entire eye scan (top), keratometry, corneal diameter and foveal scan (bottom).

4.3.4 Corneal topography

The Atlas 9000 device (Carl Zeiss Meditec, Germany) is a topographer based on the Placido disk technology and incorporates the patented Cone-of-Focus™ alignment system to evaluate the anterior corneal surface. This device provides topography data based on 22 Placido rings, with each ring containing 180 data points with an angular resolution of 2°. The small Cone-of-Focus (Figure 4.5) produces a separation in the 22 rings at the 9th location and its role is to improve the focus of the capture. Thus, the proper focus is achieved when the inner and outer rings are equidistantly separated around the cone. Further, the SmartCapture™ technology takes up to 15 captures per second and automatically select the ones with the best quality.

Figure 4.5. Atlas 9000 topographer.

Additionally, Atlas 9000 has been combined with Visante AS-OCT technology (Carl Zeiss Meditec, Germany), named as Visante omni (Figure 4.6), to obtain an evaluation of both anterior and posterior cornea. Visante OCT is based on time-domain OCT technology to provide cross-sectional images using low-coherence interferometry. Anterior corneal surface data are combined with the global pachymetric map data obtained by the Visante OCT system. The V-Trac Registration System links the topography and pachymetry data to generate reliable posterior corneal topography maps through corneal vertex alignment. This system utilizes a series of strict criteria to prevent potential

misalignment. The repeatability of corneal parameters obtained by Visante Omni is presented in APPENDIX B.

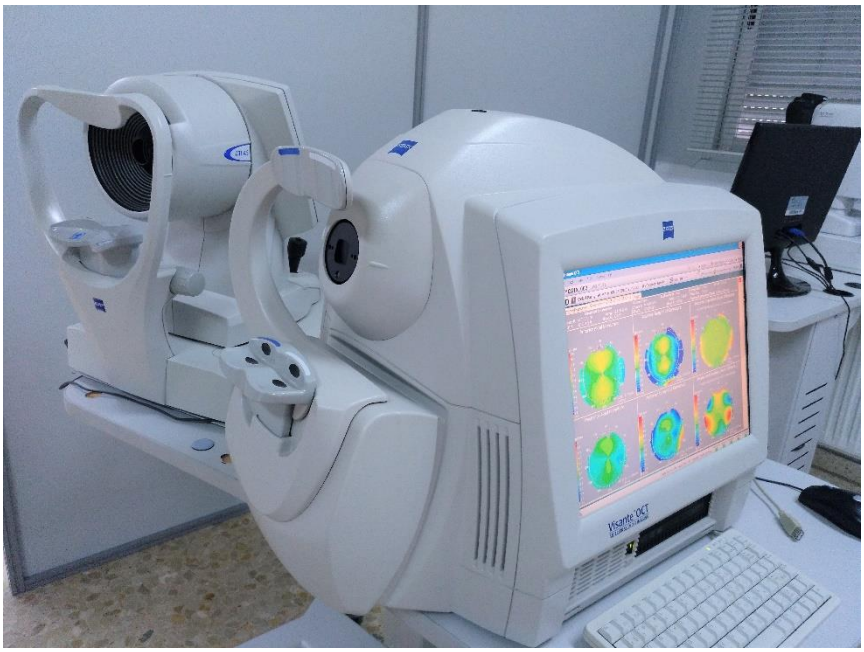

Figure 4.6. Visante omni device.

4.3.5 Anterior segment OCT

The Visante AS-OCT (Carl Zeiss Meditec, Germany) is a low-coherence interferometry-based non-contact system that uses near-infrared light with a wavelength of 1310 nm to obtain A-scans of the anterior segment ocular structures. This technology provides cross-sectional scans from limbus to limbus with dimensions of up to 16 mm wide and 6 mm deep, and with an axial resolution of 18 µm and a lateral resolution of 60 µm. The system is connected to a computer with a built-in software (Figure 4.7) that offers different options for the image capturing and biometric measurements. Anterior segment measurements of ACD, CCT, angle-to-angle distance and iridocorneal angles can be obtained with its software. The Global-Pachymetry-Map map is given as from multiple cross-sectional cornea scans and provides the CT automatically in different zones: from 0 to 2 mm; from 2 to 5 mm; from 5 to 7 mm, and from 7 to 10mm. Additionally, ciliary muscle measurements can be obtained using an attachment with mirrors and this will be described in the measurement protocol.

Figure 4.7. Anterior segment Visante OCT.

4.3.6 Aberrometry

The i.Profiler^{plus} (Carl Zeiss Meditec, Germany) is a combined topographer and aberrometer that allows assessing both corneal and ocular wavefront. This device is based on a Hartmann-Shack wavefront sensor made up of a lenslet array. An infrared laser beam is projected on the retina and then the scattered light spot returning from the retina is captured in the corneal plane. The distortion of the ocular wavefront results in a deviation of the light rays with respect to the one projected in the lenslet array and this is captured by a sensor camera. Then, the ocular wavefront distortion is quantified through the Zernike polynomials. The i.Profiler^{plus} also allows obtaining the corneal aberrations from the Placido-disk topography (Figure 4.8). Thus, corneal and ocular wavefront are computed with the same reference position, which is the line of sight as recommended previously (Thibos et al., 2002). The wavefront is fitted with Zernike coefficients up to the seven-order, obtaining low and high order aberrations. Piston and tilt coefficients are not included so as Zernike coefficients are shown from second-order onwards. Aberrations are calculated at a wavelength reference of 555 nm for 3 and 5 mm pupil size as well as for the patient's maximum pupil size.

Figure 4.8. i.Profiler^{plus} aberrometer.

4.3.7 Fundus photography

The CR-2 Plus is a digital non-mydriatic retinal camera (Canon, Tokyo) with FAF. The device acquires colour fundus images with 45 degrees' field of view to evaluate the optic nerve, macula and blood vessels. The option of 2X magnification provides images of 30 degrees' angle. The FAF mode, which uses 530-580 nm exciter filter and 640 nm barrier filter, provides information about the changes in the retina non-visible in the standard colour photography such as in the retinal pigment epithelium. The device has a built-in software to analyse the fundus images to perform measurements such as the cup to disc ratio (Figure 4.9).

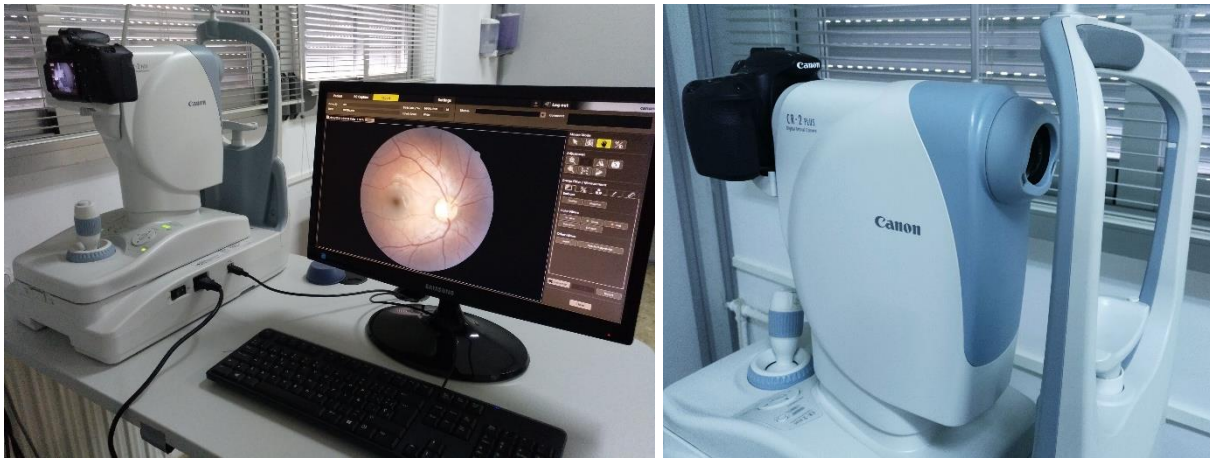

Figure 4.9. CR-2 Plus retinal camera.

4.4 Patients' classification

Patients were divided into refractive groups according to the power of the principal meridians following previous methodology (Kleinstein et al., 2003; Farbrother, Welbsy and Guggenheim, 2004). Patients who had myopia in both meridians and whose least negative meridian was ≤-0.75 D were included in the myopic group. On the other hand, the emmetropic group was made up of those whose least positive meridian was >-0.75 D and most positive meridian was ≤+0.75 D.

The classification of the subjects was based on subjective refraction without cycloplegia. Previous studies have not found great significant differences between cycloplegic and non-cycloplegic refraction in young adults (Krantz et al., 2010; Sanfilippo et al., 2014; Hashemi et al., 2015). The -0.75 D threshold was chosen following the recommendations of the IMI report (Flitcroft et al., 2019) and taking into account that the non-cycloplegic subjective refraction may overestimate myopia. Despite the fact most of the studies tend to choose -0.50 D cut-off, recent studies (Plainis and Charman, 2015; Williams et al., 2015b) have already recommended using -0.75 D instead because at this myopia level the visual acuity is significantly reduced to 6/12 (Snellen notation). Further, the cut-off of -0.75 D in the least negative meridian ensures both meridians were myopic and, therefore, simple myopic astigmatism was not considered as myopia condition.

4.5 Protocol and procedures

Calibration of the devices was performed previously to each session of measurements. The examination protocol, baseline and follow-up, was performed by the same experienced observer during a single session (NMA). The room illumination was controlled with the T-10 illuminance meter (Minolta Corp, Japan). Patients were asked not to wear contact lens at least 24 hours before each visit and to wear the spectacles with the latest prescription. Only data from the right eyes were obtained due to the similarity of the measurements between both eyes (McAlinden, Khadka and Pesudovs, 2011).

4.5.1 Baseline

Patients were provided with a verbal and written explanation of the study and informed consent was signed by every participant. The preliminary evaluation consisted of the anamnesis, refractive error status and slit-lamp examination to ensure every subject met the inclusion criteria. The online questionnaire was completed for each participant as anamnesis, obtaining the following information: birth date, gender, years studying at university, systemic and ocular health, allergies, ocular treatments, current medication, last visual revision, visual symptoms (blur vision, halos, sparks, etc.), refractive error already diagnosed with its year of first compensation, type of compensation used and hours of use, subjective vision quality (distance and near vision) and hours spent reading per day. The latest spectacle prescription was also recorded once checked in an auto lensmeter.

In the first place, objective automatic refraction was evaluated with the L67 Auto Kerato Refractometer (Luneau, France) followed by a subjective refinement. The fogging method was used adding positive power to the preliminary objective refraction in order to control the subjects' accommodation. The adopted criterion for the refraction endpoint was the maximum plus to achieve the best visual acuity while the astigmatism refinement was done with the cross-cylinder technique. All patients achieved a visual acuity with distance correction of at least 0.1 in logMAR notation.

Subsequently, the measurement protocol was performed as follows: ocular biometry, corneal topography, anterior segment OCT, aberrometry and fundus photography. Generally, patients were asked to place the chin and forehead in the device and instructed to focus their vision in the fixation light during the examination. They were also asked to perform a complete blink prior to each scan to achieve an appropriate tear film and to keep their eyes wide open during the measurement acquisition. The room had an illumination level of 100 lux.

4.5.1.1 Ocular biometry

One biometric capture was taken with IOLMaster 700, which results from the average of six consecutive scans. The quality of scans and proper patient's fixation along the visual axis was checked for each patient capture through the SD warnings and the foveal scan, respectively, in accordance with the manufacturer's recommendations. The

measurements obtained were the following: CCT defined as the distance between corneal epithelium and endothelium, ACD defined as the distance between endothelium and anterior crystalline lens surface, LT defined as the distance between anterior and posterior surfaces of the crystalline lens in its centre, AL defined as the distance between corneal epithelium and fovea and WTW defined as the horizontal width of the visible iris, K readings for identifying the flat and the steep meridians and corneal astigmatism.

4.5.1.2 Corneal topography

The patient was placed firstly in the Atlas 9000 topographer to obtain measurements of the anterior surface. After scanning, the patient information and anterior corneal topography data were automatically transferred to the Visante OCT station via a network link. Then, the subject was moved to the Visante OCT station to measure global pachymetry. In this procedure, aligning the tomography corneal centre with the anterior corneal surface topography is necessary. The correct alignment is achieved when the corneal reflex appears as a vertical white line across the central cornea. The posterior corneal elevation and curvature measurements were carried out by the system software. Three measurements were obtained for the Visante omni device (Atlas 9000 and Visante OCT combined) repeating the process explained above. Anterior keratometry was evaluated through the measurements of steep K, flat K and astigmatism in different corneal zones. The corneal shape was assessed by the data of eccentricity, asphericity and shape factor. Corneal elevation was determined by means of BFS and toric ellipsoid fit.

4.5.1.3 Anterior segment OCT

For ciliary muscle measurements, two attachments were used to place two mirrors in each side of the device (Figure 4.10 above). The attachments allowed to adjust the position of the mirror as well as the rotation. This system was performed to have the patient's gaze averted to an external stimulus so as to visualize the full length of the ciliary muscle. The external stimuli were 2 LEDs located in the wall, which could be seen through the mirrors when the patients were placed in the chin rest. In this way, patients were looking at a distance external target during measurements to ensure the relaxation of the accommodation (Figure 4.10 below). In order to see the external target without the device obstruction, the minimum eye movement required in the horizontal direction is around

40° from the internal target device according to previous methodology (Laughton et al., 2015).

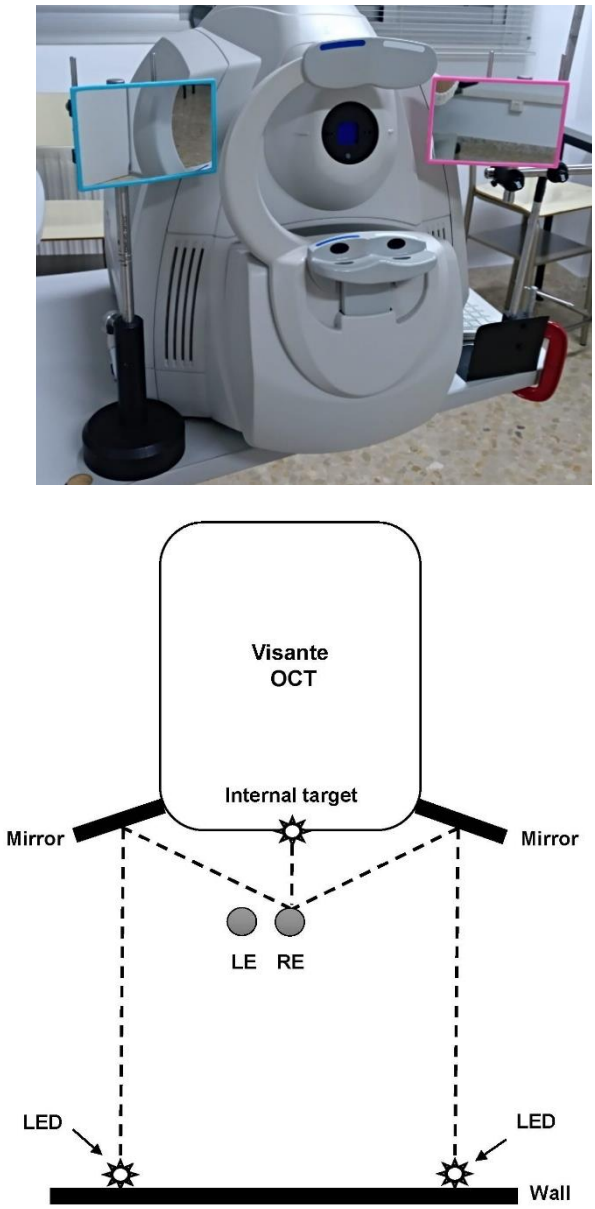

Figure 4.10. Attachments with the mirrors (above) and the scheme of the external fixation target (below) for ciliary muscle measurements.

The capture mode, in this case, was the "High-Resolution Cornea" with a 3 mm scan depth. First, patients were asked to fix on the internal target to align correctly the eye. Then they had to fix on the external target in the mirror and the alignment was refined to ensure the visibility of the scleral spur and the entire ciliary muscle. Three consecutive measurements for the temporal side (gaze to the left) were taken first and then other three for the nasal side (gaze to the right), taking a break after every single measurement.

4.5.1.4 Aberrometry

Repeated aberrometry measurements were taken with i.Profiler^{plus} under mesopic light conditions of 8 lux to ensure most of the subjects reached 5 mm of pupil size. Zernike coefficients up to seven order were obtained for both corneal and ocular wavefront.

4.5.1.5 Fundus photography

Colour fundus images with 45 degrees' field of view were taken where both disc and macula were visible.

4.5.2 One-year follow-up

The follow-up visit was performed in the same time range for most of the subjects in an attempt to avoid the influence of the ocular diurnal variations, although this is not significant for all ocular parameters (Akil et al., 2017; Xu, Penteado and Weinreb, 2018; Burfield, Patel and Ostrin, 2018). Likewise, the possible changes because of light conditions (Koktekir et al., 2014) were controlled keeping the same room illumination in both visits with the devices positioned in the same place.

In this second visit, patients were asked to answer several questions regarding any change in their vision quality, any refractive compensation change (glasses/contact lens), any ocular complication or any current medication. Then, the same measurements as in the baseline visit were performed one year later following the same protocol order, from the objective refraction onwards.

4.6 Measurements analysis

The methods used to analyse the data obtained will be exposed in every chapter such as the data transformation or the calculations as from the measurements taken.

4.7 Statistical analysis

The data analysis was performed using Excel (version 2016, Microsoft Corporation, Redmond, WA, USA) and SPSS statistical software (version 26.0, IBM Corp., Armonk, NY, USA). In this section, the main statistical procedures are explained in a general way. The specific statistical analysis will be explained in each chapter according to the variables evaluated.

4.7.1 Sample size

The sample size was not calculated a priori due to the numerous parameters analysed in the same sample. Thereby, a post hoc power calculation was performed for all statistical analysis applied with the software G*Power 3.1 (Faul et al., 2007; Faul et al., 2009).

4.7.2 Descriptive statistics

The descriptive analysis gave mainly the values of the average, SD and values range (maximum and minimum). The obtained results were shown as the mean ± SD in the results section. Histograms and box plots were constructed in order to check the data distribution and the presence of significant outliers.

4.7.3 Inferential statistics

The normality of all data sets was evaluated by means of the Shapiro–Wilk or Kolmogorov-Smirnov test. Shapiro–Wilk test was used when the sample was up to 50, otherwise Kolmogorov-Smirnov test was employed (Ghasemi and Zahediasl, 2012; Das and Imon, 2016). A p-value less than 0.05 was set to consider the distribution was statistically non-normal. Besides, the normal Q-Q plots were run in the normality analysis. The normal distribution can be seen in these graphs when the data are close to the diagonal line.

4.7.3.1 Differences between two independent groups

The comparison between two independent groups was carried out through the independent Student t-test or Mann-Whitney U test, depending on the data distribution.

The independent Student t-test was applied to compare continuous variables between two independent groups whose data followed a normal distribution. The homogeneity of the variances was checked using Levene's test. This inferential test allows determining if there is a difference between the means of the two groups.

The Mann-Whitney U test was used when the variables were continuous or ordinal but not following the normal distribution. This test compares the median differences between groups when the distribution of both groups has the same shape. Otherwise, the test analyses the differences in the mean ranks.

4.7.3.2 Chi-Square Test for independence

The Chi-Square test for independence evaluates the association of two categorical variables (ordinal or nominal). The two variables have to include at least two categories. A contingency table (also known as crosstab) was performed to obtain the frequency distribution of the two categorical variables. Then, the Chi-Square test was conducted on the crosstabs to statistically prove if both variables are related or not. A p-value less than 0.05 indicates there is a relationship between the variables.

4.7.3.3 Correlation analysis

The strength and direction of the associations between two variables were obtained through the correlation coefficients of Pearson and Spearman. The values of these coefficients range between -1 and 1, where the correlation is stronger as it gets closer to either -1 or +1. The p-value obtained with the coefficients indicates the probability that the relationship between variables would be zero. Bivariate correlations were obtained in all cases and the statistical significance was considered with a p-value less than 0.05.

The linear association between two continuous variables normally distributed was performed by Pearson's correlation. The Pearson correlation coefficient informs about the best linear fit of the data.

The non-parametric option for the correlation analysis is Spearman's correlation. This correlation analysis was applied for ordinal variables or continuous data non-normally distributed. The Spearman correlation coefficient evaluates the existence of a monotonic association between variables. In the monotonic association, the relationship between variables has the same direction but not with a constant rate as occurs in the linear relationship.

4.7.3.4 Multiple linear regression

Multiple linear regression was applied to construct models which can predict a continuous variable as from a set of variables (continuous or categorical). In all cases, the option of stepwise regression was chosen and $p < 0.05$ was taken as the criterion for statistical significance. In order to obtain appropriate estimations, the following assumptions were checked:

Linearity. The scatterplots and partial regression plots proved the linear relation between the independent and dependent variables.

Non-collinearity: The absence of an exact linear relationship between independent variables was checked with the Tolerance and VIF. Low values of Tolerance along with higher VIF denote the presence of collinearity.

Independence. The independence of the residuals can be assumed when the Durbin-Watson statistic takes values between 1.5 and 2.5.

Normality. Histogram and normal Q-Q plots of the studentized residuals were constructed to assess their normal distribution.

Homoscedasticity. The inspection of the variances' distribution around the best fit line was performed in the plot of the studentized residuals versus the unstandardised predicted values.

Influential points and outliers. Cases with a Cook's Distance above 1 (influential points) or with high values of residuals (outliers) should be detected.

The models constructed will be shown with the R^2, non-standardised and standardised regression coefficients with their significance. Standardised regression coefficients show the relative importance of each independent variable and, therefore, they determined the parameters that most contribute to the change of the dependent variable.

4.7.3.5 Repeated ANOVA

The repeated ANOVA is the one-way ANOVA for related samples. Generally, this test is used to assess the differences among repeated measurements taken over several time points or under different conditions. Thus, the independent variable, that is the within-subjects factor, has several levels according to the number of repeated measurements.

This test should be applied for continuous variables approximately normally distributed and the independent variable should have at least two levels. The outliers' presence was checked before running the analysis. Mauchly's test of sphericity was applied when there were more than 2 levels in the within-subjects factor to assess the

equality of the variances between all combinations of related groups. In the case of nonsphericity, the Greenhouse-Geisser correction was applied, which changes the freedom of the distribution of the F statistic. A p-value less than 0.05 was defined as statistically significant in all cases.

4.7.3.6 Two-factor mixed-design ANOVA

Two-factor mixed-design analysis of variance, also known as mixed-design ANOVA, assesses the differences between independent groups when subjects undertake repeated measurements. Thereby, there are two factors: one factor is the between-subjects and the other one is the within-subjects factor. This analysis was generally used to assess the differences between refractive groups (between-subjects factor) over time (within-subjects factor) for the several ocular descriptors. The within-subjects factor, time, had 2 levels: baseline and one-year follow-up measurements. Therefore, mixed ANOVA analysed whether there is an interaction between the refractive group with the changes after the follow-up.

Mixed ANOVA was applied for continuous variables with an approximately normal distribution since this analysis is robust to normality violation. The distribution of the groups' combination and outliers' presence were checked before running the analysis. The homoscedasticity between groups was checked during the analysis with the Levene's test for homogeneity of the variances. Mauchly's test of sphericity was applied when there were more than 2 levels in the within-subjects factor to assess the equality of the variances between all combinations of related groups. In the case of nonsphericity, the Greenhouse-Geisser correction was applied, which changes the freedom of the distribution of the F statistic. A p-value less than 0.05 was defined as statistically significant in all cases.

4.7.3.7 Two-factor mixed-design MANOVA

Two-factor mixed-design multivariate analysis of variance or mixed-design MANOVA analyses the effect of the between-subjects and within-subjects factor (two factors) on a group of dependent variables. The difference from the mixed ANOVA is the grouping of different dependent variables in order to carry out a multivariate analysis. Thus, this analysis was applied to evaluate the effect of the interaction between the two factors throughout several dependent variables, which is also known as the multivariate

effect. Univariate analysis was also performed when the multivariate effect resulted to be significant.

As explained in the previous section, the dependent variables had continuous data and the two factors were categorical with at least two levels. Dependent variables should have an approximately normal distribution and no multicollinearity (correlation $r<0.9$). The distribution of the groups' combination and outliers' presence were checked before running the analysis. Homogeneity of the variances was checked by Levene's test and, when required, Mauchly's test was performed to evaluate the sphericity condition. A p-value less than 0.05 was defined as statistically significant in all cases.

CHAPTER 5. STUDY SAMPLE

5.1 Methodology

The information obtained from the online questionnaire was correctly codified for further analysis. According to the years of study at university, the subjects were classified by the educative level into undergraduate level those students up to the 4th-degree course and the postgraduate level included either master or PhD students. The myopic students were divided depending on the age of onset into early-onset when the age was ≤ 16 years and late-onset when the age was >16 years, as in previous works (Grosvenor and Scott, 1993; Bullimore et al., 2006; González Blanco, Sainz Fernández and Muñoz Sanz, 2008). The reading hours were organized in 5 categories: <2h, 2-4h, 4-6h, 6-8h and >8h. Vision quality for both distance and near was evaluated as bad, normal, good or excellent.

The astigmatism was converted to Jackson's cross-cylinder power vector components J_0 and J_{45} using the method described by Thibos, Wheeler and Horner (1997). Moreover, the change of the refractive variables (sphere, cylinder and SE) was calculated as the values from the follow-up minus the baseline ones. In this way, negative values denote an increment toward negative power while positive values an increment of positive power.

5.2 Statistical analysis

Descriptive analysis of the patient's age, sex and refraction was carried out for baseline and follow-up data. Differences of age distribution between the emmetropic and myopic group were checked with the Mann-Whitney test. A contingency table and Chi-Square Test of Independence were performed to analyse the gender differences between refractive groups. The distribution between refractive groups depending on the educative level, reading hours and the visual quality was compared between refractive groups by means of the Chi-square test. The difference in years studying at university was evaluated by the Mann-Witney test.

The differences in the change of the sphere and SE over time (within-subjects factor) between refractive groups (between-subjects factor) were assessed with a mixed-design ANOVA. The change between visits (within-subjects factor) of refractive astigmatism considering both magnitude and axis (J_0 and J_{45}, dependent variables) between refractive groups (between-subjects factor) was evaluated through a mixed-

design MANOVA. Then, the variation over time for the sphere and SE within each refractive groups was evaluated by means of the non-parametric Wilcoxon test for related samples. Multiple regression analysis was applied to find the variables (from the online questionnaire) that may explain de refractive changes.

Statistical power analysis

Contingency tables. For the baseline sample, the difference in proportions between refractive groups according to the educative level, hours of reading and vision quality using the Chi-square test did not achieve the power of 0.8.

Independent sample comparison. The power of 0.8 power was achieved in all cases setting a medium effect size of 0.65 for the baseline sample while the effect size for the longitudinal sample was 0.75. In the case of J_0 and J_{45}, the analysis did not reach the 0.8 power with a small effect size *d* and, therefore, it was not able to detect very small differences between groups.

Related samples comparison. The comparison between related data (baseline vs follow-up) also presented a statistical power of 0.8 setting an effect size of 0.35.

Mixed ANOVA. This evaluation also offered a power higher than 0.8 considering an effect size f of 0.15 to detect the interaction within-between factors.

Mixed MANOVA. The multivariate analysis of J_0 and J_{45} reached the 0.8 power when the effect size was set at 0.35.

5.3 Baseline results

A sample of 89 university students was assessed and from them, 11 were excluded because they did not meet the criteria established for the refractive classification: 4 exceeded the hyperopia threshold and 7 did not reach the -0.75 D threshold in both meridians. Therefore, a total of 78 (50 females and 28 males) were enrolled in the research with a mean age of 23.46 ± 4.51 years. Although the sample had more proportion of females, there was no significant differences in SE (Mann-Whitney p=0.950) nor age (Mann-Whitney p=0.209) between genders.

Refractive groups consisted of 31 emmetropic subjects (21 females and 10 males) and 47 myopic subjects (29 females and 18 males). The mean age was 23.35 ± 3.97 and

23.53 ± 4.88 years for the emmetropic and myopic group, respectively, and it was not significantly different between groups (Mann-Whitney p = 0.918). There were also no differences in gender distribution between groups (Chi-square p=0.586).

The SE did not differ significantly between males and females within the emmetropic group (Student t-test p=0.644) nor the myopic (Mann-Whitney p=0.381). Refractive data for both groups are presented in Table 5.1. As expected, the sphere and SE differed between groups (Mann-Whitney p<0.001). Moreover, the refractive cylinder resulted to be statistically different (Mann-Whitney p=0.002). The vectorial components J_0 and J_{45} did not evidence significant differences between groups (Mann-Whitney p>0.05).

Table 5.1. Refractive results for the emmetropic and myopic group.

Parameter	Emmetropic group (n=31)	Myopic group (n=47)	p-value
Sphere (D)	0.14 ± 0.36 +0.75 to -0.5	-3.92 ± 3.10 -0.75 to -15.75	<0.001*
Cylinder (D)	-0.31 ± 0.30 0 to -1.25 D	-0.71 ± 0.65 0 to -3.00 D	0.002
SE (D)	0.00 ± 0.30 0.50 to -0.63	-4.27 ± 3.25 -0.75 to -17.25	<0.001*
J_0 (D)	0.03 ± 0.15 0.35 to -0.22	0.08 ± 0.43 1.30 to -0.82	0.564
J_{45} (D)	-0.01 ± 0.12 0.25 to -0.25	0.02 ± 0.26 0.75 to -0.97	0.497

*p-value<0.05

The distribution of undergraduates and postgraduates was similar between the emmetropic and myopic group (Chi-square p=0.221). The students informed to spend on reading mostly between 2 and 6 hours per day, and this was not different between refractive groups (Chi-square p=0.238). The total of years studying at the university neither was different between groups (Mann-Whitney p=0.715). Both refractive groups reported similar appreciation of their visual quality for near (Chi-square p=0.546) and distance (Chi-square p=0.610), considering most of them their vision as good or excellent. Within the myopic group, the average age of myopia onset was 11.72 ± 4.9 years where around 89% had early-onset (before the 16 years). Besides, only 6 emmetropic students

wore refractive compensation, spectacles just part of the day, whereas all myopic students wore compensation more than 8 hours either spectacle or soft contact lens.

5.4 Follow-up results

The follow-up was carried out in 65 of the 78 initial subjects (83.33%) after 12.66 ± 1.17 months. From the 13 who drop-out the follow-up, 6 were from the initial emmetropic group and 7 from the myopic. Thereby, the refractive groups after the follow-up resulted in 25 emmetropic subjects (17 females and 8 males) and 40 myopic subjects (25 females and 15 males). There were no significant differences in age (Mann-Whitney p=0.485) nor gender distribution between refractive groups (Chi-square p=0.652).

For the whole sample, the SE experienced a significant shift of -0.10 ± 0.17 D after a year (Wilcoxon p<0.001). Both sphere and cylinder changed significantly (Table 5.2). The SE change after one-year follow-up did not differ significantly between males and females (-0.10 D vs -0.09 D; Mann-Whitney p=0.606). No change of SE was found in 42 subjects, 21 subjects had an SE shift below -0.50 D and the other 2 subjects had -0.50 and -1.00 D change, respectively. That means more than a half of the sample, 64.62%, remained stable while 33.84% had a change up to -0.50 D. Considering as clinically significant a SE shift of at least -0.25 D, only around 25% of the sample had a significant refractive change.

Table 5.2. Refractive changes in the entire sample.

Parameter	Baseline	One year	Change	p-value
Sphere (D)	-2.58 ± 3.29	-2.66 ± 3.36	-0.07 ± 0.16	<0.001*
Cylinder (D)	-0.58 ± 0.60	-0.63 ± 0.58	-0.05 ± 0.11	0.001
SE (D)	-2.88 ± 3.45	-2.97 ± 3.52	-0.10 ± 0.17	<0.001*

*p-value<0.05

Concretely, the SE underwent a change after the follow-up in 17 initial myopes subjects and 6 initial emmetropic, thus remaining the SE stable for 57.5% of myopes and 76% of the emmetropes. The 88.23% of changing myopes (15 subjects) had a shift beneath -0.50 D and only 5% (2 subjects) exceeded -0.50 D change. Meantime, the total of the changing emmetropes had a shift up to -0.37 D, and these changes did not lead them to become myopic in any case. In general, the changes within each refractive group were not significantly different between genders (Mann-Whitney p=0.977 and p=0.600, for the

emmetropic and myopic group respectively). The average refractive changes for each refractive group are shown in Table 5.3. In the myopic group, 11 subjects underwent a sphere change of -0.25 D, one subject a -0.50 D change and another subject reached a -1.00 D change. The emmetropic group only had 2 subjects who experienced a -0.25 D change in the sphere. The cylinder had a -0.25 D change in 6 subjects in the myopic group and 5 in the emmetropic while 1 myopic subject had a -0.50 D change.

Table 5.3. Refractive changes for the emmetropic and myopic group.

Refractive group	Sample size	Sphere change (D)	Cylinder change (D)	SE change (D)
Emmetropic (n=25)	25	-0.02 ± 0.07 0 to -0.25	-0.05 ± 0.10 0 to -0.25	-0.05 ± 0.09 0 to -0.37
Myopic (n=40)	40	-0.11 ± 0.20 0 to -1.00	-0.05 ± 0.12 0 to -0.50	-0.13 ± 0.20 0 to -1.00

There was an interaction between the change over time with the refractive group for the sphere (mixed ANOVA p=0.038; Figure 5.1) and it did not reach the statistical significance for the SE (mixed ANOVA p=0.05; Figure 5.2). Further, the sphere change over time was only significant for the myopic group (Wilcoxon p=0.001).

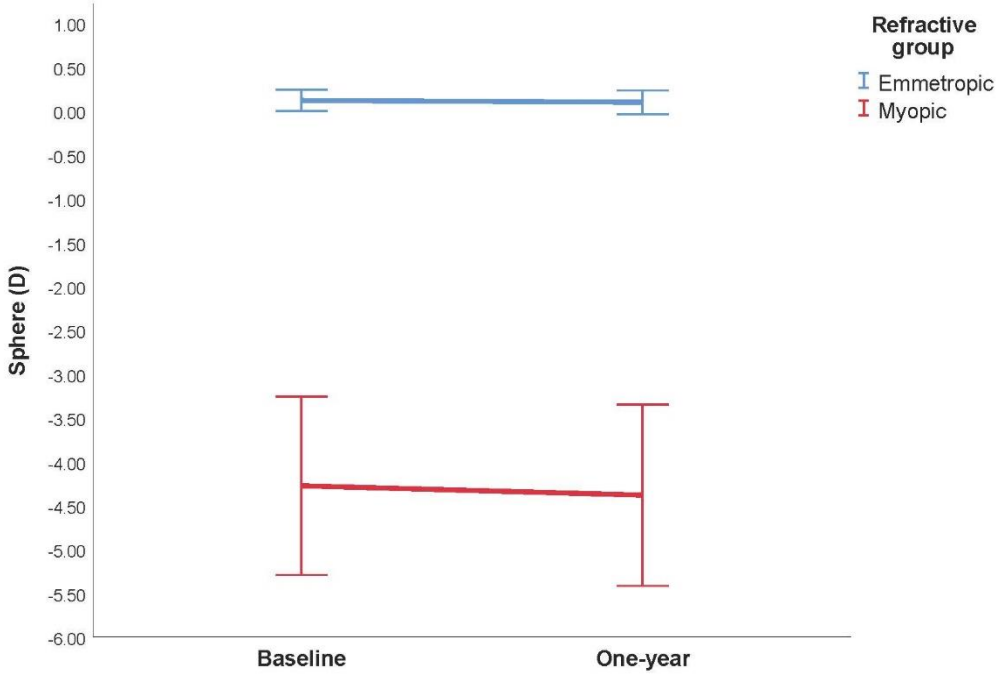

Figure 5.1. Sphere change for the emmetropic and myopic group.

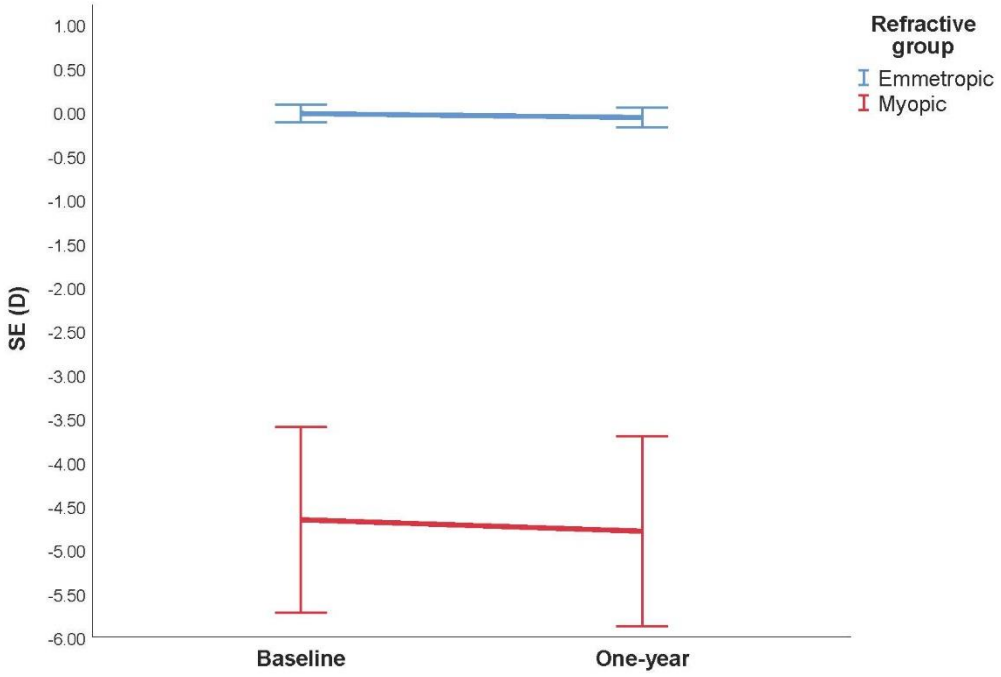

Figure 5.2. SE change for the emmetropic and myopic group.

Astigmatism changes between visits did not differ due to the refractive error considering the cylinder power (mixed ANOVA p=1.000) nor considering altogether J_0 and J_{45} (mixed MANOVA p=0.270). Therefore, the change in the sphere over time resulted to be greater in myopes towards negative values while the astigmatism change was similar between groups. From multiple regression analysis, no model resulted significant to explain the refractive changes as from the variables obtained in the online questionnaire.

5.5 Discussion

Myopia prevalence among young adults has risen over time in Europe, especially in those with higher educational level (Williams et al., 2015a). In Norway, the study of Kinge and Midelfart (1994) noticed lower myopia prevalence in the general young adult population (33%) compared with university students (47%). Besides, within the adult population, those with the highest educational level (>12 years of education) had greater myopia rate than the group with the lowest educational level (37.5% vs 30.2%). Myopia prevalence among university students has been reported to be between 23 and 58% in Caucasians (Kinge and Midelfart, 1994; Kinge, Midelfart and Jacobsen, 1998; Fledelius, 2000; Logan et al., 2005; González Blanco, Sainz Fernández and Muñoz Sanz, 2008; Jorge, Braga and Queirós, 2016). Meanwhile, the informed myopia prevalence in Asians is above

80% (Woo et al., 2004; Wei et al., 2018; Huang et al., 2019; Kato et al., 2019) and even 90% (Sun et al., 2012; Shi et al., 2018).

The present study was carried out to assess the refractive changes of Spanish university students. Our sample was composed of more myopic subjects than emmetropic due to the higher myopia prevalence in this academic population (González Blanco, Sainz Fernández and Muñoz Sanz, 2008). After a year, there was a significant negative shift of the SE in the whole sample of -0.10 ± 0.17 D on average, from -2.88 ± 3.45 D to -2.97 ± 3.52 D. Further, the SE shift was greater in the myopic group (-0.13 ± 0.20 D) than in the emmetropic (-0.05 ± 0.09 D), given also more proportion of emmetropes (76%) were stable in comparison to myopes (57.5%). In particular, the sphere changes were significantly greater in the myopic group whereas the astigmatism changes were similar between refractive groups. This research demonstrated that myopia may keep progressing in some young adults during their university studies. But generally, the refraction of our sample was quite stable since only 25% of the sample had a refractive change of at least -0.25 D.

The increase of the myopia incidence among university students has been widely demonstrated in previous follow-up researches (Lin et al., 1996; Kinge and Midelfart, 1999; Jorge, Almeida and Parafita, 2007; Jacobsen, Jensen and Goldschmidt, 2008; Lv and Zhang, 2012). Longitudinal studies in this academic population have shown refractive changes in Caucasians of -0.16 D/year (Kinge and Midelfart, 1999), -0.10 D/year (Jorge, Almeida and Parafita, 2007) and -0.13 D/year (Jacobsen, Jensen and Goldschmidt, 2008). Likewise, the investigations performed in Asian university students reported changes of -0.12 D/year (Lin et al., 1996) and -0.16 D/year (Lv and Zhang, 2012). Contrary, one study in Turkish medical students (Onal et al., 2007) informed no significant refractive change after one year of follow-up based on the cycloplegic autorefraction. Our average SE change, -0.10 ± 0.17 D/year, is aligned with other investigations performed in Caucasians (Jorge, Almeida and Parafita, 2007; Jacobsen, Jensen and Goldschmidt, 2008). However, it should be taken into account these two studies performed cycloplegic refraction while we did not.

Furthermore, the negative refraction shift was greater in our myopic group than those considered emmetropic, as it also occurred in other studies (Kinge and Midelfart, 1999; McBrien and Adams, 1997; Jacobsen, Jensen and Goldschmidt, 2008). In fact, more

proportion of myopic students had a negative change of refraction so that, in general, the myopic group had 1.77 times more relative risk of myopia progression. One 2-year longitudinal study in an occupational group (McBrien and Adams, 1997) acquired that, from among the subjects having a significant refractive change (SE change ≤ -0.37 D), the negative shift was higher in those already myopes than emmetropes (-0.77 ± 0.04 D and -0.58 ± 0.04 D, respectively). The 3-year follow-up work by Kinge and Midelfart (1999) obtained greater refractive change for the initially myopic students than for those who were emmetropic (-0.66 D and -0.48 D, respectively). The results of this same work revealed a change of -0.13 D/year for the initial myopes (SE ≤ -0.25 D) and -0.09D/year for those emmetropes (-0.25<SE<0.50 D) at baseline, changes which are lower than in the study by McBrien and Adams (1997) but quite similar to our changes per year. Alike, Danish university students who were myopic experienced an average change of -0.40 ± 0.46 D after 2 years while the emmetropic -0.14 ± 0.35 D, that is to say, -0.20 D/year and -0.07 D/year for myopic and emmetropic students, respectively.

In terms of SE, 64.62% of our sample had no change and 33.84% had a negative change up to -0.50 D, which means the refraction of most of the sample may be considered as quite stable after a year. The 2-year research by McBrien and Adams (1997) found 55% of the sample were refractively stable, considering as stability when the SE changes were > -0.37 D. The 3-year follow-up by Jorge, Almeida and Parafita (2007) obtained a myopic shift > -0.50 D in 78% of their sample while 22% had a change ≤ -0.50 D. Further, we did not find refractive differences between genders for baseline results nor the change after the follow-up. Two previous studies acquired slightly higher myopic change in females but it was not significant (Lin et al., 1996; Kinge and Midelfart 1999).

Our refractive changes were mainly produced in those who were already myopic at baseline (42.5% of the myopic group) and only a few emmetropic (24% of the emmetropic group) underwent slight changes but not becoming myopic in any case. Similarly, other authors informed that most of the initial emmetropes remained stables, although some part did also become myopic after the follow-up (McBrien and Adams, 1997; Lin et al., 1996; Kinge and Midelfart, 1999; Lv and Zhang, 2012). The cut-off value to consider one subject becoming myopic is different between studies, though, such as SE ≤ -0.25 D (Lin et al., 1996; Kinge and Midelfart, 1999), SE ≤ -0.375 D (McBrien and Adams, 1997) or SE ≤ -0.50 D (Lv and Zhang, 2012). The 48% of the initial myopes in the

work of McBrien and Adams (1997) experienced a refractive change ≤ -0.37 D after 2-years of follow-up. Kinge and Midelfart (1999) reported 30% of the progressing myopes had a shift more than -1.00 D (up to -2.38 D progression) and 70% progressed by -1.00 D or less after 3 years. Meantime, within our changing myopes, 88.23% had a SE myopic progression beneath 0.50 D while the changing emmetropes had a negative SE shift up to -0.37 D after a year.

The non-use of cycloplegia to obtain the refractive status could be a limitation of the present research. Cycloplegic refraction has been recommended especially in children due to the accommodative effect on the refractive state (Choong, Chen and Goh, 2006; Fotedar et al., 2007). Whereas some authors have considered not necessary the use of cycloplegia in studies of refraction in adults (Krantz et al., 2010; Sanfilippo et al., 2014). Sanfilippo et al. (2014) indicated that the difference between the cycloplegic and non-cycloplegic refraction was not significant in adults between 20-26 years using automatic refraction. Concretely, the refractive difference reported for myopic adults aged between 20-26 years was 0.02 ± 0.45 D. Another study (Hashemi et al., 2015) compared the subjective refraction to the cycloplegic autorefraction obtaining a difference of -0.19 D and -0.34 D for myopic and emmetropic adults, respectively, older than 20 years.

Even though the refraction without cycloplegia might lead to an overestimation of myopia, we believe the cut-off of -0.75 D applied in both meridians ensured to classify the myopic subjects correctly. Indeed, Hashemi et al. (2015) found the subjective refraction had a sensitivity rate higher than 98% to detect myopia (SE < -0.5 D) in adults between 21 and 40 years. However, the negative shift obtained in a part of our sample could be due to accommodative fluctuations between visits, particularly in the cases with small negative changes. Still, this fact would not change the results of myopic subjects since most of them underwent shifts between -0.25 and -1.00 D, a thing that is unlikely to be only due to an accommodative effect.

5.6 Conclusion

The refractive changes of this sample of young university students were mostly quite stable within a year, where around 64% of them did not have any change. However, myopic shifts did also occur in some part of the initial myopic students, though small, demonstrating that myopia may keep progressing during this academic stage.

CHAPTER 6. OCULAR BIOMETRY

6.1 Methodology

The biometric variables analysed were CCT, ACD, LT, and AL. ASL was calculated as the addition of CCT, ACD and LT to subsequently estimate the VCD. VCD represents the distance between the posterior crystalline lens surface and retina, which was determined by subtracting the ASL from the AL. The change of the biometric variables was obtained through the difference between follow-up and baseline visit so that positive values denoted an increment while negative values did a decrease of the biometric magnitudes.

6.2 Statistical analysis

The biometric differences between refractive groups were assessed through the Student t-test for independent samples or the non-parametric Mann-Whitney test, according to each variable distribution. The relationship between the SE and biometric variables as well as the relationship among them was estimated by means of Pearson and Spearman correlation coefficients. Multiple linear regression analysis was also applied. Several stepwise models were constructed to determine the predictor variables for SE, VCD, ACD and LT at baseline. The models included as independent variables the ones that resulted to be significant in the correlation analysis, controlling also for age and sex. Sex was transformed into a categorical variable where males and females were represented with 0 and 1, respectively.

The comparison between baseline and follow-up for the general sample as well as for each refractive group was performed through Student t-test for related samples or the non-parametric Wilcoxon test. Mixed-design ANOVA was carried out to evaluate the change differences between refractive groups after one year of follow-up. The change over time was also compared between refractive groups using the Student t-test for independent samples or the non-parametric Mann-Whitney test in those parameters with a significant interaction between refractive error and the change over time. The relationship between the change of SE and those of the biometric variables as well as the relationship of the biometric changes among them was estimated by means of Pearson and Spearman correlation coefficients. Multiple regression models were also constructed to determine the predictor variables for the changes of SE, VCD, ACD and LT.

Statistical power analysis

Independent sample comparison. For the baseline analysis, the power of 0.8 power was achieved in all cases setting a medium effect size around 0.65. The comparison of the change between visits among refractive groups reached a 0.8 power with a large effect size of 0.75.

Related samples comparison. The general longitudinal comparison between baseline and follow-up had a power of 0.8 with an effect size of 0.35. Power of the analysis accomplished 0.8 with a medium effect size *d* of 0.5 and 0.6 for the comparison within the myopic and emmetropic group, respectively.

Simple linear regression. Including the entire baseline sample, the correlations between SE and the biometric variables had a statistical power above 0.8 with an effect size of 0.3. The correlation analysis for each refractive group separately only reached good power with large effect size and, therefore, it was decided not to be included. For the data of the follow-up, the desired power of 0.8 allowed to detect relationships with an effect size of 0.34.

Multiple linear regression. All constructed models included firstly between 4-5 variables and the required effect size f^2 was medium, according to the correlation magnitudes between biometric parameters. Thereby, a power above 0.8 was obtained for all models in our sample size with a 0.2 effect size f^2.

Mixed ANOVA. The longitudinal changes analysis exceeded 0.8 power with an effect size of 0.15 for all biometric parameters.

6.3 Baseline results

The average magnitudes of the biometric parameters acquired for each refractive group are shown in Table 6.1. There were statistically significant differences between refractive groups for ACD (Student t-test $p<0.001$), ASL (Student t-test $p<0.001$), VCD (Mann-Whitney $p<0.001$) and AL (Mann-Whitney $p<0.001$) where higher magnitudes were found for the myopic group. LT tended to be slightly lower for the myopic group although it was not statistically significant (Student t-test $p=0.159$).

Table 6.1. Biometric magnitudes for the emmetropic and myopic group.

Parameter	Emmetropic (n=31)	Myopic (n=47)	p-value
CCT (µm)	542.00 ± 35.20	543.34 ± 29.08	0.855
ACD (mm)	3.00 ± 0.28	3.28 ± 0.25	< 0.001*
LT (mm)	3.64 ± 0.27	3.56 ± 0.21	0.159
ASL (mm)	7.19 ± 0.22	7.39 ± 0.24	< 0.001*
VCD (mm)	16.2 ± 0.86	17.71 ± 1.30	< 0.001*
AL (mm)	23.39 ± 0.84	25.10 ± 1.32	< 0.001*

*p-value<0.05

For the whole sample, more negative SE correlated with deeper ACD (Spearman $r=-0.501$, $p<0.001$; Figure 6.1) and longer VCD (Spearman $r=-0.746$, $p<0.001$; Figure 6.2). At the same time, longer VCD had a positive relationship with deeper ACD (Pearson $r=0.488$, $p<0.001$) and thinner LT (Spearman $r=-0.420$, $p<0.001$). The quadratic fit explained more variance of ACD and LT with the VCD elongation (Figure 6.3 and Figure 6.4, respectively). Thus, the ACD increase and LT decrease was seen to occur until the VCD was around 20 mm. Besides, ACD and LT interrelated negatively (Spearman $r=-0.583$, $p<0.001$).

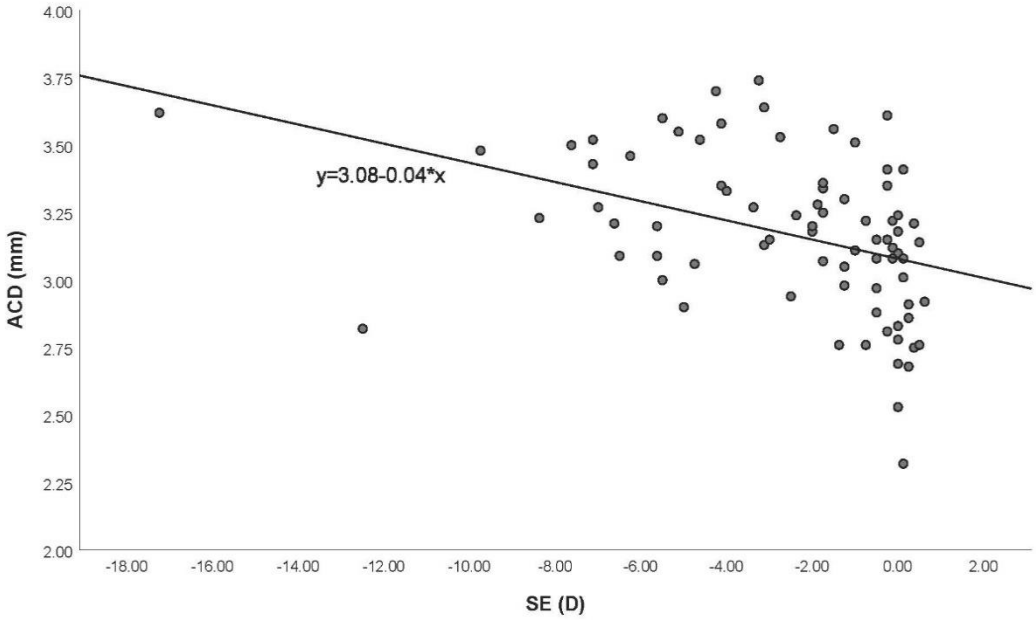

Figure 6.1. Linear relationship between SE and ACD.

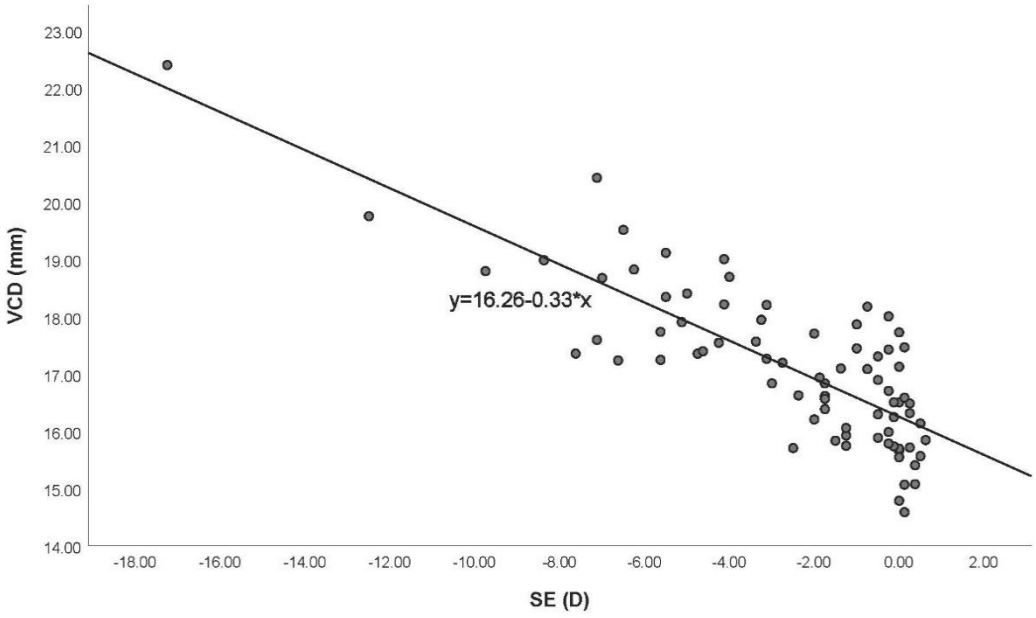

Figure 6.2. Linear relationship between SE and VCD.

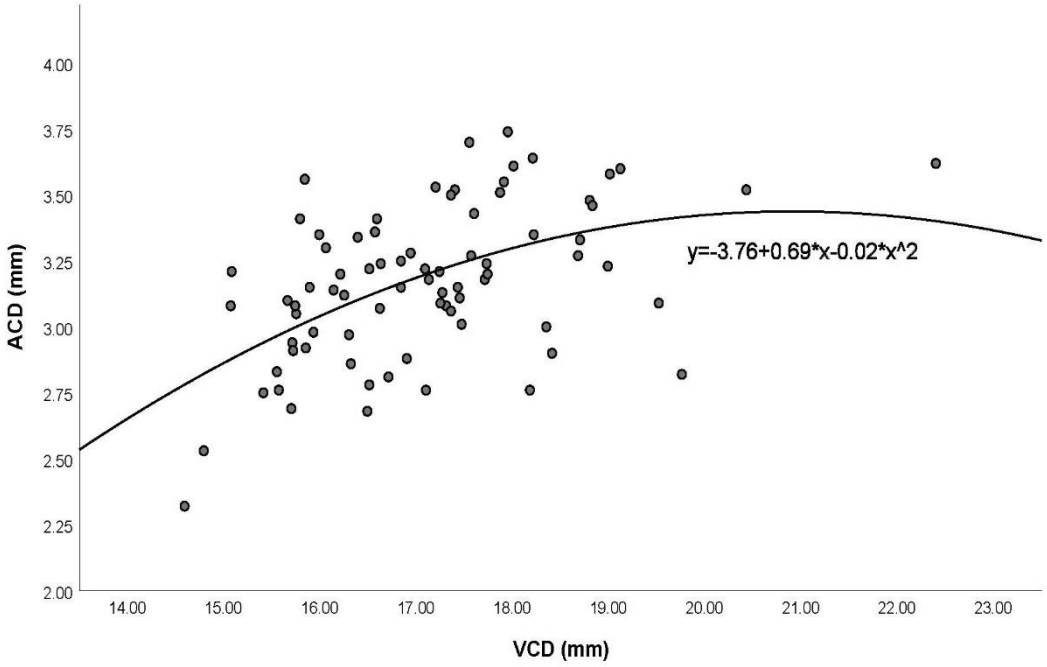

Figure 6.3. Quadratic relationship between VCD and ACD.

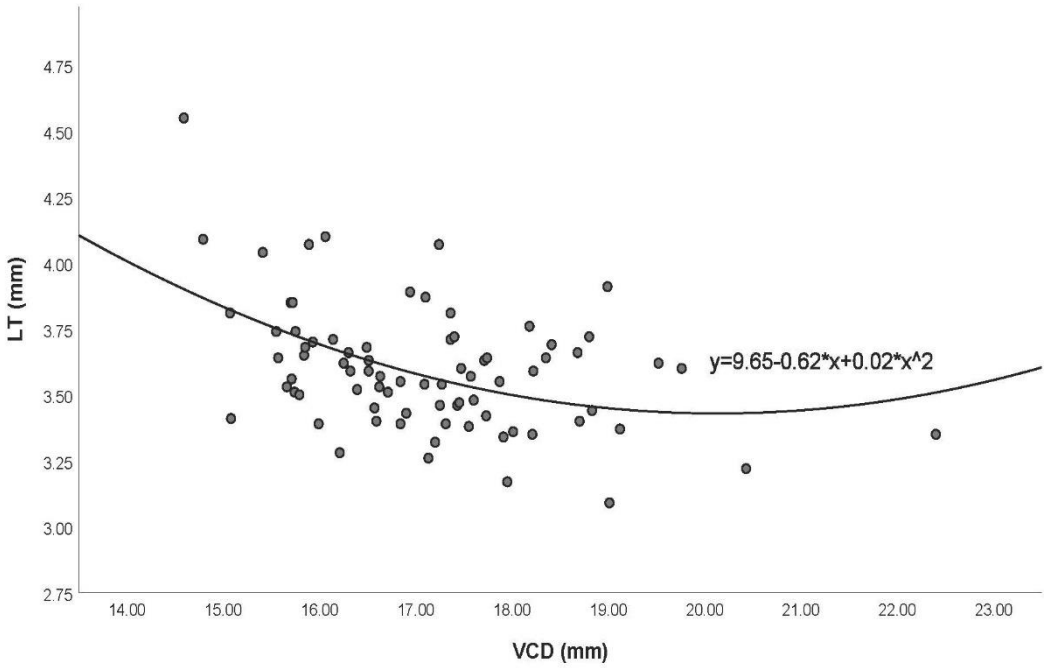

Figure 6.4. Quadratic relationship between VCD and LT.

Multiple linear regression model for SE revealed VCD and sex as significant predictors, explaining 68.2% of its variance (Table 6.2). The model indicated that more negative SE was obtained with longer VCD and that females exhibited more negative refraction. The VCD model accounted for 79.9% variance including SE, LT, sex and age (Table 6.3). More negative SE and thinner LT resulted in longer VCD. Moreover, older age

and male sex also lead to longer VCD. The most important contributor in this model was SE denoted by the higher standardised coefficient compared with the other variables.

Table 6.2. Multiple linear regression model for SE.

	R	R^2	R^2 adjusted	Error	Durbin-Watson
SE (D)	0.826	0.682	0.673	1.878	2.073

	β	SE	Sβ	p-value	Tolerance	VIF
Constant	32.579	2.783	-	p<0.001	-	-
VCD (mm)	-2.006	0.159	-0.830	p<0.001	0.981	1.019
Sex	-1.287	0.448	-0.189	p<0.001	0.981	1.019

Table 6.3. Multiple linear regression model for VCD.

	R	R^2	R^2 adjusted	Error	Durbin-Watson
VCD (mm)	0.898	0.799	0.788	0.626	2.453

	β	SE	Sβ	p-value	Tolerance	VIF
Constant	23.203	1.109	-	p<0.001	-	-
SE (D)	-0.314	0.022	-0.758	p<0.001	0.962	1.040
LT (mm)	-2.205	0.345	-0.387	p<0.001	0.754	1.327
Age (year)	0.055	0.018	0.183	0.003	0.764	1.309
Sex	-0.404	0.151	-0.144	0.009	0.956	1.046

Meanwhile, the model for ACD (Table 6.4) and LT (Table 6.5) explained lower variability (49.6% and 47.7%, respectively) than the one obtained for VCD. LT, SE and sex were predictor variables for ACD while for LT only were ACD and age. Thus, deeper ACD arose with thinner LT, more negative SE and male sex. Conversely, thicker LT was present with shallower ACD as well as an older age.

Table 6.4. Multiple linear regression model for ACD.

	R	R^2	R^2 adjusted	Error	Durbin-Watson
ACD (D)	0.705	0.496	0.476	0.211	1.863

	β	SE	Sβ	p-value	Tolerance	VIF
Constant	5.452	0.369	-	p<0.001	-	-
LT (mm)	-0.632	0.102	-0.518	p<0.001	0.973	1.027
SE (D)	-0.031	0.007	-0.347	p<0.001	0.973	1.027
Sex	-0.138	0.050	-0.230	0.007	0.987	1.014

Table 6.5. Multiple linear regression model for LT.

	R	R^2	R^2 adjusted	Error	Durbin-Watson
LT (mm)	0.690	0.477	0.463	0.175	1.962

	β	SE	Sβ	p-value	Tolerance	VIF
Constant	4.503	0.258	-	p<0.001	-	-
ACD (mm)	-0.432	0.069	-0.527	p<0.001	0.978	1.023
Age (years)	0.020	0.004	0.374	p<0.001	0.978	1.023

6.4 Follow-up results

In general, there was a significant change after one year in ACD, LT, VCD and AL (Student t-test p<0.001). LT and VCD increased significantly while ACD decreased, which turned out to an AL increment. The biometric parameters obtained in both visits are shown in Table 6.6.

Table 6.6. Biometric changes in the entire sample.

Parameter	Baseline	One year	Change	p-value
CCT (µm)	541.12 ± 30.65	541.45 ± 31.80	0.32 ± 6.52	0.691
ACD (mm)	3.19 ± 0.30	3.17 ± 0.30	-0.02 ± 0.04	<0.001*
LT (mm)	3.59 ± 0.24	3.61 ± 0.25	0.03 ± 0.05	<0.001*
ASL (mm)	7.32 ± 0.24	7.33 ± 0.25	0.01 ± 0.03	0.067
VCD (mm)	17.21 ± 1.42	17.24 ± 1.45	0.03 ± 0.07	<0.001*
AL (mm)	24.53 ± 1.48	24.57 ± 1.52	0.04 ±0.07	<0.001*

*p-value<0.05

The change between baseline and follow-up visits did not differ comparing both refractive groups for ACD, LT, CCT and ASL (mixed ANOVA p>0.05). Refractive error did have a significant effect on the change of AL (mixed ANOVA p=0.030; Figure 6.5) and for VCD it was almost significant (mixed ANOVA p=0.054; Figure 6.6). ACD underwent a significant decrease in the emmetropic (Student t-test p=0.031) and myopic group (Student t-test p=0.001). Then, LT had a significant increase in the emmetropic (Student t-test p=0.041) and myopic group (Student t-test p<0.001). Table 6.7 includes the biometric changes for each refractive group. AL changed significantly between visits within both refractive groups (Student t-test p<0.001) but the myopic group experienced higher AL change (Student t-test p=0.013). VCD underwent a significant elongation after one year in the myopic group (Wilcoxon test p=0.001) while it was not significant for the emmetropic group (Student t-test p=0.199).

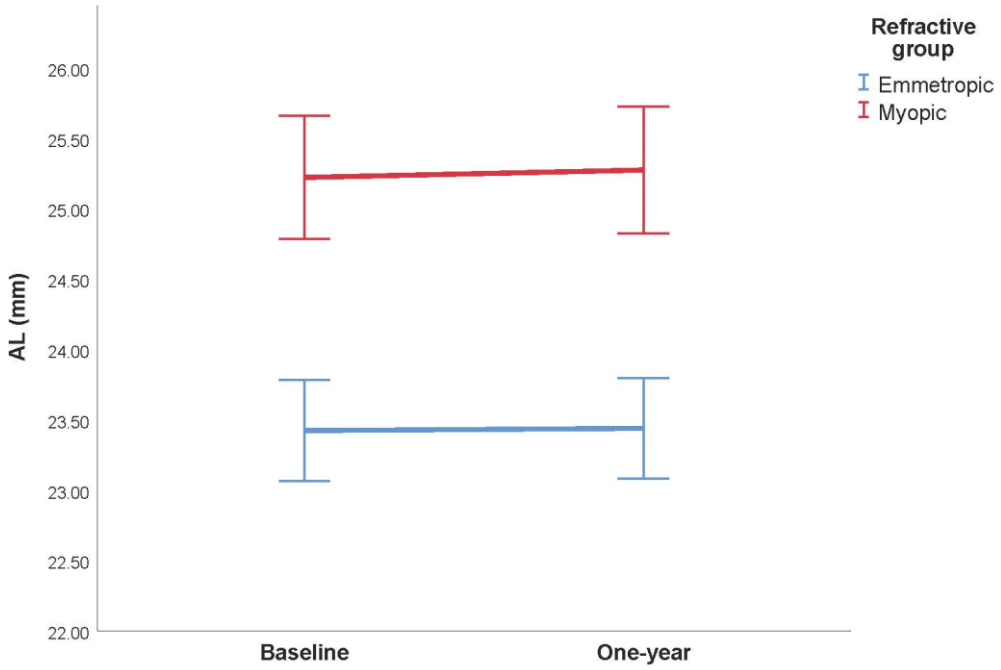

Figure 6.5. AL change obtained for the myopic and emmetropic group. Error bars: 95%CI.

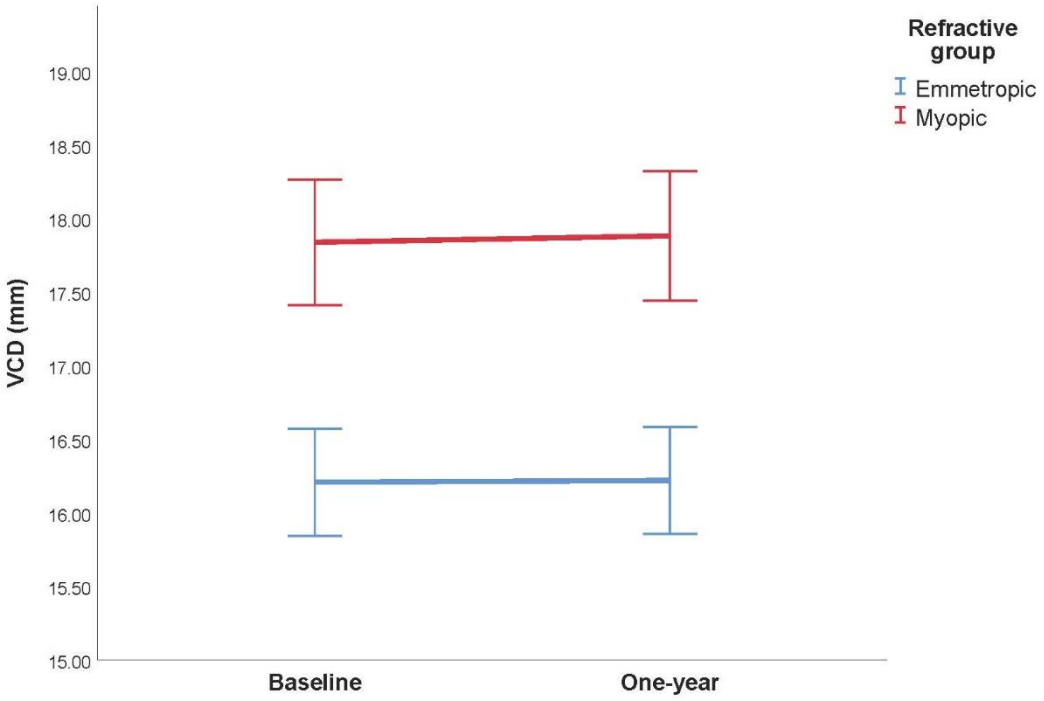

Figure 6.6. VCD change for the myopic and emmetropic group. Error bars: 95%CI.

Table 6.7. Biometric changes for the emmetropic and myopic group.

Parameter	Emmetropic (n=25)	Myopic (n=40)
Change CCT (μm)	1.24 ± 6.26	-0.25 ± 6.69
Change ACD (mm)	-0.03 ± 0.04*	-0.02 ± 0.04*
Change LT (mm)	0.02 ± 0.05*	0.03 ± 0.04 *
Change ASL (mm)	0.01 ± 0.03	0.01 ± 0.03
Change VCD (mm)	0.01 ± 0.04	0.04 ± 0.07*
Change AL (mm)	0.02 ± 0.04*	0.05 ± 0.08*

*p-value<0.05

The SE change was negatively associated with the changes of AL (Spearman r=-0.497, p<0.001) and VCD (Spearman r=-0.445, p<0.001; Figure 6.7). LT change had negative correlations with ACD change (Spearman r=-0.643, p<0.001; Figure 6.8) and with VCD change (Spearman r=-0.363, p=0.003; Figure 6.9). Overall, AL change was related to the change of ACD (Spearman r=0.245, p=0.049) and VCD (Spearman r=0.791, p<0.001).

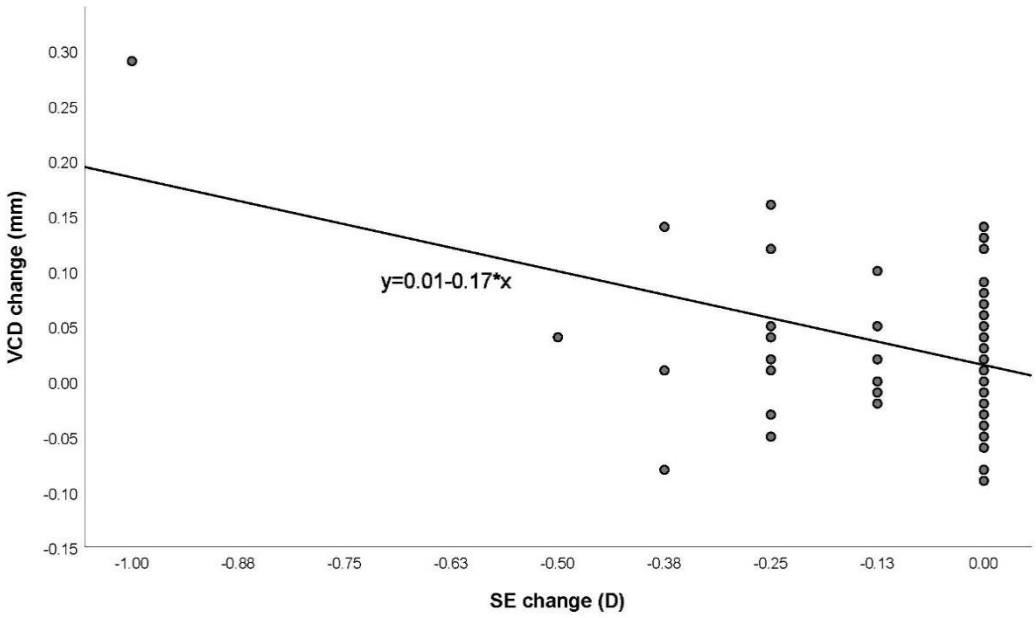

Figure 6.7. Linear relationship between the changes of SE and VCD.

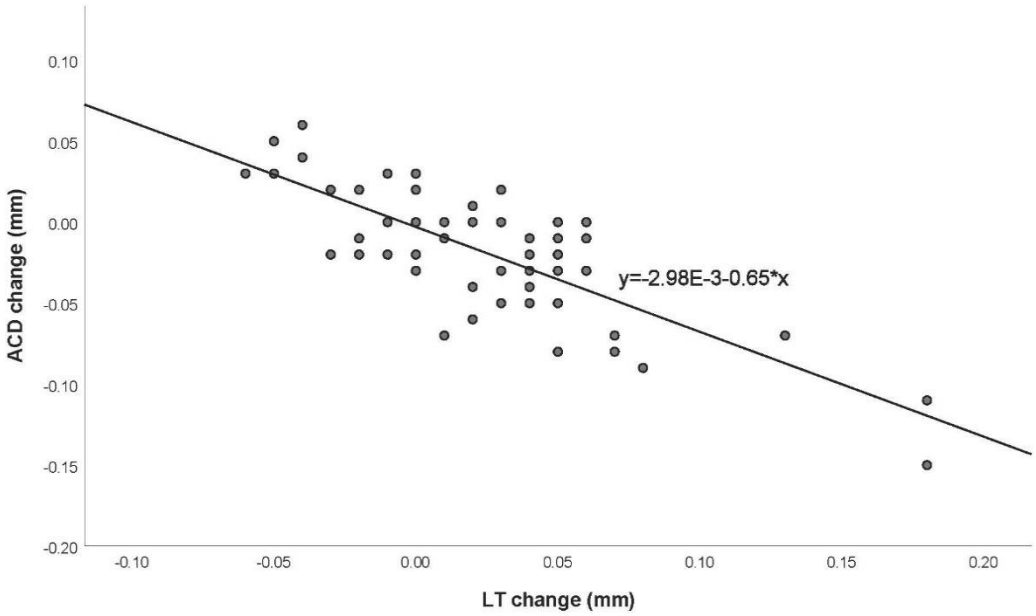

Figure 6.8. Linear relationship between the changes of LT and ACD.

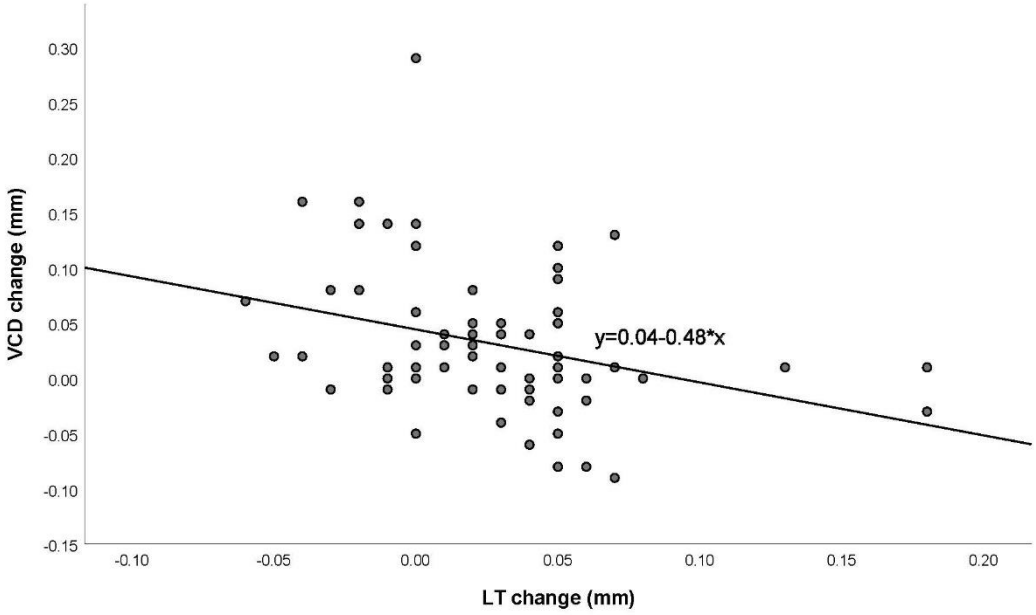

Figure 6.9. Linear relationship between the changes of LT and VCD.

Multiple regression analysis showed the VCD change as the only predictor for the SE change (Table 6.8), accounting for a small part of SE change variability (19.8%). Each 1 mm enlargement of VCD would increase the SE by -1.16 D.

Table 6.8. Multiple linear regression model for the SE change.

	R	R^2	R^2 adjusted	Error	Durbin-Watson
SE change	0.445	0.198	0.185	0.156	1.891

	β	SE	Sβ	p-value	Tolerance	VIF
Constant	-0.061	0.022	-	0.006	-	-
VCD change (mm)	-1.163	0.295	-0.445	p<0.001	1.00	1.000

At the same time, 57.2% variance of the VCD change was related to the SE change alongside the LT change and the subjects' age (Table 6.9). A negative shift of -0.50 D will result in an increment of VCD by 0.07 mm. Each 0.1 mm of LT thickening resulted in a VCD diminution of 0.04 mm. The age role in this model was that VCD lengthened less with older age.

Table 6.9. Multiple linear regression model for VCD change.

	R	R^2	R^2 adjusted	Error	Durbin-Watson
VCD change	0.572	0.327	0.294	0.055	1.957

	β	SE	Sβ	p-value	Tolerance	VIF
Constant	0.104	0.037	-	0.007	-	-
SE change (D)	-0.149	0.041	-0.391	p<0.001	0.978	1.022
LT change (mm)	-0.430	0.155	-0.293	0.007	0.987	1.013
Age (year)	-0.003	0.001	-0.226	0.036	0.987	1.022

The model for LT changes accounted for 62.9% of its variability including ACD and VCD changes (Table 6.10). Every 0.1 mm increase of ACD and VCD yielded to an LT decrease of 0.09 mm and 0.01 mm, respectively.

Table 6.10. Multiple linear regression model for LT change.

	R	R^2	R^2 adjusted	Error	Durbin-Watson
LT	0.793	0.629	0.617	0.028	1.766

	β	SE	Sβ	p-value	Tolerance	VIF
Constant	0.012	0.004	-	p<0.001	-	-
ACD change (mm)	-0.890	0.095	-0.741	p<0.001	0.950	1.053
VCD change (mm)	-0.110	0.054	-0.162	0.046	0.950	1.053

Finally, the changes of AL were produced by VCD, LT, ACD and CCT changes, accounting for 99.3% of its variance (Table 6.11). According to the standardised coefficients of the model, the VCD change was the most significant contributor to AL changes followed by LT and ACD changes.

Table 6.11. Multiple linear regression model for AL change.

	R	R^2	R^2 adjusted	Error	Durbin-Watson
AL	0.997	0.993	0.993	0.005	1.959

	β	SE	Sβ	p-value	Tolerance	VIF
Constant	0.001	0.001	-	0.419	-	-
VCD change (mm)	0.987	0.011	0.990	p<0.001	0.888	1.126
LT change (mm)	0.989	0.027	0.676	p<0.001	0.324	3.085
ACD change (mm)	0.979	0.030	0.558	p<0.001	0.368	2.716
CCT change (mm)	0.001	<0.001	0.085	p<0.001	0.871	1.149

6.5 Discussion

This part of the present research analysed the main biometric differences between emmetropes and myopes in a sample of university students. The longitudinal biometric changes after a year were also assessed alongside the refractive changes in order to determine the effect of them in myopia progression.

6.5.1 Biometric differences related to myopia

The myopic group of this study manifested deeper ACD as well as longer VCD and AL. There was also a tendency of slightly thinner LT in the myopic group, though no statistically significant, but aligned with the negative association found between VCD and LT. The main contributor to SE was the VCD where 1 mm of longer VCD yielded to -2.00 D shift within our sample.

The CCT values of this research are aligned with those obtained previously in young adults (Al-Mezaine et al., 2008; O'Donnell, Hartwig and Radhakrishnan, 2011; Ortiz et al., 2014; Martínez-Albert et al., 2018). Our sample did not exhibit significant CCT differences because of myopia nor CCT was related to the SE, VCD or AL. Likewise, most of the studies have not identified significant CCT differences between emmetropes and myopes neither an association between myopia and CCT (Tong et al., 2004b; Pedersen, Hjortdal and Ehlers, 2005; Fam et al., 2006; Al-Mezaine et al., 2008; O'Donnell, Hartwig

and Radhakrishnan, 2011; Ortiz et al., 2014; Hashmani et al., 2017). Besides, Pekel et al. (2015) acquired no significant differences in any corneal layer associated with myopia.

On the contrary, higher myopia was associated with either thinner CCT in some investigations (Chang et al., 2001; Uçakhan et al., 2008; AlMahmoud et al., 2011; Kim et al., 2016) and thicker CCT in others (Kunert et al., 2003; Wang, Dong and Wu, 2015; Mimouni et al., 2017; Kato et al., 2019). The AL range might have a role in the way CCT and myopia interrelate. Generally, CCT has not been significantly related to AL (Shimmyo and Orloff, 2005; Oliveira et al., 2006; Tomais et al., 2008; Chen et al., 2009). However, Chung and Park (2016) identified a positive relationship between CCT and AL (r=0.255) within the high myopic group (SE < -6.00 D) in spite of the fact this same group exhibited significant thinner CCT compared to the other myopic groups. Similarly, the myopic subjects with an AL > 28.5 mm presented significantly thicker CCT than those with an AL between 24.5 and 26.5 mm in the investigation by Khokhar et al. (2017). As seen, results are controversial probably due in part to the different sample characteristics and measurement methodologies employed. Nevertheless, the associations of the above studies, though significant, were weak and with little clinical relevance.

Regarding ACD, there is no consensus among studies since some authors reported deeper ACD for myopes (Grosvenor and Scott, 1991; McBrien and Adams, 1997; Onal et al., 2007; Xie et al., 2009; O'Donnell, Hartwig and Radhakrishnan, 2011) while others did not find differences between emmetropes and myopes (Goss et al., 1997; Kinge et al., 1999; Mallen et al., 2005; González Blanco, Sainz Fernández and Muñoz Sanz, 2008). The controversial findings between researches may be attributed to the differences in ACD measurement methodology. Particularly, ACD has been frequently measured from the corneal epithelium, thus ACD containing also the CCT which could act as a confounder factor. Our ACD values are aligned with those obtained by O'Donnell, Hartwig and Radhakrishnan (2011), who also measured ACD as the distance from corneal endothelium to the anterior lens surface. They found an average ACD of 2.92 ± 0.31 mm and 3.17 ± 0.29 mm for the non-myopic and myopic group, respectively. Grosvenor and Scott (1991) informed that ACD differed between youth-onset myopes and emmetropes, being not significant when adult-onset myopia was considered. Thereby, ACD differences seem not to be enough remarkable when myopia has had a few years of progression.

Simple linear regression has also shown deeper ACD associated with more myopic error in university students (Logan et al., 2005; Mallen et al., 2005; Bullimore et al., 2006; O'Donnell, Hartwig and Radhakrishnan, 2011; Kato et al., 2019) although some authors did not find this association (González Blanco, Sainz Fernández and Muñoz Sanz, 2008; Xie et al., 2009). In general, the correlation reported in preceding studies, *r* between -0.12 and -0.3, was lower than ours (Logan et al., 2005; Mallen et al., 2005; Bullimore et al., 2006; O'Donnell, Hartwig and Radhakrishnan, 2011; Kato et al., 2019). The relationship between ACD and myopic refraction is likely to be linked to the axial elongation produced in myopia. Indeed, longer VCD was related to deeper ACD in the present work (r=0.485) like in previous ones (Hosny et al., 2000; Rabsilber et al., 2003; O'Donnell, Hartwig and Radhakrishnan, 2011; Chung and Park, 2014). But, despite ACD getting deeper as myopia progresses through the eye elongation, this linear relationship seems no to be maintained when the eye exceeds certain elongation. Hosny et al. (2000) and Chung and Park (2014) determined the ACD did no increase when AL exceeded 26-27 mm (Hosny et al., 2000; Chung and Park, 2014). Likewise, it occurred in this work when VCD reached around 20 mm. Contrary, one recent investigation in myopes (Khokhar et al., 2017) did not detect this correlation between ACD and AL.

Even though not reaching the statistical significance, LT tended to be thinner in myopes (3.56 ± 0.21 mm) compared to emmetropes (3.64 ± 0.27 mm). In fact, longer VCD associated with thinner LT in both simple and multiple regression analysis. Significant thinner LT was obtained in myopes than emmetropes in two former studies in young adults (Mallen et al., 2005; O'Donnell, Hartwig and Radhakrishnan, 2011) whereas in others was not (Goss et al., 1997; Onal et al., 2007; González Blanco, Sainz Fernández and Muñoz Sanz, 2008; Xie et al., 2009; Richdale et al., 2016). Agreeing with us, longer AL was linked significantly with thinner LT (O'Donnell, Hartwig and Radhakrishnan, 2011; Xie et al., 2009; Muralidharan et al., 2019). Meanwhile, this association did not attain the significance for other authors (Goss et al., 1997; Mallen et al., 2005; Bullimore et al., 2006; González Blanco, Sainz Fernández and Muñoz Sanz, 2008; Richdale et al., 2016). The trend of LT to thin with eye elongation was maintained in our sample until VCD was around 20 mm. Further, longer AL led to a greater equatorial diameter of the crystalline lens in one recent research (Muralidharan et al., 2019) but with constant lens volume, pointing out the lens stretching and equatorial expansion in myopia are produced because of lens remodelling.

Moreover, LT and ACD manifested an inverse relationship, as in the work by O'Donnell, Hartwig and Radhakrishnan (2011), so as thinner LT was present in subjects with deeper ACD. Multiple regression revealed that the LT was thicker with older age, increasing 0.02 mm/year which agrees with other authors (Jones, Atchison and Pope, 2007; Atchison et al., 2008; Richdale et al., 2013). Consequently, ACD experiences a reduction because of the lens thickening with age (Atchison et al., 2008; Richdale et al., 2013). This reduction was also seen in our research where ACD decreased around two-thirds of the LT increment, confirming prior findings (Atchison et al., 2008; Richdale et al., 2013; Richdale et al., 2016).

Former studies in young adults have detected longer VCD in myopes (Grosvenor and Scott, 1991; Goss et al., 1997; McBrien and Adams, 1997; Kinge et al., 1999; Onal et al., 2007; Xie et al., 2009) as we also have. In Caucasian young adults (Grosvenor and Scott, 1991; Goss et al., 1997; McBrien and Adams, 1997; Kinge et al., 1999; Onal et al., 2007), the average VCD ranged between 16.12 and 16.35 mm for emmetropes while it did between 17.11 and 17.85 mm for myopes, which agree with our results. Other authors have not assessed the VCD but reported longer AL (Llorente et al., 2004; González Blanco, Sainz Fernández and Muñoz Sanz, 2008; Logan et al., 2005; O'Donnell, Hartwig and Radhakrishnan, 2011; Kato et al., 2019).

The negative association of SE with both VCD (r=-0.746) and ACD (r=-0.501) obtained in this study matches with the significantly higher values of these parameters seen in myopes. Nonetheless, only VCD proved to be a significant predictor of the SE in multiple regression analysis, explaining 69% of the SE variance. Our correlation between SE and VCD was greater than the one found anteriorly by Mallen et al. (2005) and Xie et al. (2009), which was -0.48 and -0.667, respectively. Some authors (Logan et al., 2005; O'Donnell, Hartwig and Radhakrishnan, 2011; Kato et al., 2019) did acquire a strong relationship between AL and SE (r above -0.7) whereas for others (Mallen et al., 2005; Bullimore et al., 2006) it resulted rather moderate (r around -0.5). The work of González Blanco, Sainz Fernández and Muñoz Sanz (2008) showed that this correlation was stronger in moderate myopia (r=-0.62) than low myopia (r=-0.39).

6.5.2 Biometric changes alongside myopia progression

After one year, our results demonstrated different VCD changes between refractive groups, where myopes exhibited higher VCD elongation (0.04 ± 0.07 mm) than emmetropes (0.02 ± 0.04 mm). Indeed, the VCD change was the only significant predictor of the SE change so that more VCD elongation conducted to a greater negative shift of SE. These results agreed with the greater SE change found in the myopic group (Chapter 5). Meanwhile, ACD and LT also changed between visits although these were similar for both refractive groups and were not related to the SE change.

Broadly, ACD has not shown significant changes with myopia progression in university students (Grosvenor and Scott, 1993; Lin et al., 1996; McBrien and Adams, 1997; Kinge et al., 1999; Jorge, Almeida and Parafita, 2007; Onal et al., 2007). Some authors found an ACD reduction (Jorge, Almeida and Parafita, 2007; Onal et al., 2007) as we also did. Meantime, LT manifested significant changes over time in several studies. In professional adults (McBrien and Adams, 1997), LT was thinner in myopes and those with a myopic shift of the SE after 2 years of follow-up albeit it did not produce lens power change. A thickening of LT was seen in other longitudinal studies (Kinge et al., 1999; Jorge, Almeida and Parafita, 2007; Onal et al., 2007) similar in magnitude to ours. Besides, the LT increase has been also similar comparing emmetropic and myopic subjects in these anterior studies (Kinge et al., 1999; Jorge, Almeida and Parafita, 2007; Onal et al., 2007). The regarded LT thickening was not related to refractive changes but rather was an age-related change as proved previously (Jones, Atchison and Pope, 2007; Atchison et al., 2008; Richdale et al., 2013). The ACD decrease has been also a finding related to age since is a direct consequence of the LT increment (Atchison et al., 2008; Richdale et al., 2013). Accordingly, our LT changes interrelated negatively with the ACD changes (r= -0.643).

As perceived in this research, the eye keeps growing in young adulthood (Grosvenor and Scott, 1993; Lin et al., 1996; McBrien and Adams, 1997; Kinge et al., 1999; Santodomingo-Rubido, Gilmartin and Wolffsohn, 2005; Jorge, Almeida and Parafita, 2007; Jacobsen, Jensen and Goldschmidt, 2008; Lee et al., 2020). The longitudinal researches performed in university students have evidenced an axial enlargement above ours (Lin et al., 1996; Kinge et al., 1999; Santodomingo-Rubido, Gilmartin and Wolffsohn, 2005; Jorge, Almeida and Parafita, 2007; Jacobsen, Jensen and Goldschmidt, 2008). However,

one study (Onal et al., 2007) in Turkish university students obtained no significant changes in VCD nor AL after one year of follow-up. Particularly, the reported VCD elongation rates in Caucasians are 0.09 mm/year (Kinge et al., 1999) and 0.07 mm/year (Jorge, Almeida and Parafita, 2007). The total AL increase determined formerly was 0.11 mm/year (Kinge et al., 1999; Jorge, Almeida and Parafita, 2007) and around 0.06 mm/year (Santodomingo-Rubido, Gilmartin and Wolffsohn, 2005; Jacobsen, Jensen and Goldschmidt, 2008), then again greater than our AL change. In this investigation, multiple linear regression showed that the VCD was the most contributor to the AL changes followed by LT and ACD.

When considering the type of refractive error, myopic adults have demonstrated to exhibit greater VCD enlargement than emmetropic (Grosvenor and Scott, 1993; McBrien and Adams, 1997; Kinge et al., 1999). Similar to us, Grosvenor and Scott (1993) obtained a VCD increase of 0.02 mm/year in emmetropes while a rate of 0.03 mm/year and 0.036 mm/year in youth-onset and adult-onset myopes, respectively. Greater VCD change was found in other two studies (McBrien and Adams, 1997; Kinge et al., 1999) where myopes had an increment above 0.1 mm/year. Progressing myopes had higher VCD increment than those with stable refraction in the work by McBrien and Adams (1997). Recently, one study (Lee et al., 2020) in high myopes (SE < -6.00D) reported that the annual VCD enlargement decreased from 0.18 mm/year to 0.04 mm/year after 20 years of age. Thus, axial elongation can continue to progress in adults although at a lower rate.

The total refractive shift of our sample was -0.10 ± 0.17 D (Chapter 5) where myopes underwent a significantly higher negative shift than emmetropes (-0.13 ± 0.20 D vs -0.05 ± 0.09 D). The VCD increase was the main biometric parameter responsible for the negative refractive change whereas ACD and LT changes were not related with this negative shift, conformed to the results of former investigations (Grosvenor and Scott, 1993; Lin et al., 1996; McBrien and Adams, 1997; Kinge et al., 1999; Jorge, Almeida and Parafita, 2007; Lee et al., 2020). Overall, the subjects with more VCD elongation have shown greater negative shift among studies (Grosvenor and Scott, 1993; Kinge et al., 1999; Jorge, Almeida and Parafita, 2007; Lee et al., 2020). In the work of Kinge et al. (1999), refractive changes between -0.50 and -0.99 D had an average VCD raise of 0.37 ± 0.36 mm while shifts above -1.00 D had a VCD enlargement of

0.47 ± 0.18 mm. Considering every 1 mm increase of AL generally lead to -3.00 D shift of SE, our AL changes are quite in agreement with the negative refractive changes observed.

6.6 Conclusion

This research found that the myopic students had significantly deeper ACD and longer VCD than the emmetropic. LT also tended to be slightly thinner in myopic eyes but it did not result to be significant. Longitudinal follow-up revealed that VCD, ACD and LT changed significantly after a year, nevertheless, only the VCD change was related to the refractive changes. Compared to the emmetropes, myopic students showed higher VCD elongation agreeing with their greater SE negative shift. Mostly, the VCD increment was responsible for the SE changes in both myopia and emmetropia as well as the most contributor to the total AL change.

CHAPTER 7. CORNEAL EXAMINATION

7.1 Methodology

The measurements taken on the cornea consisted of its thickness, diameter, curvature, shape and elevation. The CT was acquired in the following corneal zones: from 0 to 2 mm; from 2 to 5 mm; from 5 to 7 mm, and from 7 to 10mm. The corneal diameter, also known as WTW, was measured as the horizontal distance between the corneal limbus borders. The keratometry variables of steep K, flat K and astigmatism were firstly assessed in the central 4.5 mm. Then, keratometry was examined in the central (0-3 mm), paracentral (3-6 mm) and peripheral cornea (6-9 mm). The corneal shape analysis was carried out with data of eccentricity, asphericity and shape factor. Measurements of eccentricity at different meridional orientations (0, 10, 15, 20, 25 and 30°) were also included in the analysis. Corneal elevation was determined by means of spherical and toric fit. Thus, the BFS and toric ellipsoid, which is the fit for flat and steep meridian, were obtained at an 8 mm corneal zone. Finally, the AL/CR ratio was calculated as the ratio between AL and CR both expressed in mm. The change of all these variables was computed as the difference between follow-up and baseline visit.

7.2 Statistical analysis

The differences between refractive groups for all corneal variables were analysed using the Student t-test for independent samples. The keratometry and CT changes through different corneal zones were analysed with the repeated ANOVA in the entire sample. Mixed ANOVA was applied to find out if the change through corneal zones differed between refractive groups. Pairwise zone comparisons were done using the Student t-test for paired samples. Repeated ANOVA was also applied to assess the eccentricity change among different corneal meridians and the mixed ANOVA to subsequently assess the interaction between the eccentricity change through meridians and the refractive error. The relationship of the corneal parameters with the refractive and biometric ones was estimated using Pearson and Spearman correlation coefficients.

The student t-test was conducted to assess the longitudinal changes between baseline and one-year follow-up for the entire sample. The interaction between the changes over time and the refractive error was evaluated with mixed ANOVA analysis. The comparison between baseline and follow-up within each refractive group was performed through Student t-test for related samples or the non-parametric Wilcoxon

test. The change over time was compared between refractive groups using the Student t-test and the non-parametric Mann-Whitney test. The relationship between the change of SE and those of the corneal variables as well as the relationship of the corneal changes among them was estimated by means of Pearson and Spearman correlation coefficients. Finally, multiple linear regression analysis was also applied to determine the predictor variables for SE considering the corneal curvature and the ocular biometric variables (from Chapter 6), controlling for age and sex. Sex was transformed into a categorical variable where males and females were represented with 0 and 1, respectively.

Statistical power analysis

Independent sample comparison. The power of 0.8 power was achieved in all cases setting a medium effect size of 0.65 for the baseline sample while the effect size for the longitudinal sample was 0.75.

Related samples comparison. The power analysis was 0.8 considering an effect size of 0.35 for both baseline and longitudinal sample. The comparison within refractive groups in the longitudinal analysis accomplished 0.8 power with a medium effect size *d* of 0.5 and 0.6 for the comparison within the myopic and emmetropic group, respectively.

Repeated ANOVA. The power was above 0.8 with an effect size of 0.1 for the analysis through corneal zones as well as corneal meridians.

Mixed ANOVA. The corneal zones and meridians analysis for the baseline sample had almost 0.8 power with an effect size of 0.1. The analysis of the longitudinal changes exceeded the 0.8 power with an effect size of 0.15.

Simple linear regression. Including the entire baseline sample, the correlations between SE and the corneal variables had statistical power above 0.8 with an effect size above of 0.3. For the data of the follow-up, the desired power of 0.8 allowed to detect relationships with an effect size of 0.34.

Multiple linear regression. The SE model constructed for the baseline sample had a power above 0.8 with a 0.2 effect size f^2.

7.3 Baseline results

7.3.1 Corneal thickness and diameter

The average CT changed among the corneal zones (repeated ANOVA p<0.001; Figure 7.1) as well as the minimum and maximum values (repeated ANOVA p<0.001). There was an increase in the CT from the centre to the periphery of the cornea (Student t-test p<0.001 in all pairwise comparisons). Table 7.2 encloses the CT for the different corneal zones.

Table 7.1. CT by corneal zones in the entire sample.

Zone	Min (µm)	Average (µm)	Max (µm)
0 -2 mm	528.59 ± 30.09	536.83 ± 30.01	551.37 ± 30.79
2-5 mm	529.23 ± 30.45	555.49 ± 31.62	603.04 ± 35.51
5-7 mm	541.94 ± 32.83	591.64 ± 33.48	657.87 ± 38.41
7-10 mm	568.32 ± 35.31	649.74 ± 35.55	734. 87 ± 39.21

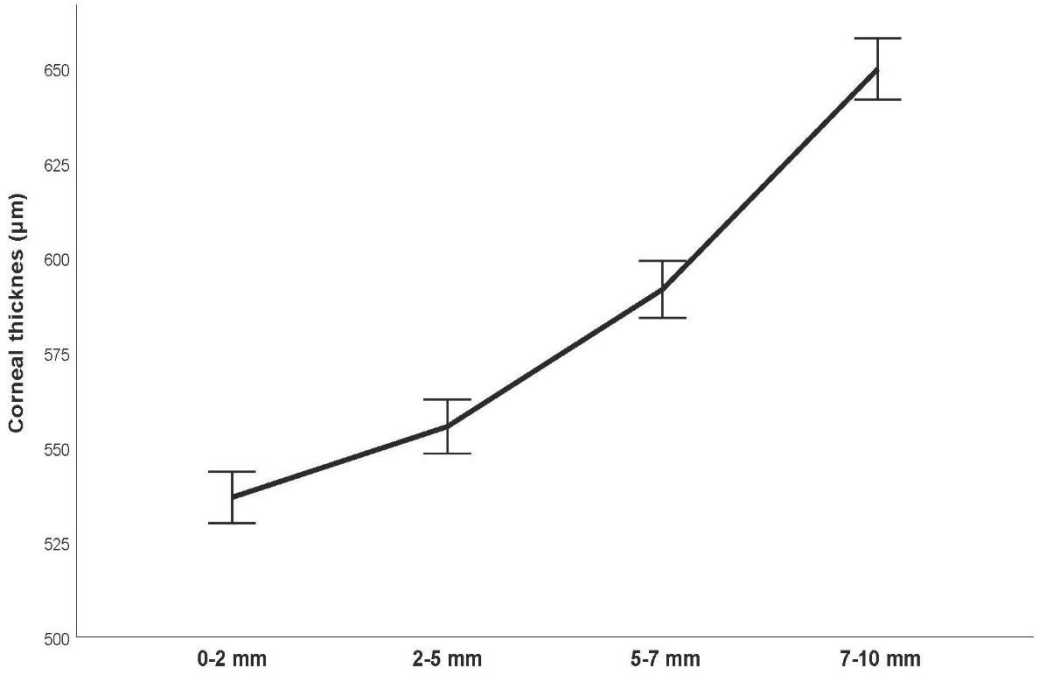

Figure 7.1. CT obtained in each corneal zone. Error bars: 95%CI.

The CT increment from centre to periphery was affected by the refractive error (mixed ANOVA p=0.002; Figure 7.2). The myopic group tended to increase the CT slightly more from 5 mm zone onwards compared to the emmetropic (Figure 7.2) but still, the pairwise comparisons were not significant in any corneal zone (Student t-test p>0.05; Table 7.2). CT did not associate with SE nor AL.

Table 7.2. CT in the different zones for the emmetropic and myopic group.

Zone	Emmetropic (n=31)	Myopic (n=47)	p-value
0 -2 mm	537.19 ± 33.98	536.60 ± 27.48	0.932
2-5 mm	555.00 ± 35.89	555.81 ± 28.87	0.913
5-7 mm	589.16 ± 38.19	593.28 ± 30.30	0.599
7-10 mm	645.03 ± 40.13	652.85 ± 32.25	0.345

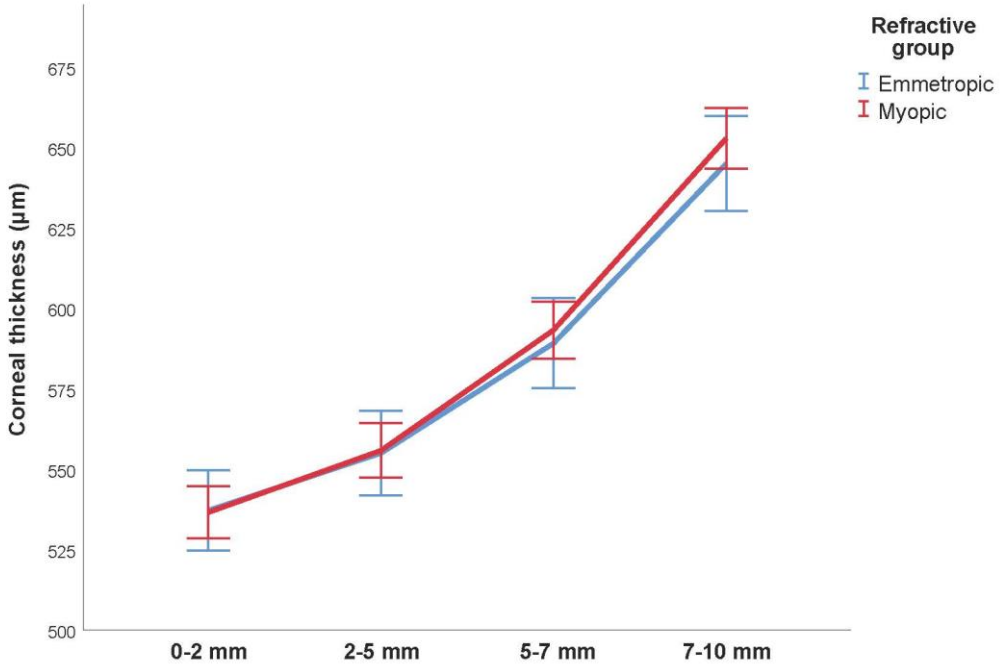

Figure 7.2. CT obtained by corneal zones for both refractive groups. Error bars: 95%CI.

The WTW was 12.26 ± 0.33 and 12.23 ± 0.36 mm for the emmetropic and myopic group, respectively. There was no difference in WTW between groups (Student t-test p=0.758). However, the AL was positively related to the WTW considering the whole sample (Spearman r=0.316, p=0.005). Further, the WTW correlated with the VCD (Spearman r=0.278, p=0.014) and ACD (Pearson r=0.406, p<0.001). The quadratic fit of the data manifested that the WTW increment with the VCD was not maintained across all range. Concretely, the WTW did not exhibit the trend to increase when the VCD reached 19-19.5 mm (Figure 7.3). The tendency of greater WTW with deeper ACD was almost linear within our ACD range (Figure 7.4).

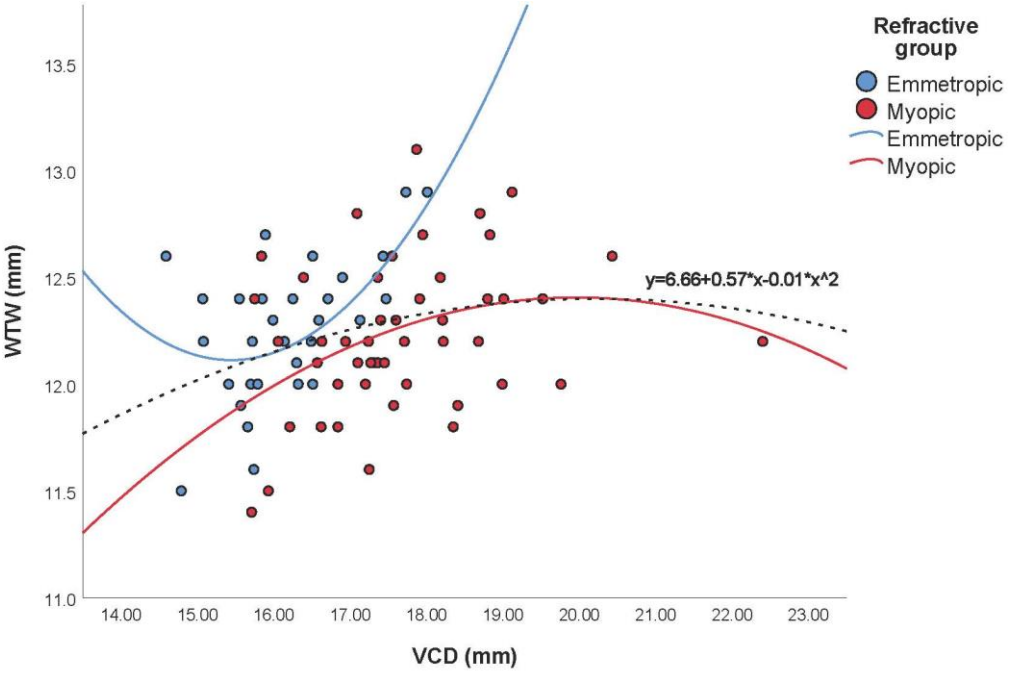

Figure 7.3. Quadratic relationship between WTW and VCD.
Dashed line: all subjects' fit.

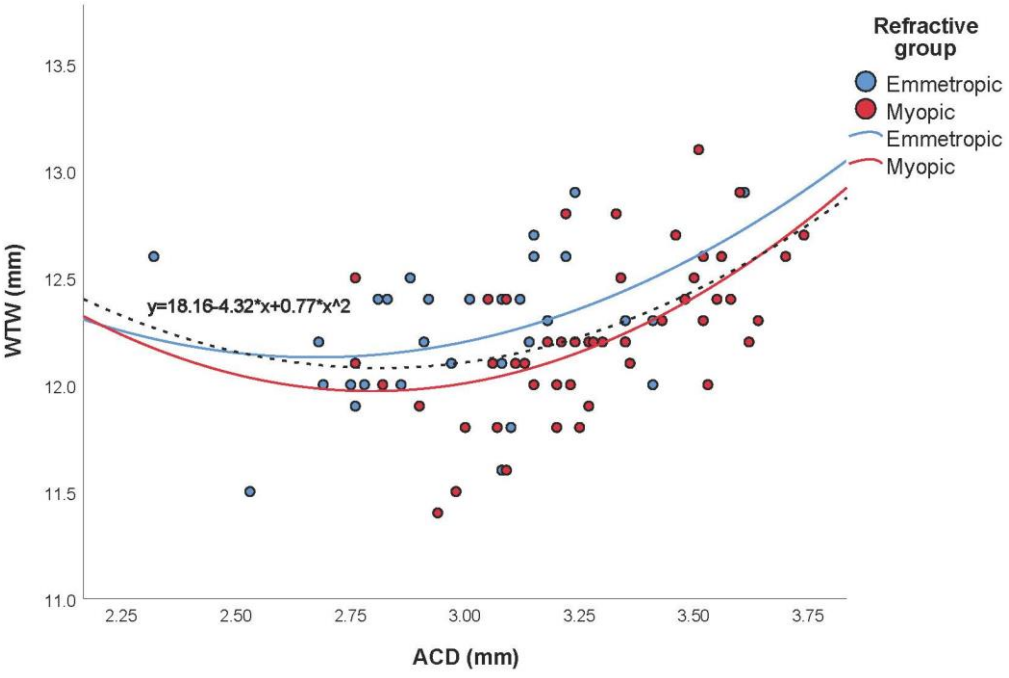

Figure 7.4. Quadratic relationship between WTW and ACD.
Dashed line: all subjects' fit.

7.3.2 Corneal curvature

The keratometric variables obtained in the 4.5 mm central cornea are contained in Table 7.3. Overall, mean K was greater in the myopic group than in the emmetropic (Student t-test p=0.043). The steep K resulted to be more powerful in myopes (Student t-test p=0.020) while the flat K was similar between groups (Student t-test p=0.100). Corneal astigmatism also manifested higher magnitude in the myopic group (Student t-test p=0.015).

Table 7.3. Keratometry parameters (4.5 mm) for the emmetropic and myopic group.

Parameter	Emmetropic (n=31)	Myopic (n=47)	p-value
Mean K (D)	43.39 ± 1.28	44.02 ± 1.34	0.043*
Steep K (D)	43.73 ± 1.34	44.48 ± 1.39	0.020*
Flat K (D)	43.06 ± 1.27	43.56 ± 1.35	0.100
Astigmatism (D)	0.67 ± 0.34	0.92 ± 0.55	0.015*

*p-value<0.05

Higher mean K associated significantly with more negative SE (Spearman r=-0.252, p=0.026; Figure 7.5). SE also had a relationship with the steep K (Spearman r=-0.296, p=0.008; Figure 7.6) and astigmatism (Spearman r=-0.271, p=0.017; Figure 7.7), so as their magnitude increased with more myopia.

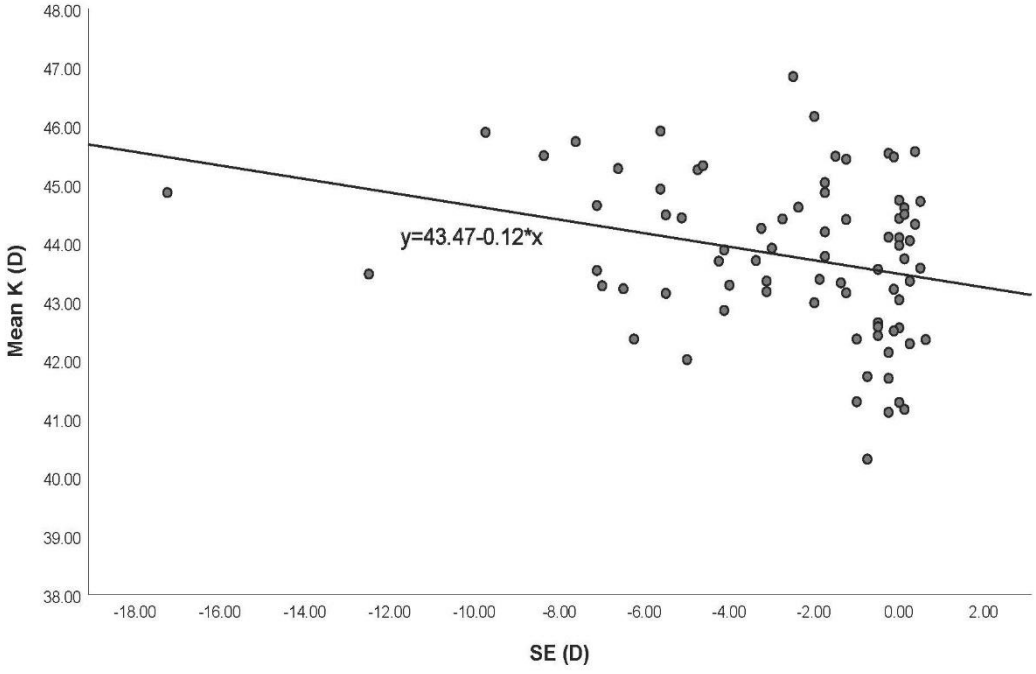

Figure 7.5. Linear relationship between SE and mean K.

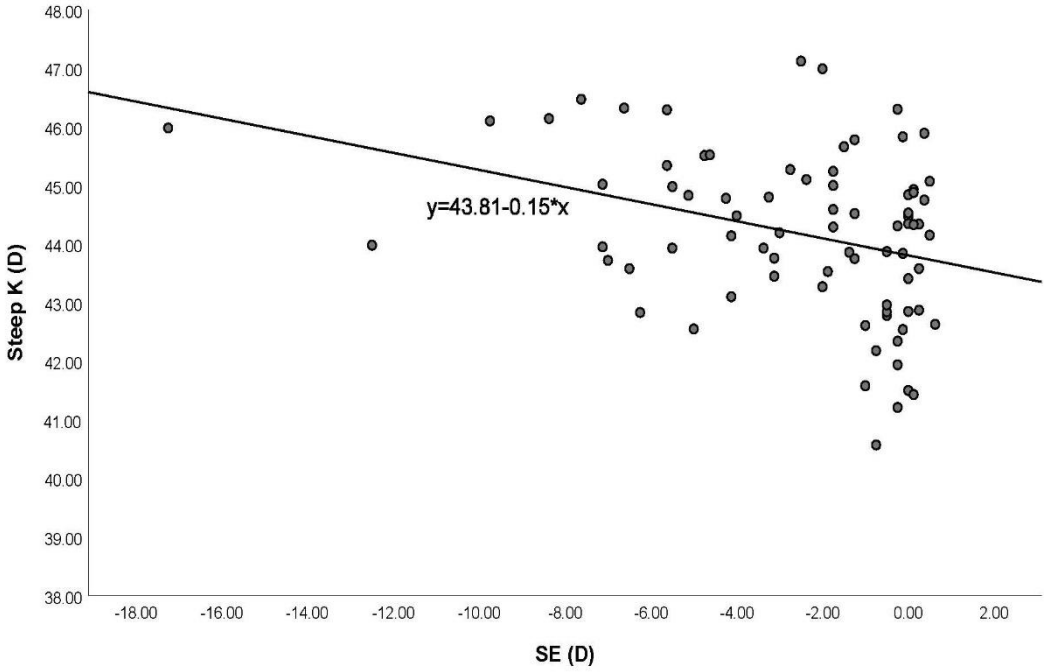

Figure 7.6. Linear relationship between SE and steep K.

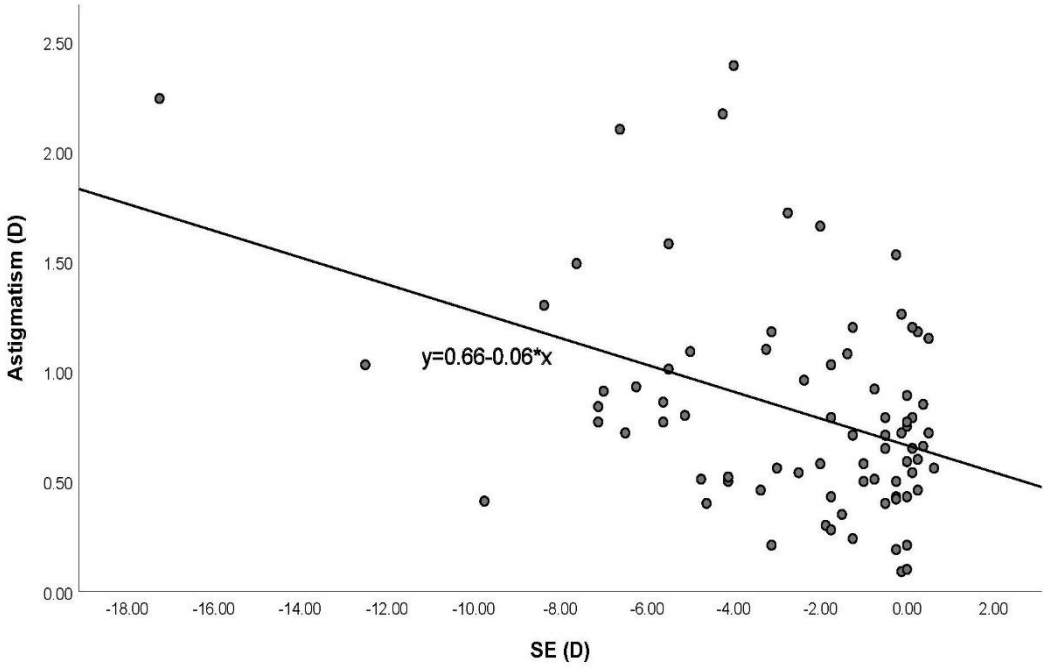

Figure 7.7. Linear relationship between SE and astigmatism.

Meanwhile, longer VCD was related to lower mean K (Spearman r=-0.272, p=0.016) and lower flat K (Spearman r=-0.318, p=0.005). This controversy can be explained because the corneal curvature was not linearly related to the VCD through all its range. The quadratic fit (Figure 7.8 and Figure 7.9) evidenced the different relationship between corneal curvature and axial elongation depending on the VCD value, particularly

in myopes. Corneal curvature flattened until the VCD reached about 19 mm, point from which the corneal power might increase. This behaviour can be seen in both steep K (**Figure 7.8**) and flat K (**Figure 7.9**).

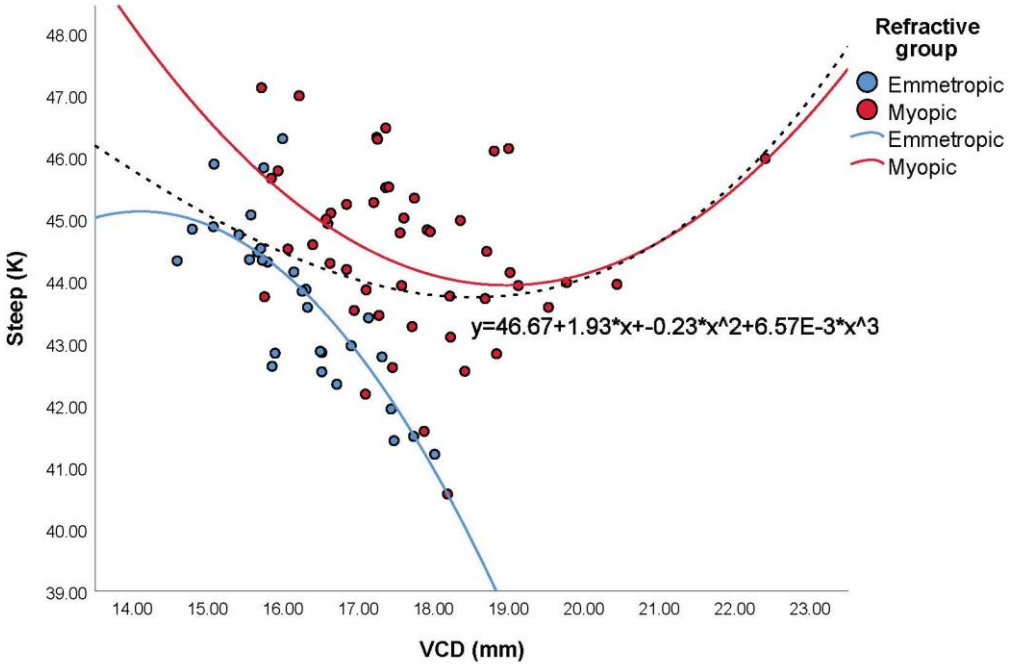

Figure 7.8. Quadratic relationship between VCD and steep K.
Dashed line: all subjects' fit.

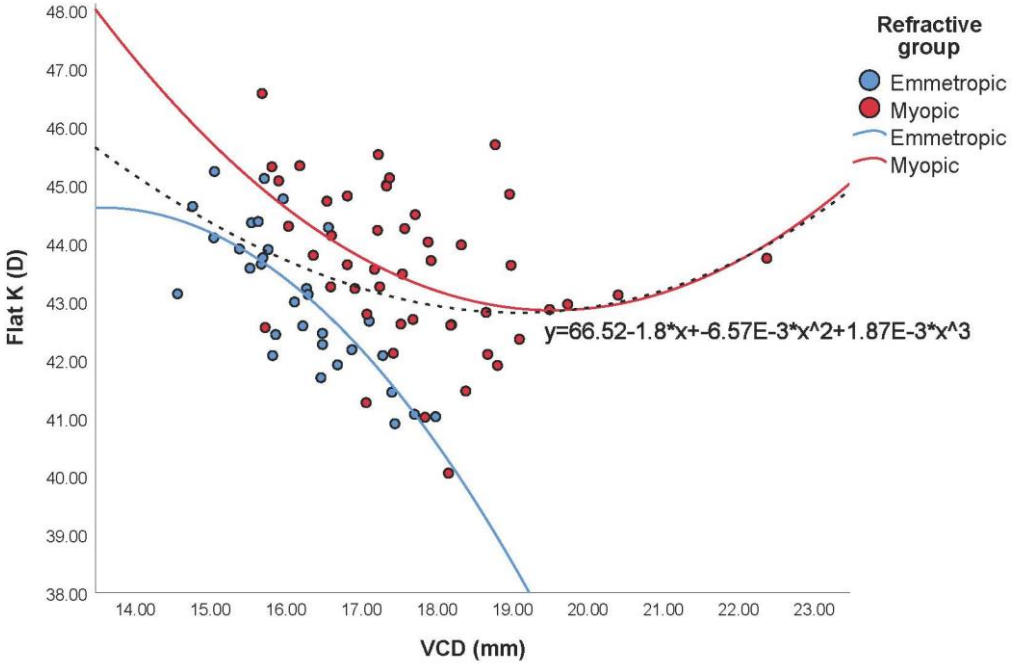

Figure 7.9. Quadratic relationship between VCD and flat K.
Dashed line: all subjects' fit.

The power of the steep and flat K decreased from central to peripheral cornea (repeated ANOVA p<0.001) whereas astigmatism increased (repeated ANOVA p<0.001). The keratometry values for the different corneal zonesa are shown in Table 7.4. Both steep K and flat K revealed significant differences in all pairwise zones comparison (Student t-test p<0.001). Meanwhile, astigmatism changed significantly between the central and peripheral cornea (Student t-test p<0.001) as well as between paracentral and peripheral cornea (Student t-test p<0.001). Therefore, the power diminution of steep and flat K was significant from the central to peripheral cornea whereas the astigmatism increment was more evident from paracentral to peripheral cornea.

Table 7.4. Keratometry by corneal zones in the entire sample.

Parameter	Central 0-3 mm	Paracentral 3-6 mm	Peripheral 6-9 mm
Steep K (D)	44.24 ± 1.40	43.92 ± 1.41	43.07 ± 1.45
Flat K (D)	43.40 ± 1.32	43.05 ± 1.32	41.99 ± 1.30
Astigmatism (D)	0.84 ± 0.52	0.87 ± 0.56	1.08 ± 0.64

The myopic group exhibited significant higher steep K in the central and paracentral cornea (Student t-test p<0.05; Table 7.5) while for the corneal periphery it was not significant. Accordingly, steep K correlated with the SE in central (Spearman r=-0.311, p=0.006), paracentral (Spearman r=-0.293, p=0.009) and periSteeppheral cornea (Spearman r=-0.234, p=0.030). There were no significant flat K differences between refractive groups in any corneal zone (Student t-test p>0.05; Table 7.5) although the SE was related to the flat K in the peripheral cornea (Spearman r=-0.275, p=0.015).

Table 7.5. Keratometry by corneal zones for the emmetropic and myopic group.

Zone	Parameter	Emmetropic (n=31)	Myopic (n=47)	p-value
Central 0-3 mm	**Steep K (D)**	43.78 ± 1.35	44.55 ± 1.38	0.016*
	Flat K (D)	43.09 ± 1.24	43.60 ± 1.34	0.089
	Astigmatism (D)	0.69 ± 0.38	0.95 ± 0.58	0.019*
Paracentral 3-6 mm	**Steep K (D)**	43.50 ± 1.32	44.20 ± 1.41	0.029*
	Flat K (D)	42.76 ± 1.23	43.23 ± 1.35	0.122
	Astigmatism (D)	0.73 ± 0.41	0.97 ± 0.63	0.072
Peripheral 6-9mm	**Steep K (D)**	42.73 ± 1.30	43.30 ± 1.52	0.091
	Flat K (D)	41.66 ± 1.13	42.21 ± 1.37	0.063
	Astigmatism (D)	1.07 ± 0.57	1.09 ± 0.69	0.940

*p-value<0.05

The curvature reduction from central to peripheral corneal did not differ significantly between refractive groups for steep and flat K (mixed ANOVA p=0.121 and p=0.509, respectively). Figure 7.10 and Figure 7.11 depict the change of the steep K and flat K through the cornea, respectively, for both refractive groups.

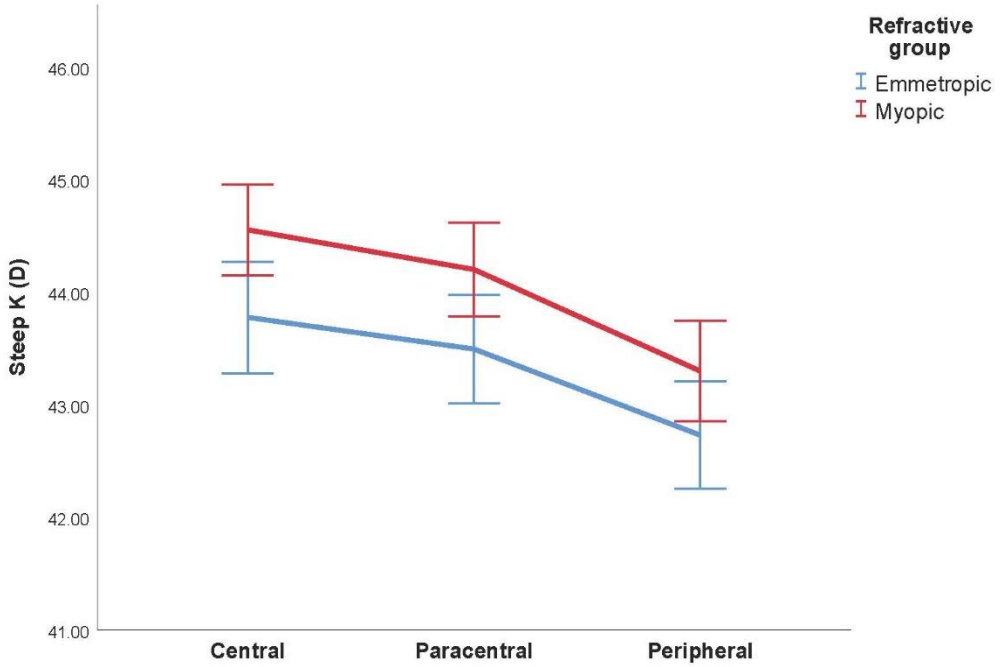

Figure 7.10. Steep K change across the corneal zones for the myopic and emmetropic group. Error bars: CI 95%.

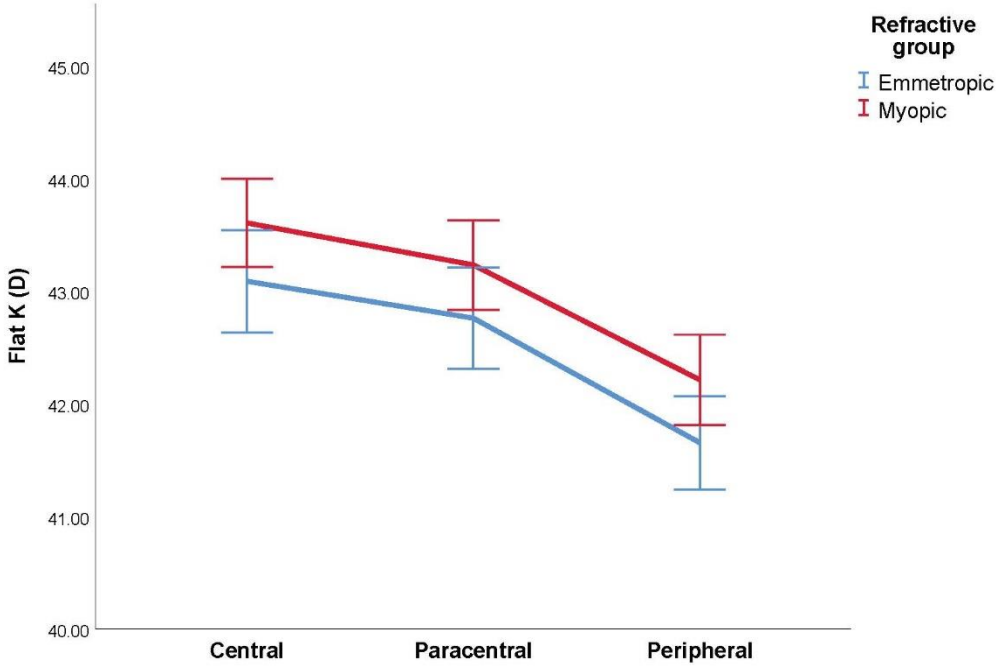

Figure 7.11. Flat K change across the corneal zones for the myopic and emmetropic group. Error bars: CI 95%.

Meantime, the myopic group presented significantly higher astigmatism magnitude in the central cornea (Student t-test p=0.019; Table 7.5). Astigmatism in paracentral corneal was also greater in myopes but it did not reach the statistical significance (Student t-test p=0.072; Table 7.5). Thus, corneal astigmatism associated with the SE in the central cornea (Spearman r=-0.231, p=0.033). Regarding the changes from central to the peripheral cornea, the refractive error influenced the astigmatism change (mixed ANOVA p=0.035; Figure 7.12). The emmetropic group revealed greater astigmatism increase (0.34 ± 0.35 D) compared to the myopic group (0.12 ± 0.48 D) from paracentral to peripheral cornea (Student t-test p=0.030). In this way, both refractive groups astigmatism ended up having analogous astigmatism in the peripheral cornea (Figure 7.12).

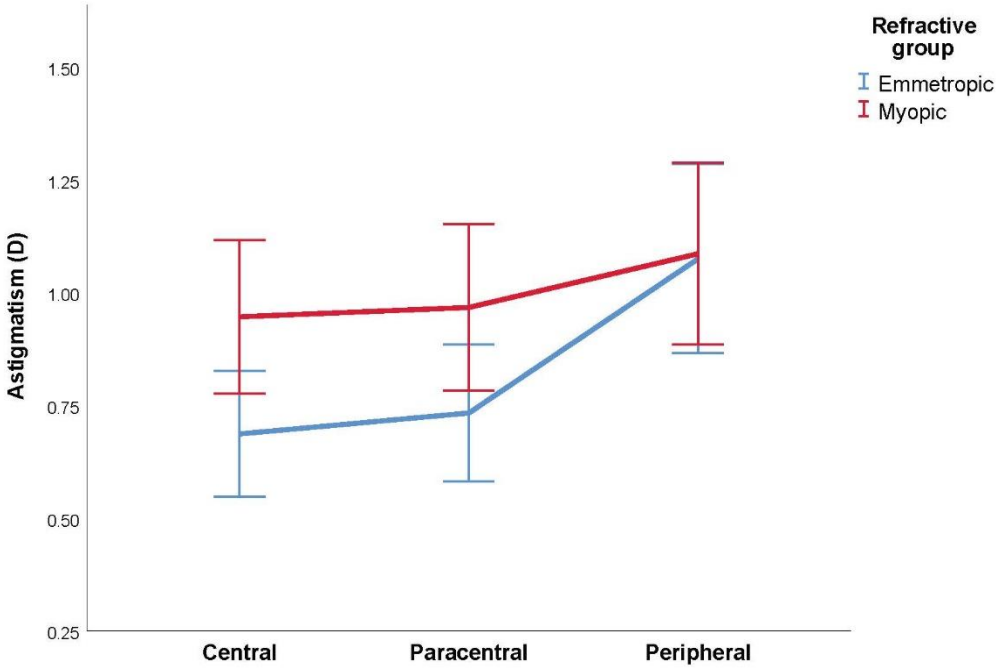

Figure 7.12. Astigmatism change across the corneal zones for the myopic and emmetropic group. Error bars: CI 95%.

7.3.3 Corneal shape

The values of the shape parameters were within the expected for a normal cornea, which is described as a prolate ellipse. The eccentricity, asphericity and shape factor did not manifested significant differences between emmetropic and myopic subjects (Student t-test p>0.05). Table 7.6 contains the average magnitudes of these shape parameters. Overall, the emmetropic and myopic group revealed mostly similar corneal flattening

from central to peripheral cornea. The corneal shape parameters did not associate with the SE nor AL.

Table 7.6. Corneal shape parameters for the emmetropic and myopic group.

Parameter	Emmetropic (n=31)	Myopic (n=47)	p-value
e	0.57 ± 0.09	0.58 ± 0.09	0.814
Q	-0.35 ± 0.11	-0.35 ±0.10	0.787
SF	0.34 ± 0.11	0.34 ± 0.10	0.850

The eccentricity in different meridian orientations is included in Table 7.7. The meridian orientation had an impact on the eccentricity value for all subjects (repeated ANOVA $p<0.001$). The meridians of 25 and 30° had significantly lower eccentricity compared to the meridians 0, 10, 15 and 20° (Student t-test $p<0.001$). Eccentricity did not differ between 25 and 30° (Student t-test $p=0.053$). Thereby, there was more curvature change, from central to the peripheral cornea, in the meridians closer to the horizontal (from 0 to 20°). The eccentricity changes through the meridians 0 to 30° did not differ significantly between refractive groups (mixed ANOVA $p=0.541$; Figure 7.13).

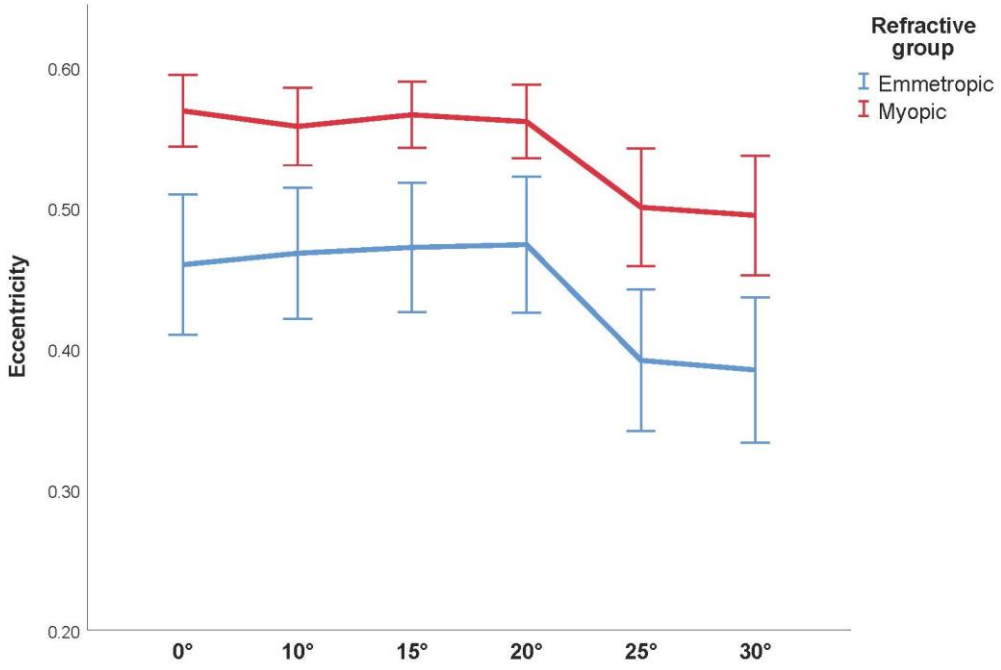

Figure 7.13. Eccentricity in different meridians orientations for the emmetropic and myopic group. Error bars: CI 95%.

Comparing the refractive groups in each meridian, myopes exhibited greater eccentricity in every meridian from 0 to 30° (Student t-test p<0.05; Table 7.7). That is to say, myopes underwent more flattening toward the periphery probably because of their more prolate cornea in the horizontal compared to emmetropes. Accordingly, the SE associated with the eccentricity at the meridians 0° (Spearman r=-0.391, p<0.001), 10° (Spearman r=-0.316, p=0.005), 15° (Spearman r=-0.336, p=0.003), 20° (Spearman r=-0.338, p=0.002), 25° (Spearman r=-0.457, p<0.001) and 30° (Spearman r=-0.449, p<0.001).

Table 7.7. Eccentricity in different meridians orientations for both refractive groups.

Meridian	All sample (n=78)	Emmetropic (n=31)	Myopic (n=47)	p-value
0°	0.52 ± 0.12	0.46 ± 0.13	0.57 ± 0.09	<0.001*
10°	0.52 ± 0.12	0.47 ± 0.13	0.58 ± 0.09	0.001*
15°	0.53 ± 0.11	0.47 ± 0.12	0.57 ± 0.08	0.001*
20°	0.53 ± 0.11	0.47 ± 0.13	0.56 ± 0.09	0.001*
25°	0.46 ± 0.15	0.39 ± 0.14	0.50 ± 0.14	0.001*
30°	0.45 ± 0.15	0.38 ± 0.14	0.49 ± 0.14	0.001*

*p-value<0.05

7.3.4 Corneal elevation

Corneal elevation values, measured as BFS and toric ellipsoid fit, are included in Table 7.8 for the emmetropic and myopic group. The BFS manifested steeper curvature in myopes for posterior surface (Student t-test p=0.023) and it was almost significant for the anterior surface (Student t-test p=0.05). When the elevation was assessed with the toric ellipsoid fit, only the anterior steep meridian showed significant higher magnitude in the myopic group (Student t-test=0.031). Figure 7.14 and Figure 7.15 depict the anterior and posterior corneal elevation, respectively, for both refractive groups.

Table 7.8. Corneal elevation for the emmetropic and myopic group.

Elevation fit	Parameter	Emmetropic (n=31)	Myopic (n=47)	p-value
Best-fit-sphere (D)	**Anterior**	42.98 ± 1.23	43.57 ± 1.34	0.050
	Posterior	-5.95 ± 0.21	-6.06 ± 0.21	0.023*
Toric ellipsoid fit (D)	**Anterior Flat**	44.33 ± 1.31	43.83 ± 1.38	0.118
	Anterior Steep	44.10 ± 1.42	44.80 ± 1.38	0.031*
	Posterior Flat	-5.95 ± 0.27	-6.01 ± 0.26	0.317
	Posterior Steep	-6.22 ± 0.30	-6.32 ± 0.27	0.144

*p-value<0.05

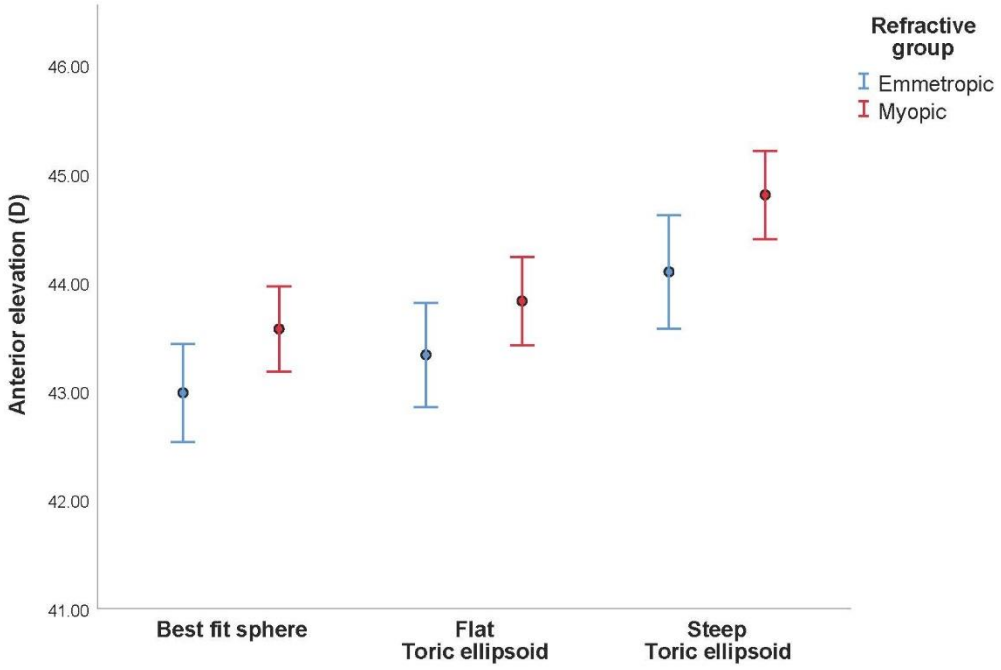

Figure 7.14. Anterior corneal elevation obtained as BFS and toric ellipsoid for the emmetropic and myopic group. Error bars: CI 95%.

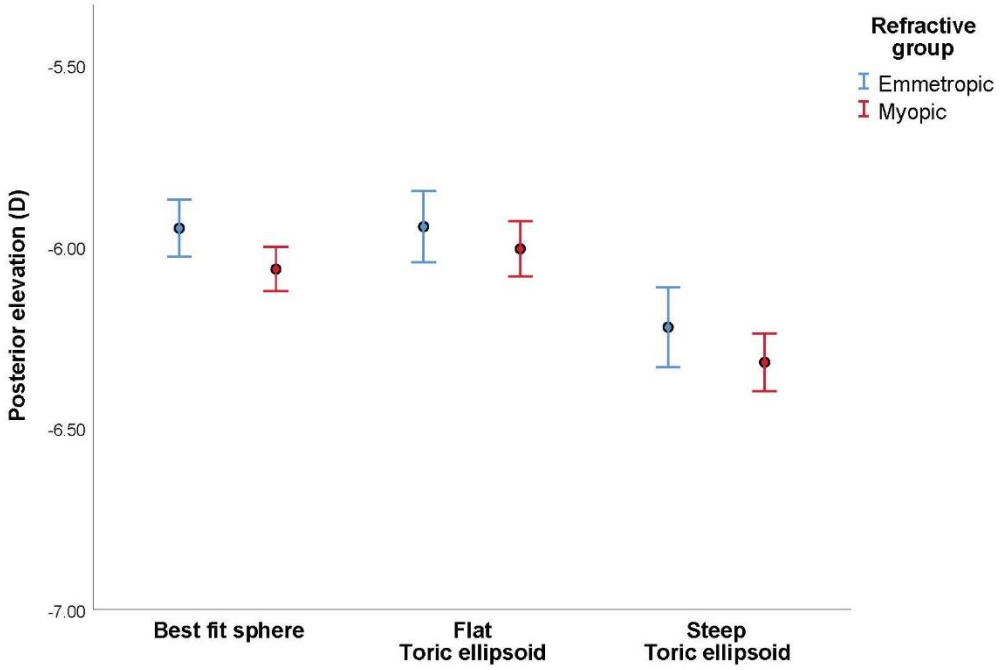

Figure 7.15. Posterior corneal elevation obtained as BFS and toric ellipsoid for the emmetropic and myopic group. Error bars: CI 95%.

There was an association of the mean K with the anterior BFS (Pearson r=0.993, p<0.001) and posterior BFS (Pearson r=-0.925, p<0.001). Myopic SE was related to the anterior steeper elevation (Spearman r=-0.272, p=0.016) and posterior BFS (Spearman

r=0.243, p=0.032). Besides, the VCD correlated with the BFS of anterior (Spearman r=-0.241, p=0.033) and posterior (Spearman r=0.275, p=0.015) surfaces. Then again, the BFS elevation revealed to flatten until a point of VCD elongation, as keratometry did (Figure 7.16 and Figure 7.17).

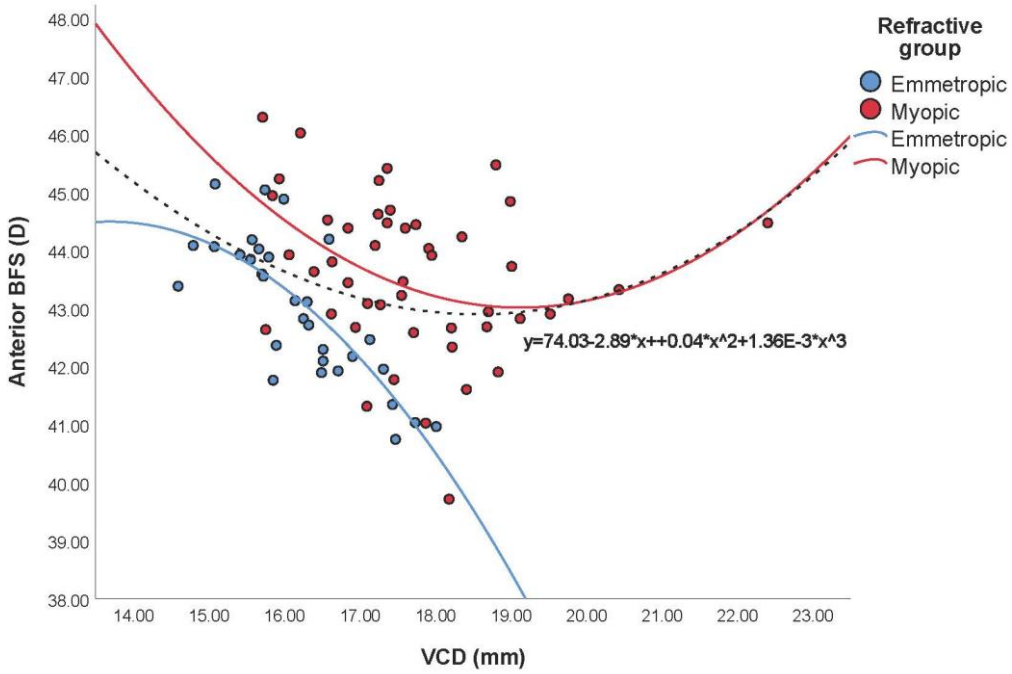

Figure 7.16. Quadratic relationship between VCD and anterior BFS. Dashed line: all subjects' fit.

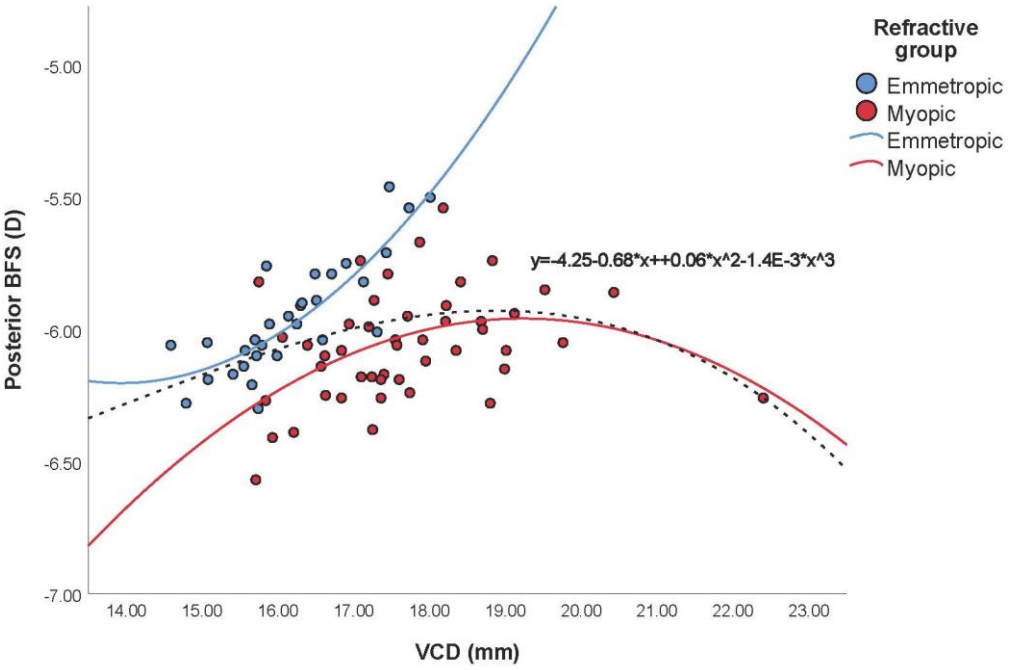

Figure 7.17. Quadratic relationship between VCD and posterior BFS. Dashed line: all subjects' fit.

7.3.5 Axial length to corneal radius ratio

The AL/CR ratio resulted in 3.00 ± 0.07 and 3.27 ± 0.18 for the emmetropic and myopic group, respectively. Myopes had significantly greater AL/CR ratio (Student t-test p<0.001) than emmetropes and it increased with more myopic SE (Spearman r=-0.909, p<0.001 Figure 7.18). Besides, AL/CR ratio was related to deeper ACD (Pearson r=0.605, p<0.001; Figure 7.19) and thinner LT (Pearson r=-0.291, p=0.010; Figure 7.20).

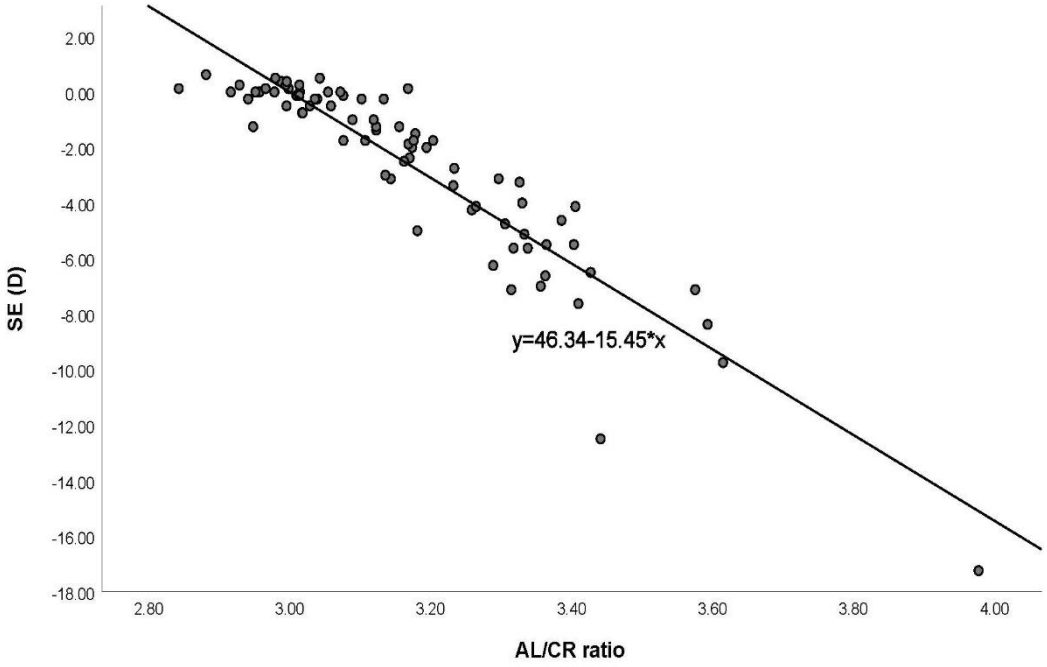

Figure 7.18. Linear relationship between AL/CR ratio and SE.

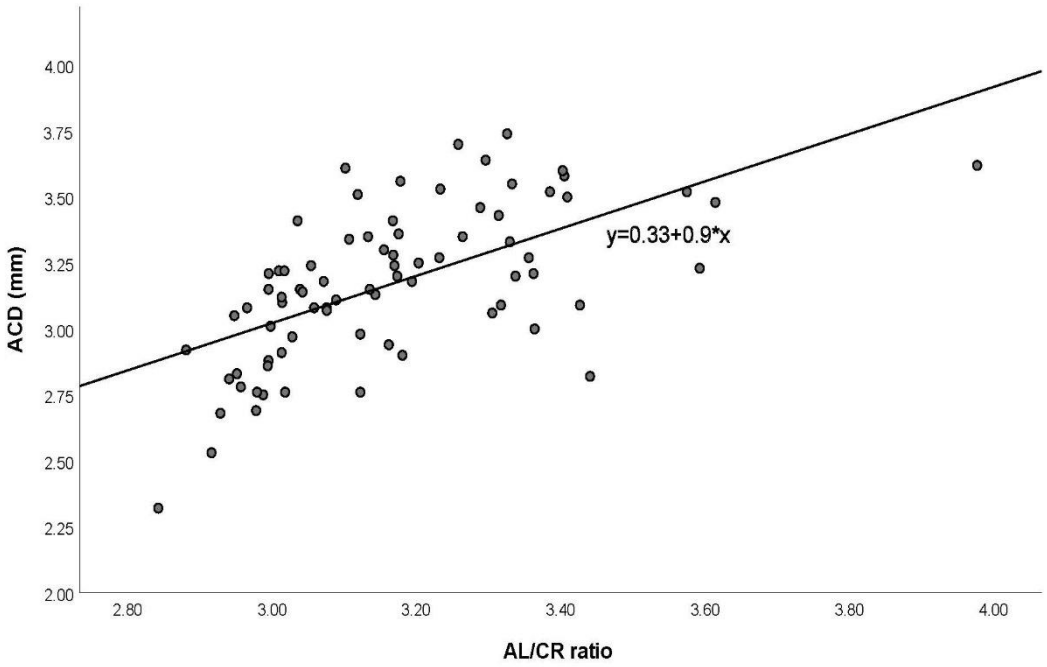

Figure 7.19. Linear relationship between AL/CR ratio and ACD.

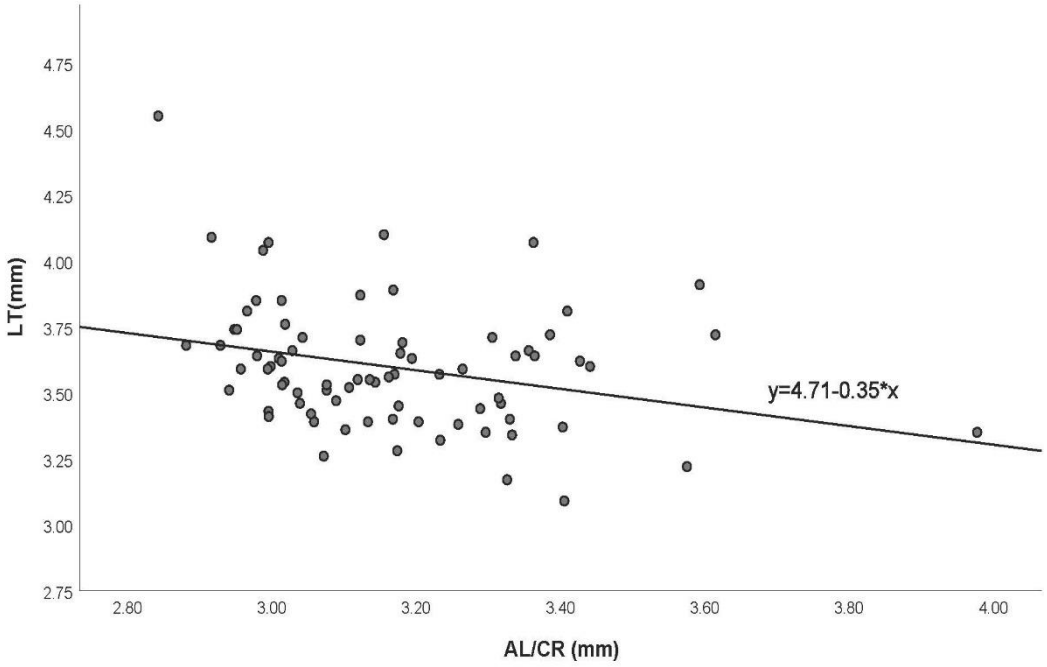

Figure 7.20. Linear relationship between AL/CR ratio and LT.

The 97.98% of the myopic students had an AL/CR ratio above 3.00 while 51.61% of the emmetropic was below 3.00 (Chi-Square p<0.001). Every 0.1 increase in the AL/CR ratio was related to a refractive myopic increase of -1.55 D (Figure 7.18), ACD increase of 0.09 mm (Figure 7.19) and LT decrease of 0.035 mm (Figure 7.20). Multiple linear regression proved that SE was better predicted when corneal curvature was included with the ocular biometry. Thereby, 91.5% of the SE variability was explained by the VCD, CR, LT and sex (Table 7.9). More myopic SE was expected with longer VCD, steeper CR and female sex. Surprisingly, thicker LT led to more negative SE, however, this may occur as a result of the LT increment with age. Older students have thicker LT and they are highly likely to be more myopic because of more time of myopia progression.

Table 7.9. Multiple linear regression model for SE.

	R	R^2	R^2 adjusted	Error	Durbin-Watson
SE	0.957	0.915	0.911	0.982	2.215

	β	SE	Sβ	p-value	Tolerance	VIF
Constant	4.608	4.505	-	0.310	-	-
VCD (mm)	-2.451	0.093	-1.014	p<0.001	0.788	1.269
CR (mm)	6.156	0.485	0.448	p<0.001	0.933	1.072
LT (mm)	-3.411	0.517	-0.248	p<0.001	0.823	1.215
Sex	-0.761	0.237	-0.112	0.002	0.954	1.048

7.4 Follow-up results

7.4.1 Corneal thickness and diameter

CT had very little changes after one year (Table 7.1) and only the change in the central 2 mm resulted significant (Student t-test p=0.030). The zone of the cornea did not influence the amount of the CT change (repeated ANOVA p=0.966; Figure 7.21).

Table 7.10. CT changes by corneal zone in the entire sample.

Parameter	Baseline	One year	Change	p-value
0 -2 mm	535.35 ± 29.41	536.58 ± 29.92±	1.23 ± 4.46	0.030*
2-5 mm	553.82 ± 30.76	554.91 ± 31.91	1.09 ± 5.28	0.100
5-7 mm	589.95 ± 32.64	590.94 ± 34.07	1.09 ± 6.65	0.190
7-10 mm	648.37 ± 35.03	649.75 ± 36.56	1.39 ± 8.20	0.178

*p-value<0.05

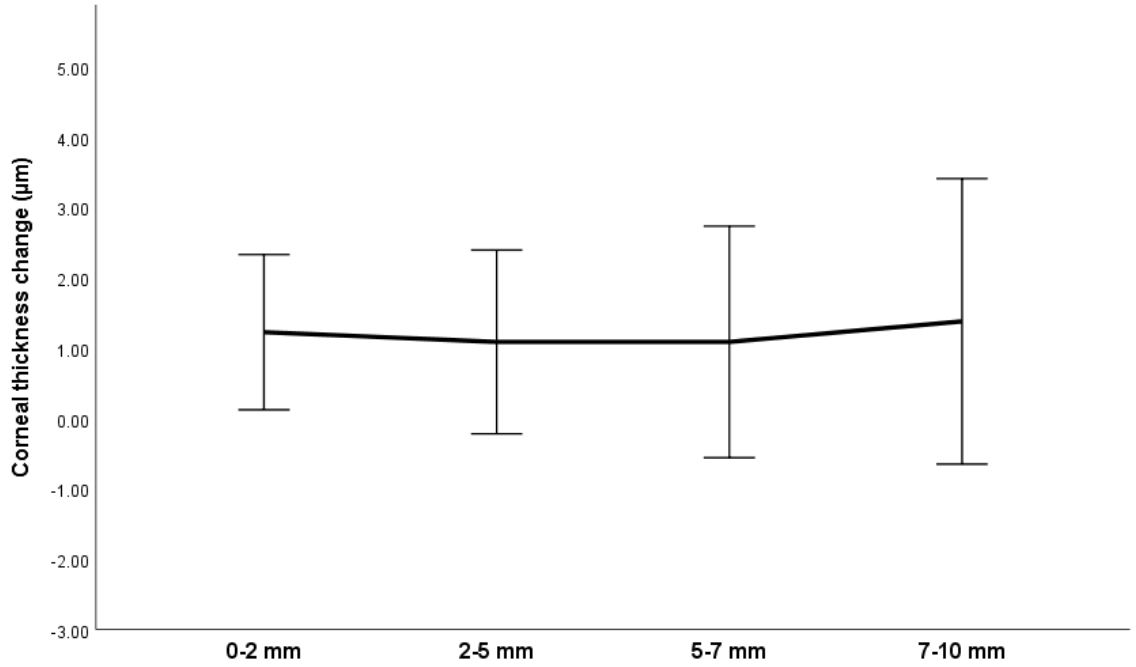

Figure 7.21. CT changes in the different corneal zones. Error bars: 95% CI.

Moreover, the CT change was similar between refractive groups in the zones 0-2 mm (mixed ANOVA p=0.489), 2-5 mm (mixed ANOVA p=0.576), 5-7 mm (mixed ANOVA p=0.630) and 7-10 mm (mixed ANOVA p=0.985). The CT changes for each refractive group are exposed in Table 7.11. Within the emmetropic group, the change in the 0-2 mm zone was marginally significant (Student t-test p=0.045).

Table 7.11. Change of the CT by zones for the emmetropic and myopic group.

Zone	Emmetropic (n=25)	Myopic (n=40)
0 -2 mm	1.72 ± 4.28*	0.93 ± 4.59
2-5 mm	1.56 ± 5.67	0.8 ± 5.06
5-7 mm	1.6 ± 6.66	0.78 ± 6.70
7-10 mm	1.36 ± 7.93	1.40 ± 8.46

*p-value<0.05

The WTW experienced a non-significant change of -0.02 ± 0.10 mm (Student t-test p=0.188), from 12.25 ± 0.35 to 12.23 ± 0.34 mm. The change of WTW was similar among refractive groups (mixed ANOVA p=0.955), which was approximately -0.02 mm for both groups. And besides, WTW changes were not related to the changes of SE, VCD/AL nor ACD.

7.4.2 Corneal curvature

In the entire sample, there was no significant change of the steep K and astigmatism after one year of follow-up (Student t-test p>0.05). The flat K did undergo a significant diminution between baseline and follow-up visit for all students (Student t-test p=0.021). Nonetheless, the change of the mean K did not reach the statistical significance (Student t-test p=0.059). Table 7.12 presents the average keratometric magnitudes in the 4.5 mm corneal zone at baseline, after one year and the consequent change.

Table 7.12. Keratometry changes (4.5 mm) in the entire sample.

Parameter	Baseline	One year	Change	p-value
Mean K (D)	43.81 ± 1.36	43.76 ± 1.35	-0.05 ± 0.22	0.059
Steep K (D)	44.24 ± 1.43	44.20 ± 1.43	-0.04 ±0.27	0.236
Flat K (D)	43.39 ± 1.33	43.33 ± 1.33	-0.07 ± 0.23	0.021*
Astigmatism (D)	0.84 ± 0.52	0.87 ± 0.55	0.03 ± 0.23	0.305

*p-value<0.05

The refractive error did not affect the change of the mean K, steep K (Figure 7.22) nor astigmatism (mixed ANOVA p>0.05). The change of the flat K was greater in the emmetropic group (Table 7.13), however, the difference ended up being no significant (mixed ANOVA p=0.097; Figure 7.23).

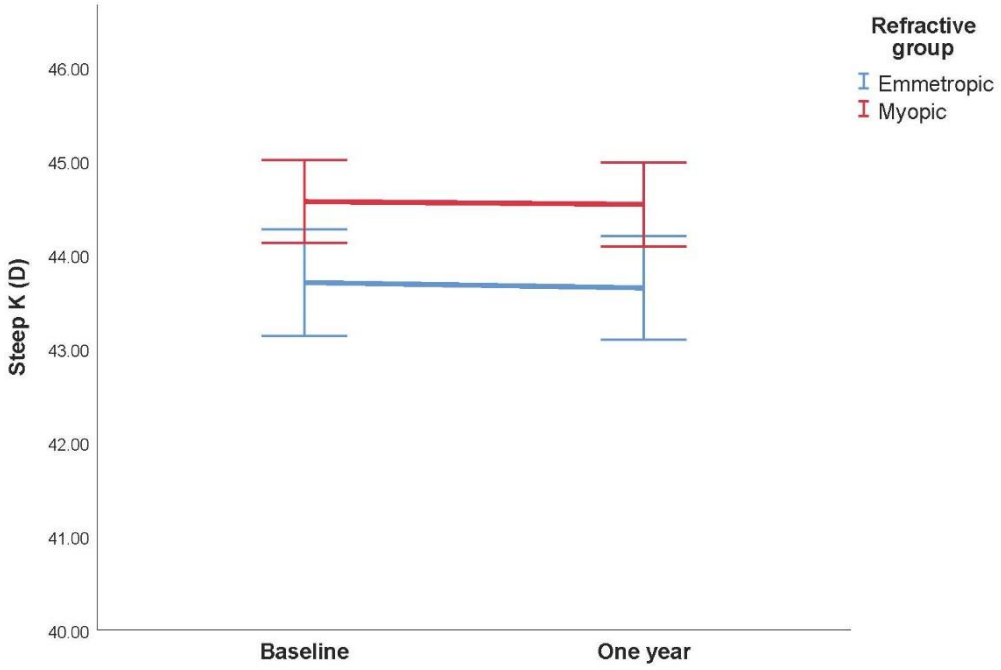

Figure 7.22. Steep K change for the myopic and emmetropic group. Error bars: 95%CI.

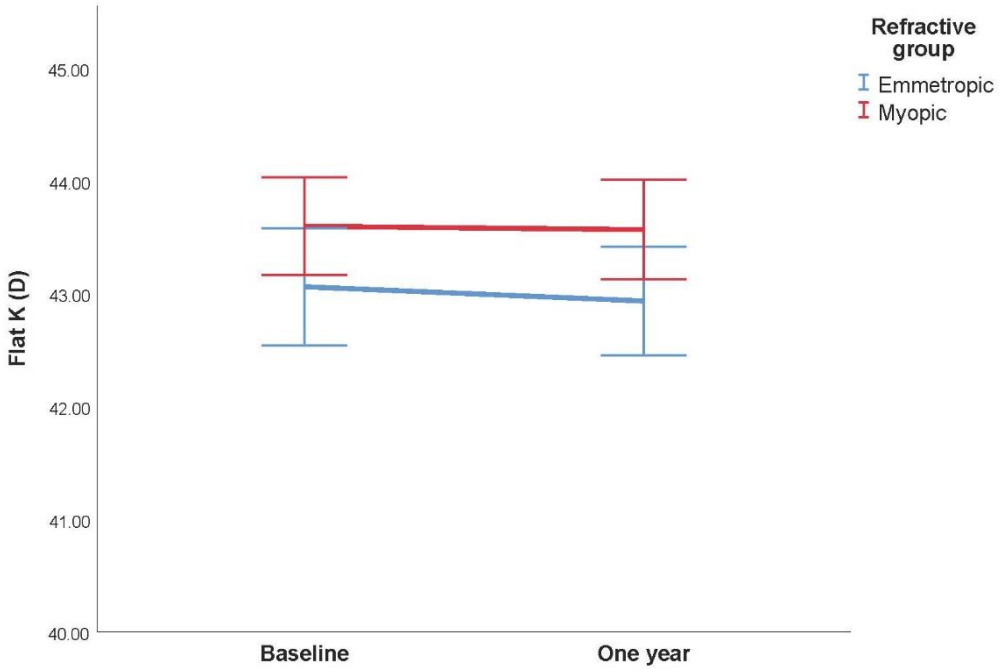

Figure 7.23. Flat K change for the myopic and emmetropic group. Error bars: 95%CI.

Within the refractive groups, there were significant changes between visits only in the emmetropic group for the mean K (Student t-test p=0.036) and flat K (Student t-test p=0.019). The changes in the keratometry in the 4.5 mm zone for each refractive group

are exposed in Table 7.13. Furthermore, the keratometry changes in the 4.5 mm corneal zone did not result to be correlated with the SE nor AL changes.

Table 7.13. Keratometry changes (4.5 mm) for the emmetropic and myopic group.

Parameter	Emmetropic (n=25)	Myopic (n=40)
Change Mean K (D)	-0.09 ± 0.21*	-0.03 ± 0.44
Change Steep K (D)	-0.06 ± 0.22	-0.03 ± 0.30
Change Flat K (D)	-0.13 ± 0.25*	-0.03 ± 0.21
Change Astigmatism (D)	0.07 ± 0.21	-0.01 ± 0.24

*p-value<0.05

Considering the different corneal zones, neither steep K and astigmatism had a significant change for any corneal zone (Student t-test p>0.05, Table 7.14). Meanwhile, the flat K decreased significantly in central, paracentral and peripheral cornea (Student t-test p<0.05; Table 7.14) in the whole sample. Although the flat K reduction was of greater magnitude in the peripheral cornea, the corneal zone did not show a significant effect on the flat K change (repeated ANOVA p=0.224; Figure 7.24). The average magnitudes at baseline and after one year altogether with their change are shown in Table 7.14 for the different corneal zones.

Table 7.14. Keratometry changes by corneal zone in the entire sample.

Zone	Parameter	Baseline	One year	Change	p-value
Central 0-3 mm	**Steep K (D)**	44.31 ± 1.43	44.29 ±1.45	-0.02 ± 0.34	0.722
	Flat K (D)	43.43 ± 1.33	43.36 ± 1.35	-0.07 ± 0.27	0.044*
	Astigmatism (D)	0.88 ± 0.55	0.93 ± 0.60	0.05 ± 0.33	0.196
Paracentral 3-6 mm	**Steep K (D)**	43.96 ± 1.43	43.95 ± 1.43	-0.02 ± 0.28	0.598
	Flat K (D)	43.08 ± 1.31	43.02 ± 1.32	-0.07 ± 0.26	0.048*
	Astigmatism (D)	0.89 ± 0.60	0.94 ± 0.63	0.05 ± 0.32	0.250
Peripheral 6-9mm	**Steep K (D)**	43.12 ± 1.44	43.07 ± 1.42	-0.05 ± 0.60	0.528
	Flat K (D)	42.04 ± 1.30	41.90 ± 1.31	-0.13 ± 0.44	0.007*
	Astigmatism (D)	1.08 ± 0.65	1.18 ± 0.73	0.10 ± 0.53	0.140

*p-value<0.05

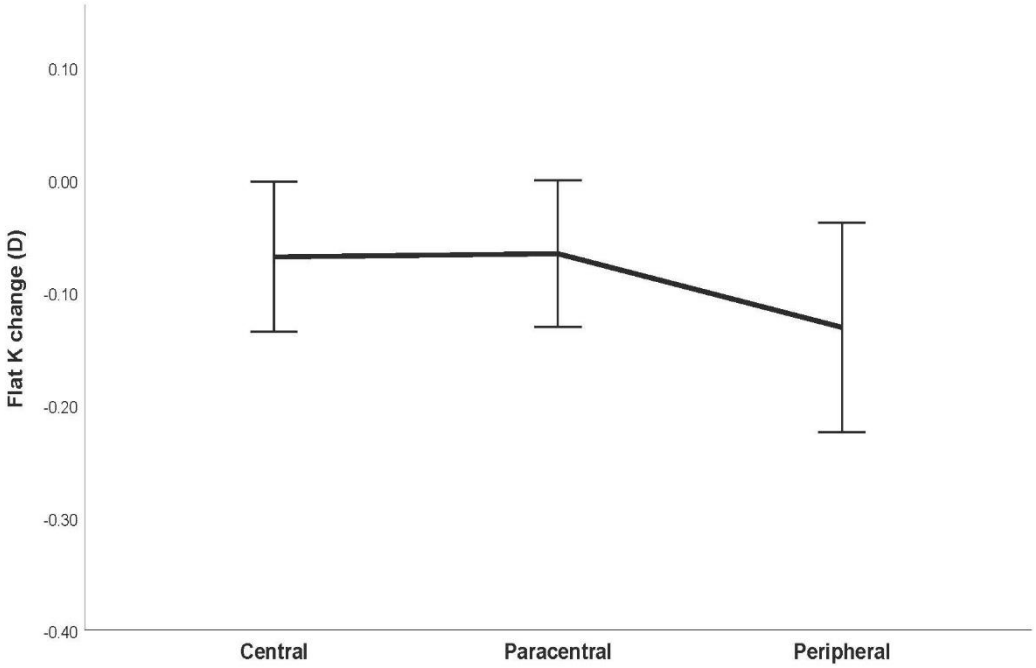

Figure 7.24. Change of flat K in the three corneal zones. Error bars: 95%CI.

The changes of the steep K and astigmatism between visits did not result to be different because of refractive error in any corneal zone (mixed ANOVA p>0.05). Table 7.15 contains the average keratometry values for both refractive groups according to the corneal zone. Astigmatism did differ significantly between visits within the emmetropic group in the peripheral cornea (Student t-test p=0.036). The flat K change did not result to differ significantly between refractive groups in any corneal zone (mixed ANOVA p>0.05; Figure 7.25) despite the fact the emmetropic group exhibited greater flat K reduction.

Table 7.15. Keratometry changes by corneal zone for the emmetropic and myopic group.

Zone	Parameter	Emmetropic (n=25)	Myopic (n=40)
Central changes 0-3 mm	**Steep K (D)**	-0.03 ± 0.22	-0.01 ± 0.40
	Flat K (D)	-0.12 ± 0.25*	-0.04 ± 0.28
	Astigmatism (D)	0.08 ± 0.24	0.03 ± 0.38
Paracentral changes 3-6 mm	**Steep K (D)**	-0.04 ± 0.27	-0.01 ± 0.29
	Flat K (D)	-0.13 ± 0.26*	-0.02 ± 0.26
	Astigmatism (D)	0.09 ± 0.27	0.02 ± 0.36
Peripheral changes 6-9mm	**Steep K (D)**	0.01 ± 0.48	-0.08 ± 0.68
	Flat K (D)	-0.18 ± 0.45	-0.10 ± 0.32
	Astigmatism (D)	0.18 ± 0.41*	0.05 ± 0.60

*p-value<0.05

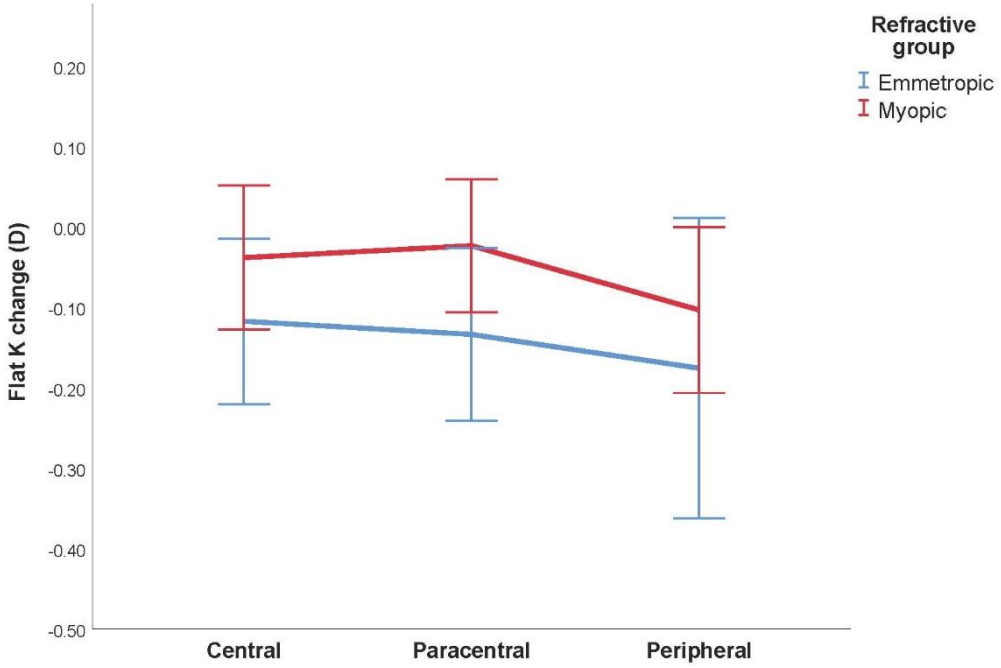

Figure 7.25. Change of flat K in the three corneal zones for the myopic and emmetropic group. Error bars: 95%CI.

The flat K change across the cornea, considering the three zones altogether, was neither affected significantly by the refractive error (mixed ANOVA p=0.739). Further, the change of the flat K in the central and paracentral cornea was significant within the emmetropic group (Student t-test p=0.027 and p=0.017, respectively; Table 7.15). In the peripheral cornea, the flat K change was nearly significant for the emmetropic (Student t-test p=0.06) and myopic group (Student t-test p=0.05). Finally, the changes in the different corneal zones of the steep K, flat K and astigmatism were not associated with the SE nor AL changes between visits.

7.4.3 Corneal shape

The sample did not experience significant changes in the shape parameters with time. Table 7.16 includes the average change for eccentricity, asphericity and shape factor. The changes of Q, e and SF were correlated to the curvature changes of the steep K in the central cornea and the flat K in the periphery. Particularly, the change to more negative Q correlated to the increase of the central steep K or the less reduction (Spearman r= -0.342, p=0.005) while to the more reduction of flat K in the periphery (Spearman r=0.264, p=0.034). The change between baseline and follow-up neither differed between the emmetropic and myopic group for eccentricity (mixed ANOVA p=0.668), asphericity

(mixed ANOVA p=0.463) and shape factor (mixed ANOVA p=0.550). The average changes in these parameters for each refractive group are in Table 7.17.

Table 7.16. Change of the shape parameters in the entire sample.

Parameter	Baseline	One year	Change	p-value
e	0.58 ± 0.09	0.59 ± 0.11	0.02 ± 0.07	0.072
Q	-0.35 ± 0.11	-0.36 ± 0.14	-0.01 ± 0.09	0.273
SF	0.34 ± 0.11	0.36 ± 0.14	0.02 ± 0.09	0.077

Table 7.17. Change of the shape parameters for the emmetropic and myopic group.

Parameter	Emmetropic (n=25)	Myopic (n=40)
e	0.02 ± 0.09	0.01 ± 0.08
Q	-0.02 ± 0.11	-0.01 ± 0.10
SF	0.03 ± 0.11	0.01 ± 0.10

The eccentricity in the 0° and 10° meridians experienced a significant change (Student t-test p<0.05; Table 7.18) while in the meridians from 15° to 30° the change was not significant. That led to a significant different eccentricity change among meridians (repeated ANOVA p=0.009; Figure 7.26). Overall, the change of 0° and 10° meridians was greater compared to the meridians 25° (Student t-test p=0.006 and p<0.001, respectively) and 30° (Student t-test p=0.012 and p<0.001, respectively).

Table 7.18. Eccentricity change by meridians in the entire sample.

Meridian	Baseline	One year	Change	p-value
0°	0.53 ± 0.12	0.56 ± 0.12	0.03 ± 0.09	0.011*
10°	0.52 ± 0.11	0.55 ± 0.12	0.03 ± 0.09	0.012*
15°	0.53 ± 0.10	0.55 ± 0.12	0.02 ± 0.08	0.072
20°	0.53 ± 0.11	0.54 ± 0.12	0.02 ± 0.09	0.164
25°	0.46 ± 0.14	0.46 ± 0.15	-0.01 ± 0.09	0.636
30°	0.46 ± 0.15	0.45 ± 0.15	-0.01 ± 0.09	0.760

*p-value<0.05

The changes in the meridians 0° and 10° were related to the changes of the central steep K (Spearman r=0.377, p=0.002; r=0.291, p=0.019, respectively) and the peripheral flat K (Spearman r=-0.308, p=0.012; r=0.249, p=0.045, respectively). Meanwhile, the meridians 15° and 20° associated with the changes of the flat K in paracentral (Spearman

r=-0.300, p=0.015; r=-0.292, p=0.018, respectively) and peripheral cornea (Spearman r=0.662, p<0.001; r=0.630, p<0.001, respectively).

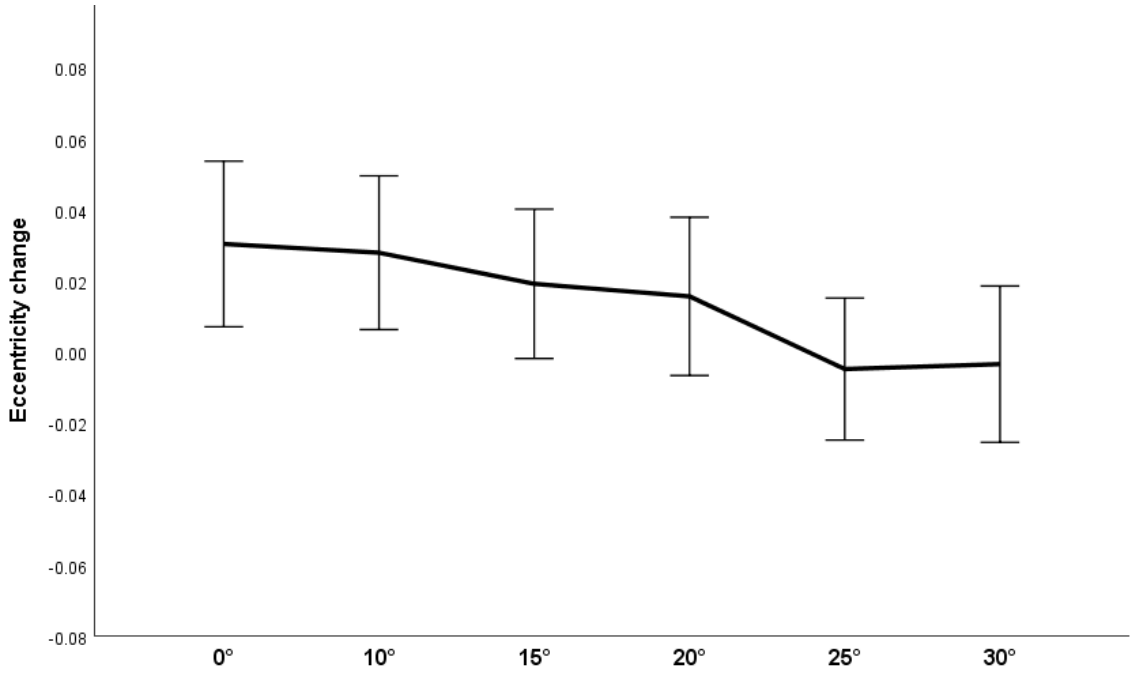

Figure 7.26. Eccentricity changes for the different meridians. Error bars: 95%CI.

Emmetropes evidenced a little higher eccentricity change in the meridians 0 to 20°, however, the change was not significantly different among groups for 0° (mixed ANOVA p=0.170), 10° (mixed ANOVA p=0.325), 15° (mixed ANOVA p=0.312) nor 20° (mixed ANOVA p=0.169). The eccentricity changes were also similar for 25° (mixed ANOVA p=0.706) and 30° (mixed ANOVA p=0.722). The average changes in each refractive group are shown in Table 7.19. The emmetropic group showed a significant eccentricity change in 0° (Student t-test p=0.035) and 10° (Student t-test p=0.046) meridians. Additionally, the shape changes were not related to the SE nor AL changes in any case.

Table 7.19. Change of eccentricity by meridians for the emmetropic and myopic group.

Meridian	Emmetropic (n=25)	Myopic (n=40)
0°	0.05 ± 0.11*	0.02 ± 0.08
10°	0.04 ± 0.10*	0.02 ± 0.08
15°	0.03 ± 0.10	0.01 ± 0.07
20°	0.04 ± 0.10	0.01 ± 0.08
25°	-0.01 ± 0.09	0.01 ± 0.07
30°	-0.01 ± 0.08	0.01 ± 0.07

*p-value<0.05

7.4.4 Corneal elevation

Anterior BFS exhibited a reduction after one year (Student t-test p=0.015). Nevertheless, there were no significant changes in the anterior corneal elevation when evaluated with the toric ellipsoid. The elevation of the posterior steep meridian also reduced its negative power but not reaching the statistical significance (Student t-test p=0.053). Table 7.20 contains the corneal elevation changes after one year. Figure 7.27 and Figure 7.28 depict the elevation changes for anterior and posterior cornea, respectively.

Table 7.20. Corneal elevation changes in the entire sample.

Parameter	Baseline	One year	Change	p-value
Anterior BFS	43.38 ± 1.32	43.32 ± 1.31	-0.06 ± 0.21	0.015*
Anterior Flat	43.67 ± 1.38	43.60 ± 1.38	-0.06 ± 0.30	0.104
Anterior Steep	44.57 ± 1.45	44.56 ± 1.49	-0.02 ± 0.33	0.683
Posterior BFS	-6.02 ± 0.22	-6.02 ± 0.22	0.01 ± 0.04	0.611
Posterior Flat	-5.98 ± 0.26	-5.96 ± 0.28	0.01 ± 0.16	0.592
Posterior Steep	-6.28 ± 0.29	-6.24 ± 0.32	0.04 ± 0.16	0.053

*p-value<0.05

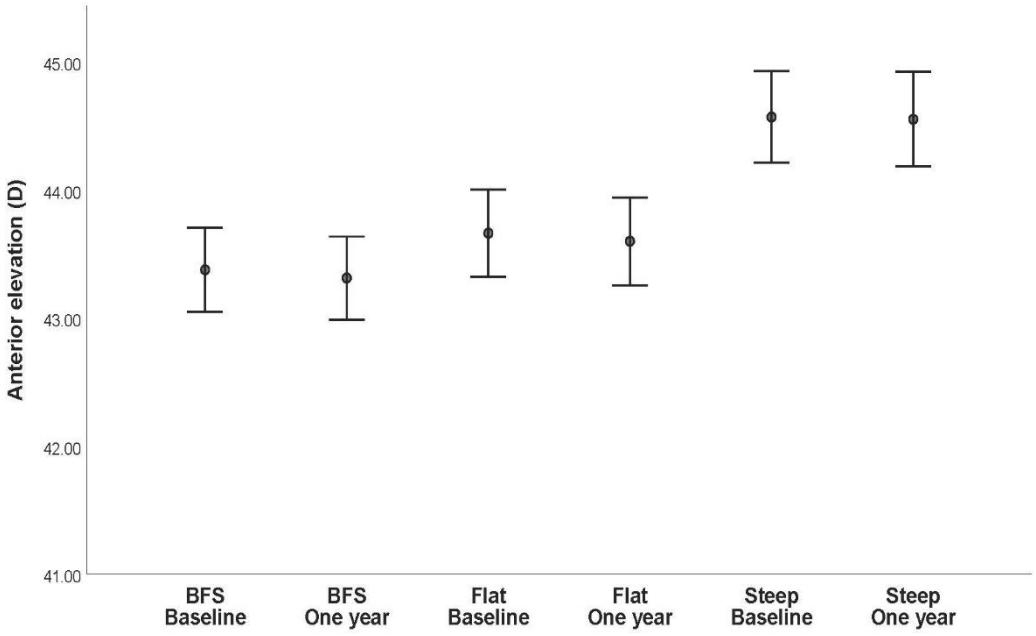

Figure 7.27. Anterior elevation changes obtained as BFS and toric ellipsoid. Error bars: 95%CI.

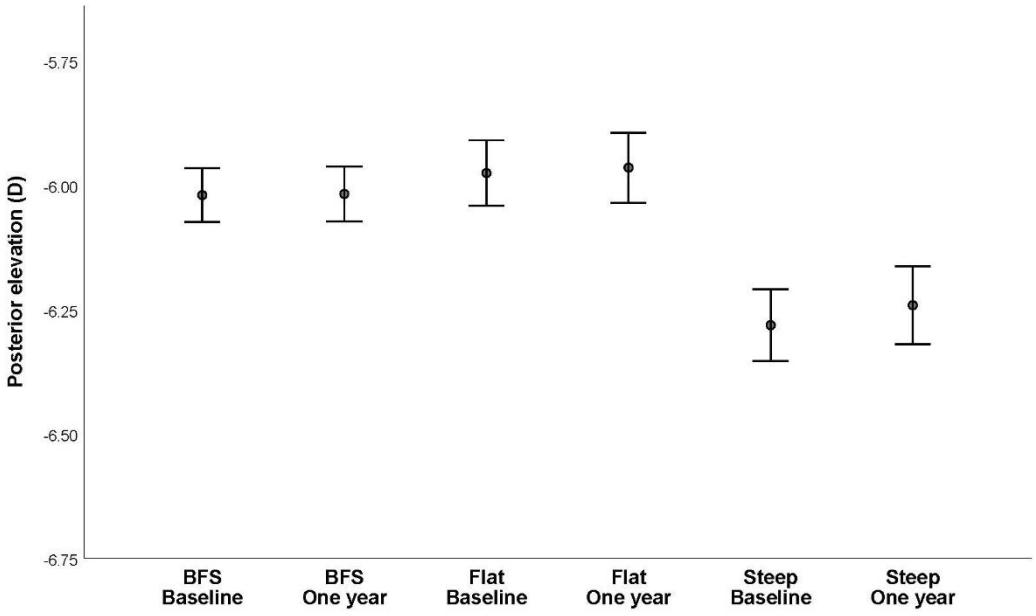

Figure 7.28. Posterior elevation changes obtained as BFS and toric ellipsoid. Error bars: 95%CI.

The change of the anterior BFS was similar among groups (mixed ANOVA p=0.208) as well as the change of the anterior elevation of the flat (mixed ANOVA p=0.277) and steep (mixed ANOVA p=0.372) meridians. Alike, the changes of the posterior BFS (mixed ANOVA p=0.135) and the elevation of posterior flat (mixed ANOVA p=0.079) and steep (mixed ANOVA p=0.163) meridians did not show significant differences. The average elevation changes for each refractive group are presented in Table 7.21. Besides, the anterior BFS (Student t-test p=0.025) and the elevation of the posterior steep meridian (Student t-test p= 0.027) changed significantly in the emmetropic group.

Table 7.21. Corneal elevation changes for the emmetropic and myopic group.

Parameter	Emmetropic	Myopic
Anterior BFS	-0.10 ± 0.22*	-0.04 ± 0.20
Anterior Flat	-0.12 ± 0.34	-0.03 ± 0.28
Anterior Steep	-0.06 ± 0.31	0.01 ± 0.35
Posterior BFS	0.01 ± 0.03	-0.01 ± 0.04
Posterior Flat	0.06 ± 0.16	-0.02 ± 0.16
Posterior Steep	0.08 ± 0.16*	0.02 ± 0.16

*p-value<0.05

7.4.5 Axial length to corneal radius ratio

For the entire sample, the AL/CR ratio did not change significantly between baseline (3.18 ± 0.21) and follow-up (3.19 ± 0.21) visit (Wilcoxon p=0.650). Among refractive groups, the change of the AL/CR ratio was significantly different (mixed ANOVA p=0.048; Figure 7.29). The myopic group experienced an increase of 0.005 ± 0.019 whereas the emmetropic had an AL/CR reduction on average -0.004 ± 0.015. The change within each refractive group was not significant nor was correlated with the SE changes.

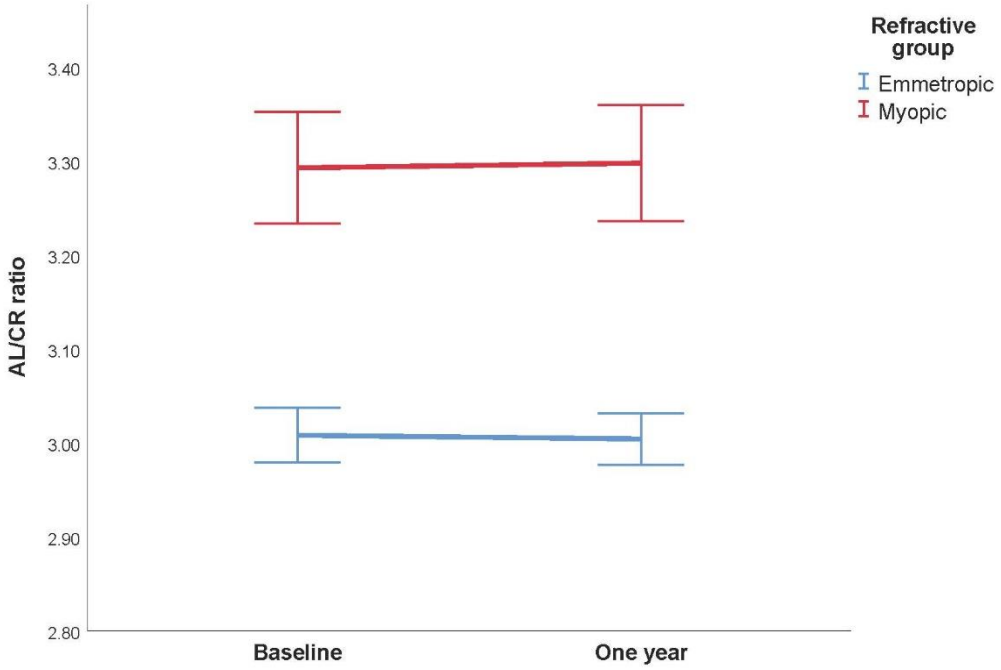

Figure 7.29. AL/CR change for the myopic and emmetropic group. Error bars: 95%CI.

7.5 Discussion

7.5.1 Corneal thickness and diameter

CT revealed an increment from central to peripheral cornea conformed to anterior results (Fares et al., 2012; Jonuscheit et al., 2014; Ortiz et al., 2014). Our increase from the centre to the periphery was quite similar between emmetropic and myopic subjects. Most of the studies have not identified significant CCT differences between emmetropes and myopes neither association between myopia and CCT (Tong et al., 2004b; Pedersen, Hjortdal and Ehlers, 2005; Fam et al., 2006; Al-Mezaine et al., 2008; O'Donnell, Hartwig and Radhakrishnan, 2011; Ortiz et al., 2014; Hashmani et al., 2017). In this chapter, the CT has shown to be similar in every corneal zone between myopes and emmetropes.

Central and peripheral corneal has not manifested to be related to the SE or AL in the work by Ortiz et al. (2014) agreeing with us.

The CT had very little changes after one year and although the change in central corneal was significant, it can be considered as clinically negligible. Previous cross-sectionals researches have informed of corneal thinning with age (Jonuscheit and Doughty, 2009; Galgauskas et al., 2013; Hashemi et al., 2011). One 5-year follow-up study (Hashemi et al., 2016) acquired corneal thinning in the centre and periphery in subjects older than 40, but non clinically significant. Refractive error did not influence the thinning experienced over time in this same study. Meanwhile, our refractive groups showed similar thickness changes across corneal zones. Besides, these changes were within the range of the expected differences between repeated measurements (Huang et al., 2010).

Corneal diameter did not differ between refractive groups aligned with two former investigations (Cosar and Sener, 2003; O'Donnell, Hartwig and Radhakrishnan, 2011). Other studies have informed of lower WTW with higher myopic degree in adults (Zha et al., 2012; Martin, Ortiz and Rio-Cristobal, 2013). The WTW was significantly smaller in median myopes (SE between -3.00 and -6.00 D) and high myopes (SE ≤-6.00 D) in comparison to emmetropic and low myopic group (SE between -0.50 and -3.00 D) in Asians adults (Zha et al., 2012). In Caucasians (Martin, Ortiz and Rio-Cristobal, 2013), lower WTW was found when high (SE < -6.00 D) and extremely myopes (SE < -12.00 D) were compared to low myopes (SE > -6.00 D). Another work (Khokhar et al., 2017) acquired significant higher WTW in myopic subjects with an AL > 28.5 mm.

Some authors reported a weak relationship between WTW and SE. Cosar and Sener (2003) and Martin, Ortiz and Rio-Cristobal (2013) identified a positive relationship in Caucasians so that the WTW was lower in higher myopes. Contrary, the study by Kato et al. (2019) in Asians found a negative relationship. Aligned with the findings of O'Donnell, Hartwig and Radhakrishnan (2011), there was a positive association between the WTW and AL rather than with the refractive error per se in this work. This positive relationship was also present in the study by Khokhar et al. (2017) for the myopic eyes with an AL between 26.5 and 28.5 mm but it was not for myopes with an AL above 28.5 mm. Conformed to this latter research, our WTW data revealed to increase with the VCD up to about 19 mm to then showing no dependency on the eye elongation.

Finally, the changes of the WTW after a year were similar between the emmetropic and myopic group and no significant in any case. Several authors discerned the WTW decreased with age (Rüfer, Schröder and Erb, 2005; Lee et al., 2010; Gharaee et al., 2014) while others did not find this relationship (Alfonso et al., 2010; Hashemi et al., 2010).

7.5.2 Corneal curvature

The mean power of the central corneal was broadly higher in our myopic group. Likewise, some authors have also perceived steeper cornea in myopic than emmetropic adults (Grosvenor and Scott, 1991; Goss et al., 1997; González Blanco, Sainz Fernández and Muñoz Sanz, 2008; O'Donnell, Hartwig and Radhakrishnan, 2011). Llorente et al. (2004) also detected steeper apical radius in myopes albeit it did not result to be significant. In Spanish university students, the mean corneal radius was even smaller in moderate myopes (SE ≤ -3.00 D) in comparison to low myopes (González Blanco, Sainz Fernández and Muñoz Sanz, 2008). In our case, myopes manifested greater steep K in central but also in paracentral cornea whereas flat K did not present significant differences in any zone. In the work by O'Donnell, Hartwig and Radhakrishnan (2011), myopic subjects (SE ≤ -0.50 D) had significant greater steep K but also flat K in the central cornea.

Myopes evidenced higher astigmatism in the central cornea while in paracentral corneal it did not reach the significance. Former studies have also determined higher astigmatism magnitudes in myopic adults in comparison to emmetropic (Muftuoglu and Erdem, 2008; Leung, Lam and Kee, 2013; Manny et al., 2016). In the periphery, astigmatism was similar between our refractive groups because of the greater increment of astigmatism from paracentral to peripheral corneal in the emmetropic group.

A negative association of the SE with the mean K and steep K was observed in our sample. This relationship was stronger in the central and paracentral cornea, although the correlation was still significant in the periphery. More myopic SE has been anteriorly associated with greater corneal curvature (Goss et al., 1997; Mallen et al., 2005; Logan et al., 2005; Bullimore et al., 2006; AlMahmoud et al., 2011). On the contrary, other authors have not detected this association (González Blanco, Sainz Fernández and Muñoz Sanz, 2008; Xie et al., 2009; Kato et al., 2019). Despite the significant steeper cornea in myopes, the study by O'Donnell, Hartwig and Radhakrishnan (2011) neither found a relationship between SE and corneal curvature. Moreover, several investigations (Chang

et al., 2001; Bao et al., 2010; Jonas et al., 2016a) informed of flatter corneal curvature with longer AL.

Similar to us, Scott and Grosvenor (1993) realised longer eyes showed flatter cornea regardless of the refractive error even though myopic eyes showed steeper corneal curvature. González Blanco, Sainz Fernández and Muñoz Sanz (2008) identified that the correlation between the mean corneal radius and AL tended to be stronger in emmetropia (r = 0.65) and low myopia (r = 0.59) in comparison to moderate myopia (r = 0.45). Thereby, the corneal flattening with longer AL appeared to be less effective in moderate myopes, which agrees with our results. Our relationship between the corneal curvature and VCD was better explained with a quadratic fit, particularly for myopes. This evidenced that cornea may steepen when the eye exceeds certain elongation, which was approximately beyond the 19 mm of VCD. In the study by Khokhar et al. (2017), there was a trend to greater keratometry in the subjects with an AL between 26.5-28.5 mm than those with an AL within 24.5-26.5 mm. All these findings might be explained according to the stretching theory by van Alphen (1961), as a reduction or even loss of the corneal compensation to the axial elongation in myopia.

Overall, the mean K did not manifest significant changes after a year in the present work. Similarly, previous longitudinal researches have not found significant changes in corneal curvature (Grosvenor and Scott, 1993; Lin et al., 1996; McBrien and Adams, 1997; Kinge et al., 1999; Jorge, Almeida and Parafita, 2007; Onal et al., 2007; Jacobsen, Jensen and Goldschmidt, 2008). When assessing the principal meridians apart, the power of flat K underwent a significant decrease in the central, paracentral and peripheral cornea. In the work by Lin et al. (1996) the corneal curvature flattened from 7.77 to 7.81 mm after 5 years, though it was not statistically significant.

A slight flattening of the corneal radius was seen in those with refractive changes between 0 and -0.25 D in the 3-year follow-up by Kinge et al. (1999). In the same way, our flat K changes were not related to the SE changes and even they tended to be greater in the emmetropic group. This indicated that apparently some students still may compensate the eye elongation with the corneal flattening and, therefore, the emmetropization could remain in young adulthood. Furthermore, our results proved than myopia did not occur or progress in young adults because of the corneal changes confirming the results of previous authors (Grosvenor and Scott, 1993; Lin et al., 1996;

McBrien and Adams, 1997; Kinge et al., 1999; Jorge, Almeida and Parafita, 2007; Onal et al., 2007; Jacobsen, Jensen and Goldschmidt, 2008).

7.5.3 Corneal shape

The refractive groups mostly had no differences in the shape parameters (e, Q, SF). Previous works have not noticed a relationship between corneal Q and refractive error (Budak et al., 1999; Nieto-Bona, Lorente-Velázquez and Montés-Micó, 2008; Yazdani et al., 2016). Agreeing with us, two previous studies (Nieto-Bona, Lorente-Velázquez and Montés-Micó, 2008; Scholz et al. 2009) have not perceived significant Q differences between myopes and emmetropes.

Carney, Mainstone and Henderson (1997) obtained less flattening (more positive Q) in myopes in spite of the greater corneal radius in myopia. More flattening would be expected with steeper curvature on central cornea. This paradox was explained through the stretch factor (van Alphen, 1961) so they believed the peripheral cornea could also steep as a result of the ACD increase. Budak et al. (1999) found less negative Q values in moderate myopes even though there was no association between Q and refractive error.

Meantime, several studies in Asians (Zhang et al., 2011; Leung, Lam and Kee, 2013; Xiong et al., 2017) have obtained more negative Q in myopia. This research proved that the eccentricity was greater for myopes in the meridians from 0 to 30° so that myopic subjects experienced more flattening from centre to periphery in these meridians. More negative values have also been observed in young adults with greater corneal astigmatism as well as considering larger corneal diameter (González-Méijome et al. 2007; Nieto-Bona, Lorente-Velázquez and Móntes-Micó, 2008). Corneal astigmatism is mostly WTR in young adulthood (Sanfilippo et al., 2015) so that flat K is located close to the horizontal. Therefore, our findings are likely due to myopes manifested a bit more corneal curvature of flat K in the central cornea, though non-significant, as well as higher astigmatism.

Despite the no significant changes in e, Q nor SF after a year, the corneal shape changes were related to the changes in the curvature of the central steep K and the peripheral flat K. This pointed out that more negative Q, that is more prolate cornea, was accounted by more flattening change in the peripheral than in the central cornea. The eccentricity increased by 0.02 on average as in the work by Jorge, Almeida and Parafita (2007), however, in our case not reaching the significance. The eccentricity increment was

significant in the horizontal when assessed by meridians. The meridians 0 and 10° became more prolate and it was also related to the changes in the curvature of the central steep K and the peripheral flat K. These meridians were more prolate particularly in the emmetropic group since the curvature decrease of flat K showed a non-significant tendency of greater decrease in the peripheral cornea in this refractive group.

7.5.4 Corneal elevation

The results of this research for anterior BFS are within those reported previously in myopes (Wei et al., 2006; Uçakhan et al., 2008; Mehravaran et al., 2013) and emmetropes (Uçakhan et al., 2008; Mehravaran et al., 2013). The posterior BFS results measured with Orbscan are not directly comparable to ours since the power equivalent of this BFS is converted as for the anterior surface that is using the keratometric index of 1.3375 and the air. In order to compare the results among investigations, their power equivalence was recalculated using the index of the cornea (1.336) and the aqueous humour (1.376) as Visante omni device does. Accordingly, the posterior BFS in these studies (Wei et al., 2006; Uçakhan et al., 2008; Mehravaran et al., 2013) was steeper than ours for both myopes (between -6.16 and -6.30 D) and emmetropes (between -6.16 and -6.23 D).

There were no significant differences in anterior nor posterior BFS between myopic and emmetropic subjects in former works (Uçakhan et al., 2008; Mehravaran et al., 2013). Nonetheless, moderate and high myopes evidenced BFS values above emmetropes in the study by Mehravaran et al. (2013). We did observe myopes had significant more curvature than emmetropes in anterior and posterior BFS. Besides, more myopic SE was related to steeper BFS for anterior and posterior corneal surfaces. Then, the toric ellipsoid fit revealed significant differences only in the elevation of the anterior steep meridian. On the whole, the steeper anterior BFS in myopia occurs as a result of the steeper central curvature in myopes but with similar asphericity than emmetropes (Gatinel et al., 2011). Indeed, the corneal curvature has shown to be associated with the anterior and posterior BFS in this work and previous ones (Wei et al., 2006; Mehravaran et al., 2013). Furthermore, the VCD demonstrated to have a dichotomous relationship with the BFS of both corneal surfaces. Our BFS (anterior and posterior) flattened until reaching 19-19.5 mm of VCD to then steepen.

Only a few cross-sectional researches have reported changes in the corneal elevation related to age (Mehravaran et al., 2013; Namba et al., 2018). Anterior BFS significantly increased with age in subjects from 14 to 60 years (Mehravaran et al., 2013). Contrary to this, we acquired a diminution of the anterior corneal elevation in young subjects, albeit the present study was longitudinal. In subjects older than 35 years, Namba et al. (2018) found that the central elevation (measured in microns) of the horizontal meridian decreased with age while it increased for the vertical according to the corneal astigmatism age-related changes from WTR to ATR (Sanfilippo et al., 2015). Meanwhile, the posterior elevation has not demonstrated to undergo significant changes with age (Mehravaran et al., 2013; Namba et al., 2018). Still, our longitudinal changes of BFS are aligned with the keratometry ones. Anterior BFS experienced a significant flattening, which was significant within the emmetropic group. Likewise, the elevation of the posterior steep meridian also tended to decrease its curvature within the emmetropes.

7.5.5 Axial length to corneal radius ratio

The AL/CR ratio was first suggested as a myopia predictor by Grosvenor (1988). According to the data of young emmetropic eyes, AL/CR is expected to be close to 3.00 in the eyes whose elongation is coordinated with the corneal curvature changes. Therefore, AL/CR > 3.00 has been considered as a risk factor for myopia development (Grosvenor, 1988; Grosvenor and Scott, 1994; Goss and Jackson, 1995).

Our AL/CR ratio is comparable to that obtained in a former work in Spanish university students (González Blanco, Sainz Fernández and Muñoz Sanz, 2008). Greater AL/CR ratio has been observed in myopic eyes compared to emmetropic in young adults (Grosvenor and Scott, 1991; Grosvenor and Scott, 1994; McBrien and Adams, 1997; Llorente et al., 2004; González Blanco, Sainz Fernández and Muñoz Sanz, 2008) conforming with us. AL/CR tended to increase in eyes with more myopia as seen before (Grosvenor and Scott, 1994; González Blanco, Sainz Fernández and Muñoz Sanz, 2008). In fact, the AL/CR ratio has demonstrated to have a stronger relationship with the refractive error than the one of the SE with AL or CR separately (Llorente et al., 2004; Mallen et al., 2005; González Blanco, Sainz Fernández and Muñoz Sanz, 2008; Hashemi et al., 2013).

Moreover, our AL/CR ratio was higher in the students with deeper ACD and thinner LT. During the emmetropization process, the power of the crystalline lens is

expected to decrease as the AL/CR ratio increases (Grosvenor and Scott, 1994). For a given ametropia, eyes with greater AL/CR will present lower lens power whereas those with lower AL/CR will have higher lens power (Grosvenor and Scott, 1994). Thereby, the thinner LT seen in myopia may occur because of the axial and equatorial eye expansion as well as the loss of the crystalline power in an attempt to compensate the AL/CR increase. Opposite to us, González Blanco, Sainz Fernández and Muñoz Sanz (2008) did not find a significant association between AL/CR and LT in emmetropes nor myopes. The multiple regression model in the study by González Blanco, Sainz Fernández and Muñoz Sanz (2008) yielded to AL and CR as significant predictors of the SE explaining 68.68% of its variance. AL and CR were also the most important predictors of SE in our model that alongside LT and the sex accounted for more than 95% of the SE variance.

The AL/CR ratio did not undergo significant changes after a year in our sample of university students. McBrien and Adams (1997) acquired no different initial AL/CR of those who were emmetropic and became myopic compared to those remaining emmetropic after 2 years. Similar AL/CR ratio was also obtained in the progressing and stable myopes in this same work. In children, the longitudinal COMET study (Scheiman et al., 2016) identified an increment of AL/CR ratio from 3.15 to 3.31 along with myopia progression after 14 years of follow-up. However, the association between AL/CR and SE progression was not significant in children (Scheiman et al., 2016; Jong et al., 2018) as it was not in this research in young adults. Therefore, the AL/CR ratio seems to be useful to determine the risk of developing myopia or the myopia degree but not to monitor myopia progression.

7.6 Conclusion

7.6.1 Corneal differences related to myopia

The CT has not manifested differences in any corneal zone due to myopia. Despite the similar WTW between myopes and emmetropes, WTW increased with longer VCD until reaching about 19 mm but subsequently showed no dependency on the eye elongation. Myopes exhibited greater corneal curvature than emmetropes, especially the steep meridian in central and paracentral cornea. Likewise, higher corneal astigmatism was also found in myopic eyes in central cornea. Then, the corneal curvature reduction from centre to periphery did not differ on account of myopia, on the whole myopes and

emmetropes showed similar corneal asphericity. Consequently, the anterior BFS was steeper for myopes as a result of the greater elevation of the steep meridian. Posterior BFS was also steeper in myopes but the toric ellipsoid fit did not reveal significant differences. The VCD had a dichotomous relationship with the corneal curvature and elevation so that the eye elongation led the cornea to flatten until the VCD reached 19-19.5 mm, point from which the cornea could no longer compensate the eye enlargement and it even steepened. Thus, greater AL/CR was seen in myopes than in emmetropes, where myopes were mostly above 3.00 in this ratio. Every 0.1 increase in the AL/CR ratio led to a negative refractive shift of about 1.5 D. Moreover, the AL/CR ratio was higher in the students with deeper ACD and thinner LT.

7.6.2 Corneal changes alongside myopia progression

After a year, the CT and WTW had very little changes and these were not related to the SE nor AL changes. The curvature of the flat meridian experienced a general decrease in central, paracentral and peripheral cornea. However, the reduction of flat K in the central and paracentral cornea was only significant within the emmetropic group. These changes did not associate with the SE changes and tended to be even greater for emmetropes. Aligned with that, anterior BFS underwent a flattening which also tended to be higher in emmetropes. The corneal curvature changes found in this study pointed out that axial elongation still may be compensated by corneal flattening in young adults, particularly among emmetropes. Myopia was then proved not to occur or progress in adults because of the corneal changes. The AL/CR ratio change differed among groups, where the myopic group experienced a slight increase whereas the emmetropic a reduction. Nonetheless, AL/CR ratio changes were not significant nor related to SE changes and, therefore, the AL/CR ratio was not useful to monitor or quantify myopia progression in young adults.

CHAPTER 8. ABERROMETRY EXAMINATION

8.1 Methodology

Corneal and ocular wavefront measurements yielded to the obtaining of Zernike polynomials for 3 and 5 mm pupil size. Then, the internal wavefront was obtained subtracting the corneal coefficients from the ocular coefficients (Artal et al., 2001). So that Zernike coefficients from second to seventh-order were analysed for corneal, internal and ocular wavefront. Zernike coefficients were expressed in microns and presented according to the standards of the Optical Society of America (Thibos et al., 2002) and the American National Standard Institute (ANSI, 2004). Further, the calculation of several RMS was done using the following formula:

$$RMS = \sqrt{\sum_{n,m} (C_n^m)^2}$$

Where C_n^m are the successive Zernike coefficients. The LOA RMS was computed considering the second-order coefficients while the HOA RMS accounted for all the coefficients from third to seventh-order. The RMS was also calculated in each high order separately (3rd, 4th, 5th, 6th and 7th). Moreover, the calculation of the RMS for low order astigmatism (Z_2^{-2} and Z_2^2), high order astigmatism ($Z_4^{-2}, Z_4^2, Z_6^{-2}, Z_6^2$), spherical aberration (Z_4^0 and Z_6^0), coma-like aberration (Z_3^{-1}, Z_3^1, Z_5^{-1}, Z_5^1, Z_7^{-1}, Z_7^1), and trefoil-like aberration ($Z_3^{-3}, Z_3^3, Z_5^{-3}, Z_5^3, Z_7^{-3}, Z_7^3$) was carried out.

The wavefront data obtained with the 5 mm pupil size was used to evaluate the compensation between optic elements. This pupil size was chosen because this diameter offers a large sampling area where HOA usually take greater values. In order to assess the contribution of the internal wavefront to the ocular, the CF was calculated following previous methodology (Artal et al., 2002):

$$CF = 1 - \frac{W_{Ocular}}{W_{Corneal}}$$

Where W_{Ocular} and $W_{Corneal}$ are the coefficients or the RMS correspondent to the ocular and corneal wavefront, respectively. The CF is equal to 1 when there is total compensation between corneal and internal optics whereas it takes the value 0 when there is no compensation at all. Values below 0 are obtained when the internal optics aggregates

aberrations. Finally, values above 1 indicate that the internal optics have overcompensated the corneal wavefront, adding aberrations but in the opposite direction.

Firstly, the general compensation was evaluated through the RMS for the whole sample and subsequently for each refractive group. Then, the CF was further analysed for the different Zernike coefficients. The relationship between corneal and internal Zernike coefficients was also plotted to observe the different compensation pattern in the individual subjects. Figure 8.1 depicts a diagram indicating the zones that were marked on the plots to differentiate the compensation patterns.

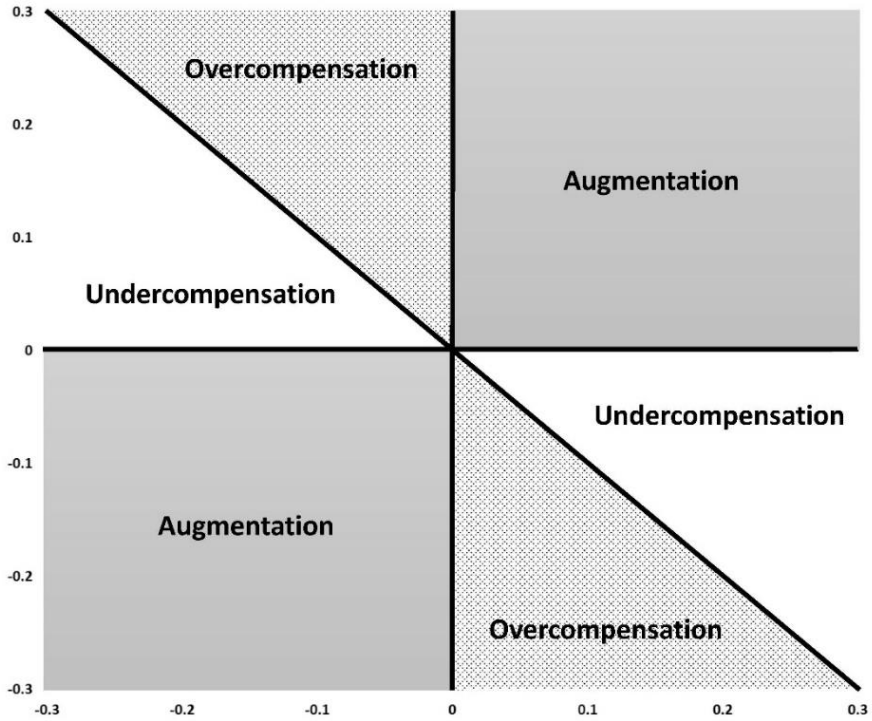

Figure 8.1. Diagram of the relationship between corneal and internal Zernike coefficients.

Basically, the augmentation occurs when the corneal and internal wavefront have the same signs. When corneal and internal wavefront have opposite signs, either undercompensation or overcompensation can happen. The internal optics compensate part of the corneal wavefront in the undercompensation zone. If the internal wavefront is oppositely signed but greater than the corneal then overcompensation is seen. The diagonal line in the diagram represents the total compensation (y= -x).

Additionally, the longitudinal aberrometry allowed for the analysis of the change of corneal, internal and ocular Zernike coefficients and RMS after a year. The change of the coefficients was computed as the difference between follow-up and baseline visit. The follow-up analysis was only performed for a 3 mm pupil size because not all patients reached the 5 mm pupil size in both visits.

8.2 Statistical analysis

The wavefront differences, namely Zernike coefficients and RMS, between refractive groups were assessed by the Student t-test for independent samples or Mann-Whitney test, depending on the groups' distribution. Pearson and Spearman correlation coefficients were employed to determine the relationship between the individual Zernike coefficients and RMS with the sphere, cylinder and VCD. Simple linear regression also provided the R^2, that is to say, the variability part of each Zernike coefficient that was explained by the sphere and/or VCD. Then, multiple regression was applied to evaluate which ocular Zernike coefficients accounted for the variability of the SE and VCD, controlling for age and sex. Sex was transformed into a categorical variable where males and females were represented with 0 and 1, respectively. The same analysis was performed for 3 and 5 mm pupil size data. For the compensation between optic elements (5 mm), ocular, corneal and internal Zernike RMS were compared in the general sample through the Student t-test for paired samples or the non-parametric Wilcoxon test. For each refractive group, the CF was checked to be significantly different from zero through the Student t-test or Wilcoxon test for one sample.

The data comparison between baseline and after one year was performed by means of Student t-test for paired samples or the non-parametric Wilcoxon test in the general sample and also within each refractive group. The differences in the change among refractive groups were assessed by the mixed ANOVA analysis. Pearson and Spearman correlation coefficients were also used to evaluate the relationship of the aberrometry changes with the refractive (sphere, cylinder) and biometric (ACD, LT, VCD) changes. Finally, two multiple regression models were constructed to obtain which changes in the ocular coefficients explained the variance of the SE and VCD changes.

Statistical power analysis

Independent sample comparison. For the baseline analysis, the power of 0.8 was achieved for both data of 3 and 5 mm pupil size setting a medium effect size of 0.65 and 0.7, respectively.

Related samples comparison. The power analysis was 0.8 considering an effect size of 0.35 for both baseline and longitudinal sample. Power of the analysis accomplished 0.8 with a medium effect size *d* of 0.5 and 0.6 for the comparison within the myopic and emmetropic group, respectively.

Simple linear regression. The power analysis was 0.8 considering an effect size of 0.35 for baseline data (3 and 5 mm). For the data of the follow-up, the desired power of 0.8 allowed to detect relationships with an effect size of 0.34.

Multiple linear regression. The models constructed to predict SE, VCD and their changes had a power above 0.8 with a 0.2 effect size f^2 for baseline and longitudinal sample.

Mixed ANOVA. The longitudinal changes analysis exceeded 0.8 power with an effect size of 0.15.

8.3 Baseline results

8.3.1 Pupil size 3 mm

8.3.1.1 Corneal wavefront

The corneal defocus Z_2^0 took the value zero and was not included in the analysis. Oblique astigmatism Z_2^{-2} and WTR/ATR astigmatism Z_2^2 coefficients were similar between myopic and emmetropic subjects (Table 8.1). Nevertheless, more negative WTR/ATR astigmatism Z_2^2 did correlate with more myopic sphere (Spearman r=0.269, p=0.017).

Table 8.1. Corneal LOA for the emmetropic and myopic group (3mm).

Coefficient	Emmetropic (n=31)	Myopic (n=47)	p-value
Z_2^{-2} (µm)	0.006 ± 0.081	0.031 ± 0.121	0.304
Z_2^2 (µm)	-0.142 ± 0.126	-0.182 ± 0.198	0.280

No significant differences were found between refractive groups for most of the HOA (Table 8.2). The emmetropic group exhibited significantly more positive values of oblique astigmatism Z_4^{-2} (Student t-test p=0.004) while more negative trefoil Z_7^{-3} (Mann-Whitney p=0.028) and pentafoil Z_7^5 (Mann-Whitney p=0.033) in comparison with the myopic. Longer VCD associated with less negative horizontal coma Z_3^1 (Pearson r=0.229, p=0.044) despite not differing significantly between refractive groups. Likewise, more myopic sphere had a relationship with more negative oblique astigmatism Z_4^{-2} (Spearman r=0.256, p=0.023) and the trefoil Z_7^3 (Spearman r=0.226, p=0.047).

Total corneal RMS (Mann-Whitney p=0.015) was significantly higher for the myopic group and correlated with the sphere (Spearman r=-0.259, p=0.022), cylinder (Spearman r=-0.380, p=0.001) and VCD (Spearman r=0.246, p=0.030). Table 8.3 presents the different calculated RMS for both refractive groups. Low order astigmatism RMS also manifested greater values in the myopic group (Mann-Whitney p=0.018) whereas the high order astigmatism RMS was similar between groups. Indeed, low order astigmatism RMS was related to the sphere (Spearman r=-0.279, p=0.013), cylinder (Spearman r=-0.408, p<0.001) and VCD (Spearman r=0.248, p=0.029). Additionally, the cylinder power had an association with HOA (Spearman r=0.226, p=0.047) and fourth-order RMS (Spearman r=0.328, p=0.003).

Table 8.2. Corneal HOA for the emmetropic and myopic group (3 mm).

Order	Coefficient	Emmetropic (n=31)	Myopic (n=47)	p-value
3rd	Z_3^{-3} (µm)	-0.006 ± 0.040	0.004 ± 0.033	0.222
	Z_3^{-1} (µm)	0.002 ± 0.031	0.005 ± 0.032	0.693
	Z_3^{1} (µm)	-0.009 ± 0.030	-0.001 ± 0.022	0.194
	Z_3^{3} (µm)	-0.009 ± 0.026	-0.008 ± 0.026	0.859
4th	Z_4^{-4} (µm)	0.004 ± 0.014	-0.004 ± 0.022	0.071
	Z_4^{-2} (µm)	0.006 ± 0.015	-0.004 ± 0.014	0.004*
	Z_4^{0} (µm)	0.020 ± 0.019	0.013 ± 0.026	0.277
	Z_4^{2} (µm)	0.000 ± 0.025	0.004 ± 0.018	0.173
	Z_4^{4} (µm)	0.000 ± 0.018	0.004 ± 0.021	0.244
5th	Z_5^{-5} (µm)	-0.005 ± 0.013	-0.007 ± 0.019	0.728
	Z_5^{-3} (µm)	0.004 ± 0.021	0.001 ± 0.016	0.431
	Z_5^{-1} (µm)	0.000 ± 0018	-0.004 ± 0.014	0.767
	Z_5^{1} (µm)	0.000 ± 0.016	-0.001 ± 0.019	0.951
	Z_5^{3} (µm)	0.004 ± 0.012	0.001 ± 0.019	0.154
	Z_5^{5} (µm)	0.000 ± 0.012	-0.001 ± 0.016	0.374
6th	Z_6^{-6} (µm)	-0.004 ± 0.011	-0.002 ± 0.013	0.494
	Z_6^{-4} (µm)	0.002 ± 0.011	0.002 ± 0.015	0.884
	Z_6^{-2} (µm)	-0.001 ± 0.012	-0.002 ± 0.013	0.627
	Z_6^{0} (µm)	0.005 ± 0.034	0.003 ± 0.029	0.733
	Z_6^{2} (µm)	-0.002 ± 0.015	-0.003 ± 0.016	0.786
	Z_6^{4} (µm)	-0.003 ± 0.013	-0.005 ± 0.016	0.475
	Z_6^{6} (µm)	-0.004 ± 0.013	-0.003 ± 0.023	0.884
7th	Z_7^{-7} (µm)	0.003 ± 0.010	0.004 ± 0.013	0.947
	Z_7^{-5} (µm)	0.005 ± 0.011	0.001 ± 0.014	0.085
	Z_7^{-3} (µm)	-0.004 ± 0.015	0.004 ± 0.016	0.028*
	Z_7^{-1} (µm)	0.000 ± 0.011	-0.001 ± 0.013	0.683
	Z_7^{1} (µm)	-0.004 ± 0.014	-0.001 ± 0.013	0.779
	Z_7^{3} (µm)	-0.002 ± 0.012	-0.001 ± 0.016	0.169
	Z_7^{5} (µm)	-0.004 ± 0.010	0.000 ± 0.017	0.033*
	Z_7^{7} (µm)	-0.003 ± 0.010	0.000 ± 0.017	0.886

*p-value<0.05

Table 8.3. Calculated corneal RMS for the emmetropic and myopic group (3 mm).

RMS (μm)	Emmetropic (n=31)	Myopic (n=47)	p-value
Low order astigmatism (2nd)	0.170 ± 0.115	0.248 ± 0.161	0.018*
HOA (3rd to 7th)	0.099 ± 0.035	0.098 ± 0.046	0.543
Total	0.208 ± 0.102	0.274 ± 0.134	0.015*
3rd order	0.059 ± 0.026	0.052 ± 0.026	0.211
4th order	0.042 ± 0.020	0.041 ± 0.025	0.628
5th order	0.033 ± 0.020	0.036 ± 0.023	0.219
6th order	0.041 ± 0.020	0.043 ± 0.025	0.894
7th order	0.032 ± 0.012	0.036 ± 0.023	0.441
High order astigmatism (4th and 6th)	0.030 ± 0.018	0.028 ± 0.014	0.963
Spherical aberration (4th and 6th)	0.038 ± 0.023	0.036 ± 0.020	0.858
Coma-like (3rd to 7th)	0.046 ± 0.025	0.045 ± 0.020	0.255
Trefoil-like (3rd to 7th)	0.052 ± 0.024	0.047 ± 0.028	0.670

*p-value<0.05

Simple linear regression manifested that the sphere accounted for 7.2% of the variance in WTR/ATR astigmatism Z_2^2 and trefoil Z_7^3, while 4.5% of the oblique astigmatism Z_4^{-2}. The VCD explained 5.2% of the horizontal coma Z_3^1 variability. Meanwhile, the sphere explained 10.9% and 11% of the LOA RMS and low order astigmatism RMS variance, respectively. The VCD accounted for lower variability in LOA RMS and low order astigmatism RMS (7.6% and 7%, respectively) than the sphere. Besides, part of the HOA RMS (5.6%) and fourth-order RMS (9.7%) variance was explained by the cylinder power as well as for the LOA RMS (31.6%).

8.3.1.2 Internal wavefront

From the internal LOA (Table 8.4), the defocus Z_2^0 and WTR/ATR astigmatism Z_2^2 were significantly greater for the myopic group (Mann-Whitney p<0.05).

Table 8.4. Internal LOA for the emmetropic and myopic group (3mm).

Coefficient	Emmetropic (n=31)	Myopic (n=47)	p-value
Z_2^{-2} (μm)	0.013 ± 0.074	-0.012 ± 0.092	0.226
Z_2^0 (μm)	0.078 ± 0.153	1.400 ± 0.943	<0.001*
Z_2^2 (μm)	0.099 ± 0.101	0.138 ± 0.090	0.042*

*p-value<0.05

Greater defocus Z_2^0 associated significantly with more myopic sphere (Spearman r=-0.973, p<0.001) and longer VCD (Spearman r=0.736, p<0.001). Further, several higher-order coefficients differed between refractive groups (Table 8.5).

Table 8.5. Internal HOA for the emmetropic and myopic group (3 mm).

Order	Coefficient	Emmetropic (n=31)	Myopic (n=47)	p-value
3rd	Z_3^{-3} (µm)	-0.008 ± 0.028	-0.025 ± 0.032	0.019*
	Z_3^{-1} (µm)	-0.001 ± 0.029	0.008 ± 0.021	0.135
	Z_3^{1} (µm)	0.019 ± 0.026	0.010 ± 0.023	0.082
	Z_3^{3} (µm)	0.017 ± 0.027	0.020 ± 0.024	0.595
4th	Z_4^{-4} (µm)	-0.003 ± 0.014	0.005 ± 0.022	0.048*
	Z_4^{-2} (µm)	-0.006 ± 0.016	0.004 ± 0.015	0.008*
	Z_4^{0} (µm)	-0.009 ± 0.022	-0.006 ± 0.024	0.561
	Z_4^{2} (µm)	-0.001 ± 0.023	-0.007 ± 0.020	0.038*
	Z_4^{4} (µm)	-0.001 ± 0.019	-0.005 ± 0.021	0.270
5th	Z_5^{-5} (µm)	0.005 ± 0.014	0.007 ± 0.020	0.610
	Z_5^{-3} (µm)	-0.003 ± 0.021	0.000 ± 0.017	0.434
	Z_5^{-1} (µm)	0.000 ± 0.018	0.004 ± 0.014	0.886
	Z_5^{1} (µm)	0.000 ± 0.017	0.001 ± 0.019	0.717
	Z_5^{3} (µm)	-0.005 ± 0.012	-0.002 ± 0.019	0.196
	Z_5^{5} (µm)	0.000 ± 0.012	-0.001 ± 0.017	0.803
6th	Z_6^{-6} (µm)	0.037± 0.011	0.002 ± 0.013	0.525
	Z_6^{-4} (µm)	-0.002 ± 0.011	-0.002 ± 0.014	0.911
	Z_6^{-2}(µm)	0.001 ± 0.011	0.002 ± 0.013	0.632
	Z_6^{0} (µm)	-0.006 ± 0.034	-0.003 ± 0.029	0.738
	Z_6^{2} (µm)	0.002 ± 0.015	0.003 ± 0.015	0.735
	Z_6^{4} (µm)	0.003 ± 0.013	0.005 ± 0.016	0.507
	Z_6^{6} (µm)	0.004 ± 0.013	0.006 ± 0.023	0.862
7th	Z_7^{-7} (µm)	-0.003 ± 0.010	-0.004 ± 0.013	0.955
	Z_7^{-5} (µm)	-0.005 ± 0.011	-0.001 ± 0.014	0.089
	Z_7^{-3} (µm)	0.004 ± 0.015	-0.004 ± 0.016	0.028*
	Z_7^{-1} (µm)	0.000 ± 0.011	0.001 ± 0.012	0.705
	Z_7^{1} (µm)	0.004 ± 0.014	0.001 ± 0.013	0.775
	Z_7^{3} (µm)	-0.002 ± 0.012	0.001 ± 0.016	0.144
	Z_7^{5} (µm)	0.004 ± 0.010	0.000 ± 0.017	0.036*
	Z_7^{7} (µm)	0.003 ± 0.010	0.000 ± 0.017	0.955

*p-value<0.05

Myopes revealed significantly more negative trefoil Z_3^{-3} (Student t-test p=0.019). Despite non-significant differences among groups, more positive vertical coma Z_3^{-1} correlated with more negative sphere (Spearman r=-0.245, p=0.031) while less positive horizontal coma Z_3^1 did with more cylinder (Spearman r=0.264, p=0.019) and longer VCD (Spearman r=-0.230, p=0.043). More positive tretrafoil Z_4^{-4} was seen in the myopic group (Mann-Whitney p=0.048) and the correlation with the sphere was significant (Spearman r=-0.228, p=0.045). Secondary astigmatism differed between groups where myopes had more positive values of oblique astigmatism Z_4^{-2} (Student t-test p=0.008) and more negative values of WTR/ATR astigmatism Z_4^2 (Mann-Whitney p=0.038). Consistently, the sphere had an association with both oblique astigmatism Z_4^{-2} (Spearman r=-0.230, p=0.043) and WTR/ATR astigmatism Z_4^2 (Spearman r=0.267, p=0.018). WTR/ATR astigmatism Z_4^2 also showed more negative values with longer VCD (Spearman r=-0.267, p=0.018). Then, the seventh-order coefficients Z_7^{-3} (Mann-Whitney p=0.028) and Z_7^5 (Mann-Whitney p=0.036) differed among emmetropes and myopes, though these differences can be considered as negligible.

Greater LOA RMS (Mann-Whitney p<0.001) was observed in myopes and consequently total RMS (Mann-Whitney p<0.001). No other RMS had significant differences between refractive groups for the internal aberrations (Table 8.6).

Table 8.6. Calculated internal RMS for the emmetropic and myopic group (3 mm).

RMS (μm)	Emmetropic (n=31)	Myopic (n=47)	p-value
LOA (2nd)	0.214 ± 0.092	1.418 ± 0.935	<0.001*
HOA (3rd to 7th)	0.094 ± 0.035	0.098 ± 0.046	0.748
Total	0.238 ± 0.087	1.425 ± 0.930	<0.001*
3rd order	0.054 ± 0.028	0.054 ± 0.028	0.854
4th order	0.040 ± 0.017	0.042 ± 0.023	0.898
5th order	0.034 ± 0.019	0.037 ± 0.023	0.561
6th order	0.041 ± 0.020	0.043 ± 0.025	0.890
7th order	0.026 ± 0.010	0.030 ± 0.022	0.939
Low order astigmatism (2nd)	0.139 ± 0.078	0.168 ± 0.086	0.135
High order astigmatism (4th and 6th)	0.029 ± 0.019	0.030 ± 0.014	0.222
Spherical aberration l (4th and 6th)	0.036 ± 0.020	0.033 ± 0.019	0.690
Coma-like (3rd to 7th)	0.046 ± 0.025	0.042 ± 0.016	0.690
Trefoil-like (3rd to 7th)	0.046 ± 0.026	0.053 ± 0.031	0.151

*p-value<0.05

LOA RMS had a relationship with the sphere (Spearman r=-0.937, p<0.001), cylinder (Spearman r=-0.431, p<0.001) and VCD (Spearman r=0.711, p<0.001). Similarly, total RMS associated with the sphere (Spearman r=-0.936, p<0.001), cylinder (Spearman r=-0.429, p<0.001) and VCD (Spearman r=0.726, p<0.001). Furthermore, HOA RMS had an association with the cylinder (Spearman r=0.279, p=0.013).

The 98.3% and 65.8% of the defocus Z_2^0 variance was explained by the sphere and VCD, respectively. The sphere also accounted for the variability of vertical coma Z_3^{-1} (5.4%), horizontal coma Z_3^1 (2.3%), tretrafoil Z_4^{-4}(1.2%), oblique astigmatism Z_4^{-2} (3.7%), WTR/ATR astigmatism Z_4^2 (1.4%) and trefoil Z_7^3 (7.5%). The VCD accounted for more variability for horizontal coma Z_3^1 (4.9%) and WTR/ATR astigmatism Z_4^2 (6%). The sphere explained 98.1% of the LOA RMS variance while VCD did 64.5%. The cylinder accounted for the 32% of the LOA RMS variability and 6.3% of the HOA RMS.

8.3.1.3 Ocular wavefront

As expected, the defocus Z_2^0 was significantly different between groups (Mann-Whitney test p<0.001). The defocus Z_2^0 was greater with more negative sphere (Spearman r=-0.973, p<0.001) and longer VCD (Spearman r=0.736, p<0.001). Meanwhile, oblique astigmatism Z_2^{-2} and WTR/ATR astigmatism Z_2^2 did not show significant differences. However, the sphere did correlate with the WTR/ATR astigmatism Z_2^2 (Spearman r=0.272, p=0.016). Table 8.7 presents the second-order Zernike coefficients for both refractive groups.

Table 8.7. Ocular LOA aberrations for the emmetropic and myopic group (3 mm).

Coefficient	Emmetropic (n=31)	Myopic (n=47)	p-value
Z_2^{-2} (µm)	0.019 ± 0.063	0.019 ± 0.113	0.397
Z_2^0 (µm)	0.078 ± 0.153	1.400 ± 0.943	<0.001*
Z_2^2 (µm)	-0.044 ± 0.078	-0.044 ± 0.183	0.985

*p-value<0.05

There were no significant differences between emmetropes and myopes for the HOA except for the vertical coma Z_3^{-1} (Mann-Whitney p=0.043). The coefficient Z_7^7 also resulted to differ between groups (Mann-Whitney p=0.020) although this coefficient only took values different from zero in 5 subjects (4 myopes and 1 emmetrope). The Zernike coefficients for HOA, third to fifth-order, are contained in Table 8.8. The HOA of sixth- and

seventh-order were not shown in Table 8.8 since these coefficients were lower than 0.001 μm.

Table 8.8. Ocular HOA for the emmetropic and myopic group (3 mm).

Order	Coefficient	Emmetropic (n=31)	Myopic (n=47)	p-value
3rd	Z_3^{-3} (μm)	-0.014 ± 0.028	-0.021 ± 0.024	0.264
	Z_3^{-1} (μm)	0.001 ± 0.025	0.012 ± 0.027	0.043*
	Z_3^{1} (μm)	0.010 ± 0.019	0.008 ± 0.020	0.656
	Z_3^{3} (μm)	0.008 ± 0.016	0.012 ± 0.017	0.302
4th	Z_4^{-4} (μm)	0.001 ± 0.006	0.001 ± 0.006	0.981
	Z_4^{-2} (μm)	0.000 ± 0.006	-0.001 ± 0.006	0.887
	Z_4^{0} (μm)	0.012± 0.014	0.008 ± 0.014	0.196
	Z_4^{2} (μm)	-0.002 ± 0.007	-0.003 ± 0.007	0.394
	Z_4^{4} (μm)	-0.001 ± 0.007	0.000 ± 0.006	0.759
5th	Z_5^{-5} (μm)	0.000 ± 0.003	0.000 ± 0.005	0.661
	Z_5^{-3} (μm)	0.001 ± 0.004	0.002 ± 0.002	0.580
	Z_5^{-1} (μm)	0.000 ± 0.005	0.000 ± 0.003	0.503
	Z_5^{1} (μm)	0.000 ± 0.004	0.000 ± 0.003	0.841
	Z_5^{3} (μm)	-0.001 ± 0.002	-0.002 ± 0.003	0.426
	Z_5^{5} (μm)	0.000 ± -0.002	-0.002 ± 0.003	0.102

*p-value<0.05

The total RMS resulted to be significantly greater in the myopic group (Mann-Whitney p<0.001) because of the higher RMS of LOA (Mann-Whitney p<0.001). Table 8.9 presents the different calculated RMS for both refractive groups. LOA RMS correlated with the sphere (Spearman r=-0.934, p<0.001), cylinder (Spearman r=-0.479, p<0.001) and VCD (Spearman r=0.717, p<0.001). The RMS of all combined HOA did not differ between refractive groups (Mann-Whitney p=0.424) nor the RMS for each order separately (Mann-Whitney p>0.05). The cylinder power associated with both HOA RMS (Spearman r=-0.239, p=0.035) and fifth-order RMS (Spearman r=-0.256, p=0.024).

The RMS of low order astigmatism took higher values in myopes compared to emmetropes (Mann-Whitney p=0.005) whereas the RMS of the high order astigmatism did not differ between groups (Mann-Whitney p=0.567). Accordingly, the RMS of low order astigmatism was related to the sphere (Spearman r=-0.465, p<0.001), cylinder (Spearman r=-0.817, p<0.001) and VCD (Spearman r=0.380, p<0.001). Besides, the spherical aberration RMS manifested significantly lower values in the myopic group

(Mann-Whitney p=0.044). Meantime, the RMS of coma-like and trefoil-like did not manifest significant differences (Mann-Whitney p<0.05).

Table 8.9. Calculated ocular RMS for the emmetropic and myopic group (3 mm).

RMS (μm)	Emmetropic (n=31)	Myopic (n=47)	p-value
LOA (2nd)	0.177 ± 0.100	1.417 ± 0.943	<0.001*
HOA (3rd to 7th)	0.051 ± 0.019	0.054 ± 0.019	0.424
Total	0.187 ± 0.097	1.142 ± 0.943	<0.001*
3rd order	0.044 ± 0.018	0.049 ± 0.019	0.163
4th order	0.020 ± 0.010	0.018 ± 0.009	0.272
5th order	0.007 ± 0.005	0.007 ± 0.004	0.951
6th order	0.001 ± 0.001	0.001 ± 0.001	0.327
7th order	0.000 ± 0.001	0.000 ± 0.001	0.789
Low order astigmatism (2nd)	0.092 ± 0.061	0.173 ± 0.134	0.005*
High order astigmatism (4th and 6th)	0.008 ± 0.005	0.008 ± 0.006	0.567
Spherical aberration (4th and 6th)	0.016 ± 0.010	0.012 ± 0.010	0.044*
Coma-like (3rd to 7th)	0.029 ± 0.016	0.032 ± 0.018	0.497
Trefoil-like (3rd to 7th)	0.031 ± 0.017	0.034 ± 0.016	0.272

*p-value<0.05

Simple linear regression revealed that the sphere accounted for 98.3% of the defocus Z_2^0 variance, 7.4% of the WTR/ATR astigmatism Z_2^2, 97.8% of LOA RMS and 21.6% of low order astigmatism RMS. The 65.8% defocus Z_2^0, 64.4% of LOA RMS and 14.5% of low order astigmatism RMS variability was explained by the VCD. Furthermore, the cylinder predicted 33.7% of the LOA RMS variance, 83.7% of the low order astigmatism RMS, 3.8% of HOA RMS and 8.1% of fifth-order RMS.

The multiple regression analysis manifested that the SE was predicted including all Zernike coefficients from second to fifth-order (99.1%) but no significant model resulted including only HOA. Thus, the SE was more negative with greater positive defocus Z_2^0 and third-order trefoil Z_3^{-3} (Table 8.10). Then, 68.4% of the VCD variance was explained by the defocus Z_2^0 and secondary WTR/ATR astigmatism Z_4^2 (Table 8.11). Longer VCD was related to greater positive defocus Z_2^0 and more negative astigmatism Z_4^2.

Table 8.10. Multiple linear regression model for the SE (3 mm).

	R	R^2	R^2 adjusted	Error	Durbin-Watson
SE (D)	0.995	0.991	0.990	0.324	1.876

	β	SE	Sβ	p-value	Tolerance	VIF
Constant	0.266	0.056	-	<0.001	-	-
Z_2^0 (µm)	-3.329	0.038	-0.995	<0.001	1.000	1.000
Z_3^{-3} (µm)	-3.826	1.462	-0.029	0.011	1.000	1.000

Table 8.11. Multiple linear regression model for VCD (3 mm).

	R	R^2	R^2 adjusted	Error	Durbin-Watson
VCD (mm)	0.827	0.684	0.676	0.774	1.955

	β	SE	Sβ	p-value	Tolerance	VIF
Constant	16.066	0.121	-	<0.001	-	-
Z_2^0 (µm)	1.113	0.090	0.804	<0.001	0.998	1.002
Z_4^2 (µm)	-29.524	11.827	-0.162	0.015	0.998	1.002

8.3.2 Pupil size 5 mm

From the total baseline sample (n=78), 71 subjects reached the pupil size of 5 mm and, therefore, 7 subjects (4 emmetropes and 3 myopes) were excluded in this analysis.

8.3.2.1 Corneal wavefront

Oblique astigmatism Z_2^{-2} and WTR/ATR astigmatism Z_2^2 did not differ significantly between myopic and emmetropic subjects (Table 8.12). Nonetheless, more negative WTR/ATR astigmatism Z_2^2 did associate with more myopic sphere (Spearman r=0.266, p=0.025).

Table 8.12. Corneal LOA for the emmetropic and myopic group (5 mm).

Coefficient	Emmetropic (n=27)	Myopic (n=44)	p-value
Z_2^{-2} (µm)	0.034 ± 0.193	0.049 ± 0.329	0.836
Z_2^2 (µm)	-0.432 ± 0.319	-0.491 ± 0.529	0.557

There were significant differences between groups for horizontal coma Z_3^1 (Mann-Whitney p=0.041), oblique astigmatism Z_4^{-2} (Student t-test p=0.037) and Z_6^{-2} (Student t-test p=0.048), and tretafoil Z_6^4 (Mann-Whitney p=0.048). The rest of the

higher-order coefficients did not show significant differences between groups (Table 8.13).

Table 8.13. Corneal HOA for the emmetropic and myopic group (5 mm).

Order	Coefficient	Emmetropic (n=27)	Myopic (n=44)	p-value
3rd	Z_3^{-3} (µm)	-0.048 ± 0.093	-0.039 ± 0.079	0.651
	Z_3^{-1} (µm)	-0.016 ± 0.070	0.015 ± 0.105	0.181
	Z_3^{1} (µm)	-0.042 ± 0.081	-0.006 ± 0.081	0.041*
	Z_3^{3} (µm)	-0.025 ± 0.057	-0.039 ± 0.065	0.356
4th	Z_4^{-4} (µm)	0.003 ± 0.018	-0.005 ± 0.037	0.291
	Z_4^{-2} (µm)	0.003 ± 0.018	-0.009 ± 0.026	0.037*
	Z_4^{0} (µm)	0.123 ± 0.020	0.128 ± 0.044	0.476
	Z_4^{2} (µm)	-0.012 ± 0.030	-0.017 ± 0.031	0.544
	Z_4^{4} (µm)	-0.003 ± 0.026	-0.011 ± 0.042	0.376
5th	Z_5^{-5} (µm)	-0.009 ± 0.017	-0.011 ± 0.029	0.878
	Z_5^{-3} (µm)	-0.005 ± 0.019	-0.005 ± 0.018	0.926
	Z_5^{-1} (µm)	0.006 ± 0.014	0.001 ± 0.016	0.239
	Z_5^{1} (µm)	-0.007 ± 0.016	-0.005 ± 0.019	0.134
	Z_5^{3} (µm)	0.004 ± 0.013	-0.002 ± 0.024	0.089
	Z_5^{5} (µm)	0.000 ± 0.018	-0.001 ± 0.021	0.785
6th	Z_6^{-6} (µm)	-0.004 ± 0.016	-0.002 ± 0.019	0.868
	Z_6^{-4} (µm)	0.000 ± 0.014	0.005 ± 0.018	0.263
	Z_6^{-2} (µm)	-0.005 ± 0.015	0.005 ± 0.013	0.002*
	Z_6^{0} (µm)	0.002 ± 0.015	0.002 ± 0.022	0.947
	Z_6^{2} (µm)	-0.003 ± 0.019	-0.007 ± 0.019	0.355
	Z_6^{4} (µm)	0.001 ± 0.014	-0.006 ± 0.020	0.048*
	Z_6^{6} (µm)	-0.001 ± 0.012	0.000 ± 0.020	0.868
7th	Z_7^{-7} (µm)	0.009 ± 0.011	0.007 ± 0.012	0.297
	Z_7^{-5} (µm)	0.005 ± 0.014	0.005 ± 0.017	0.892
	Z_7^{-3} (µm)	-0.003 ± 0.016	0.002 ± 0.016	0.362
	Z_7^{-1} (µm)	0.006 ± 0.011	0.002 ± 0.012	0.090
	Z_7^{1} (µm)	-0.002 ± 0.013	0.001 ± 0.014	0.854
	Z_7^{3} (µm)	-0.001 ± 0.014	0.001 ± 0.014	0.488
	Z_7^{5} (µm)	-0.002 ± 0.010	-0.001 ± 0.015	0.896
	Z_7^{7} (µm)	-0.002 ± 0.009	0.000 ± 0.017	0.374

*p-value<0.05

More positive horizontal coma Z_3^1 associated with more negative sphere (Spearman r=-0.380, p=0.001) and longer VCD (Pearson r=0.296, p=0.012). Meanwhile, more negative oblique astigmatism Z_4^{-2} was related to more myopic sphere (Spearman r=0.283, p=0.017) and longer VCD (Pearson r=-0.363, p=0.002). Contrary, the astigmatism Z_6^{-2} tended to be more positive with more negative sphere (Spearman r=-0.290, p=0.014) and longer VCD (Spearman r=0.307, p=0.009). Additionally, the tetrafoil Z_6^4 took more negative values as the myopic sphere increased (Spearman r=0.261, p=0.028).

Total RMS and low order astigmatism RMS tended to be higher in myopes but it was not statistically significant (Table 8.14). Indeed, low order astigmatism RMS increased with greater myopic sphere (Spearman r=-0.346, p=0.003), more cylinder (Spearman r-=-0.579, p<0.001) and longer VCD (Spearman r=-0.382, p=0.001). HOA RMS and high order astigmatism RMS were similar among refractive groups (Table 8.14). Fourth-order RMS resulted to be significantly higher in the myopic group (Student t-test p=0.048) increasing with the sphere (Spearman r=-0.255, p=0.032). No differences were found for the rest of higher-order RMS, spherical aberration nor coma- and trefoil-like aberration RMS.

Table 8.14. Calculated corneal RMS for the emmetropic and myopic group (5 mm).

RMS (μm)	Emmetropic (n=27)	Myopic (n=44)	p-value
Low order astigmatism (2nd)	0.493 ± 0.285	0.659 ± 0.440	0.185
HOA (3rd to 7th)	0.220 ± 0.040	0.239 ± 0.069	0.342
Total	0.554 ± 0.260	0.725 ± 0.405	0.096
3rd order	0.157 ± 0.056	0.163 ± 0.066	0.711
4th order	0.132 ± 0.018	0.147 ± 0.044	0.048*
5th order	0.039 ± 0.018	0.043 ± 0.033	0.906
6th order	0.037 ± 0.017	0.041 ± 0.031	0.850
7th order	0.034 ± 0.014	0.036 ± 0.022	0.661
High order astigmatism (4th and 6th)	0.041 ± 0.016	0.045 ± 0.024	0.962
Spherical aberration (4th and 6th)	0.123 ± 0.020	0.130 ± 0.043	0.391
Coma-like (3rd to 7th)	0.106 ± 0.053	0.120 ± 0.066	0.953
Trefoil-like (3rd to 7th)	0.112 ± 0.056	0.108 ± 0.055	0.314

*p-value<0.05

The sphere demonstrated to explain part of the variance of several coefficients: 7.1% of WTR/ATR astigmatism Z_2^2, 12.8% of horizontal coma Z_3^1, 4.6% of astigmatism Z_4^{-2}, 3.7% of astigmatism Z_6^{-2} and 4.7% of tetrafoil Z_6^4. The VCD accounted for less variability of horizontal coma Z_3^1 (7.7%) while more for the astigmatism Z_4^{-2} (13.2%) and Z_6^{-2} (6.2%). Low order astigmatism RMS was mainly explained by the cylinder power (33.5%) but also by the sphere (12%) and the VCD (7.2%). Finally, the sphere predicted 4.3% of the fourth-order RMS variability.

8.3.2.2 Internal wavefront

The defocus Z_2^0 was significantly higher in the myopic group (Mann-Whitney p<0.001, Table 8.15) and was related to the sphere (Spearman r=-0.959, p<0.001) and VCD (Spearman r=0.760, p<0.001). Astigmatism did not manifest significant differences between groups (Table 8.15) although WTR/ATR astigmatism Z_2^2 had slightly higher values in the myopic group.

Table 8.15. Internal LOA for the emmetropic and myopic group (5 mm).

Coefficient	Emmetropic (n=27)	Myopic (n=44)	p-value
Z_2^{-2} (µm)	0.015 ± 0.174	-0.003 ± 0.173	0.669
Z_2^0 (µm)	0.381± 0.447	3.903 ± 2.637	<0.001*
Z_2^2 (µm)	0.278 ± 0.228	0.341 ± 0.230	0.264

*p-value<0.05

There were significant differences between refractive groups for the following HOA (Table 8.16): vertical coma Z_3^{-1} (Student t-test p=0.034), horizontal coma Z_3^1 (Student t-test p=0.020), trefoil Z_3^3 (Mann-Whitney p=0.013), oblique astigmatism Z_4^{-2} (Student t-test p=0.034), coma Z_5^{-1} (Mann-Whitney p=0.045) and oblique astigmatism Z_6^{-2} (Mann-Whitney p=0.002). The myopic sphere also associated with more negative values of horizontal coma Z_3^1 (Spearman r=0.268, p=0.024), spherical aberration Z_4^0 (Spearman r=0.294, p=0.013) and oblique astigmatism Z_6^{-2} (Spearman r=0.329, p=0.005) while more positive values of vertical coma Z_3^{-1} (Spearman r=-0.323, p=0.006) and trefoil Z_3^3 (Spearman r=-0.329, p=0.005). Longer VCD also was related to more positive vertical coma Z_3^{-1} (Pearson r=0.367, p=0.002) and more negative oblique astigmatism Z_6^{-2} (Spearman r=-0.302, p=0.010).

Table 8.16. Internal HOA for the emmetropic and myopic group (5 mm).

Order	Coefficient	Emmetropic (n=27)	Myopic (n=44)	p-value
3rd	Z_3^{-3} (µm)	-0.008 ± 0.049	-0.017 ± 0.051	0.484
	Z_3^{-1} (µm)	-0.006 ± 0.060	0.026 ± 0.062	0.034*
	Z_3^{1} (µm)	0.083 ± 0.059	0.051 ± 0052	0.020*
	Z_3^{3} (µm)	0.038 ± 0.044	0.059 ± 0.048	0.013*
4th	Z_4^{-4} (µm)	0.009 ± 0.025	0.014 ± 0.037	0.529
	Z_4^{-2} (µm)	-0.010 ± 0.020	0.001 ± 0.021	0.034*
	Z_4^{0} (µm)	-0.056 ± 0.083	-0.081 ± 0.056	0.129
	Z_4^{2} (µm)	0.006 ± 0.023	0.009 ± 0.031	0.673
	Z_4^{4} (µm)	0.012 ± 0.030	0.011 ± 0.031	0.986
5th	Z_5^{-5} (µm)	0.005 ± 0.022	0.007 ± 0.035	0.910
	Z_5^{-3} (µm)	0.011 ± 0.026	0.014 ± 0.019	0.477
	Z_5^{-1} (µm)	-0.012 ± 0.017	-0.004 ± 0.015	0.045*
	Z_5^{1} (µm)	0.006 ± 0.020	0.003 ± 0.021	0.209
	Z_5^{3} (µm)	-0.008 ± 0.015	-0.007 ± 0.026	0.915
	Z_5^{5} (µm)	-0.007 ± 0.024	-0.007 ± 0.026	0.794
6th	Z_6^{-6} (µm)	0.005 ± 0.020	0.003 ± 0.020	0.582
	Z_6^{-4} (µm)	-0.001 ± 0.017	-0.004 ± 0.018	0.522
	Z_6^{-2}(µm)	0.004 ± 0.016	-0.006 ± 0.014	0.002*
	Z_6^{0} (µm)	-0.007 ± 0.015	-0.004 ± 0.021	0.528
	Z_6^{2} (µm)	0.006 ± 0.017	0.008 ± 0.016	0.524
	Z_6^{4} (µm)	0.001 ± 0.015	0.006 ± 0.017	0.112
	Z_6^{6} (µm)	0.002 ± 0.013	-0.004 ± 0.020	0.184
7th	Z_7^{-7} (µm)	-0.009 ± 0.011	-0.007 ± 0.016	0.473
	Z_7^{-5} (µm)	-0.005 ± 0.015	-0.003 ± 0.020	0.831
	Z_7^{-3} (µm)	0.001 ± 0.015	-0.004 ± 0.017	0.404
	Z_7^{-1} (µm)	-0.006 ± 0.013	-0.003 ± 0.012	0.477
	Z_7^{1} (µm)	0.001 ± 0.015	-0.001 ± 0.014	0.840
	Z_7^{3} (µm)	0.004 ± 0.016	0.001 ± 0.014	0.413
	Z_7^{5} (µm)	0.003 ± 0.011	0.003 ± 0.015	0.896
	Z_7^{7} (µm)	0.002 ± 0.011	0.003 ± 0.020	0.981

*p-value<0.05

As seen in Table 8.17, greater LOA RMS (Mann-Whitney p<0.001) was observed in myopes and consequently total RMS (Mann-Whitney p<0.001). LOA RMS associated with more negative sphere (Spearman r=-0.932, p<0.001), greater cylinder (Spearman r=-0.446, p<0.001) and longer VCD (Spearman r=0.722, p<0.001). The high order astigmatism RMS increased with the cylinder power (Spearman r=0.272, p=0.022). Although the spherical aberration RMS was slightly greater in myopes, it did not reach the significance (Table 8.17). The trefoil-like RMS resulted to be significantly higher in myopes (Mann-Whitney p=0.003) and to be related to the sphere (Spearman r=-0.300, p=0.011). Fourth-order RMS had a weak correlation with the sphere (Spearman r=-0.240, p=0.044) and the differences between groups were almost significant (Mann-Whitney p=0.055).

Table 8.17. Calculated internal RMS for the emmetropic and myopic group (5 mm).

RMS (μm)	Emmetropic (n=27)	Myopic (n=44)	p-value
LOA (2nd)	0.659 ± 0.250	3.941 ± 2.617	<0.001*
HOA (3rd to 7th)	0.183 ± 0.068	0.192 ± 0.057	0.356
Total	0.688 ± 0.247	3.950 ± 2.611	<0.001*
3rd order	0.129 ± 0.054	0.130 ± 0.040	0.919
4th order	0.095 ± 0.060	0.109 ± 0.042	0.055
5th order	0.050 ± 0.021	0.052 ± 0.035	0.627
6th order	0.039 ± 0.020	0.044 ± 0.024	0.227
7th order	0.032 ± 0.012	0.035 ± 0.022	0.991
Low order astigmatism (2nd)	0.355 ± 0.180	0.402 ± 0.190	0.236
High order astigmatism (4th and 6th)	0.037 ± 0.017	0.040 ± 0.020	0.661
Spherical aberration (4th and 6th)	0.077 ± 0.065	0.091 ± 0.045	0.068
Coma-like (3rd to 7th)	0.113 ± 0.049	0.097 ± 0.037	0.138
Trefoil-like (3rd to 7th)	0.071 ± 0.047	0.093 ± 0.042	0.003*

**p-value<0.05*

The 97.7% and 63.7% of the defocus Z_2^0 variance was explained by the sphere and VCD, respectively. The sphere also accounted for the variability of vertical coma Z_3^{-1} (7.7%), horizontal coma Z_3^1 (5.2%), trefoil Z_3^3 (3%), spherical aberration Z_4^0 (3%) and oblique astigmatism Z_6^{-2} (5.8%). The VCD explained more variability of vertical coma Z_3^{-1} (13.5%) and oblique astigmatism Z_6^{-2} (6.5%). The sphere explained 97.6% of the LOA RMS variance while the VCD did 62.6%. The cylinder accounted for the 32.9% of the LOA RMS

variability and 1.9% of the HOA RMS. Additionally, the sphere predicted a small part of the trefoil-like RMS (1.3%) and fourth-order RMS (1.1%).

8.3.2.3 Ocular wavefront

The ocular defocus Z_2^0 exhibited significantly higher values in the myopic group (Mann-Whitney p<0.001; Table 8.18), being greater with more negative sphere (Spearman r=-0.959, p<0.001) and longer VCD (Spearman r=0.706, p<0.001). Despite no significant differences in second-order astigmatism coefficients between refractive groups (Table 8.18), the sphere correlated with the WTR/ATR astigmatism Z_2^2 (Spearman r=0.265, p=0.026).

Table 8.18. Ocular LOA for the emmetropic and myopic group (5 mm).

Coefficient	Emmetropic (n=27)	Myopic (n=44)	p-value
Z_2^{-2} (µm)	0.049 ± 0.163	0.045 ± 0.297	0.804
Z_2^0 (µm)	0.381 ± 0.447	3.903 ± 2.637	<0.001*
Z_2^2 (µm)	-0.154 ± 0.242	-0.150 ± 0.500	0.967

*p-value<0.05

From the HOA, only the primary vertical coma Z_3^{-1} showed significant differences between groups (Student t-test p=0.0041; Table 8.19) where the myopic group manifested more positive values. Thus, more positive vertical coma Z_3^{-1} associated with more myopic sphere (Spearman r=-0.261, p=0.028) and longer VCD (Pearson r=0.273, p=0.021). Furthermore, VCD had an association with the tetrafoil Z_4^4 (Spearman r=-0.248, p=0.037), spherical aberration Z_4^0 (Spearman r=-0.243, p=0.041) and hexafoil Z_6^{-6} (Spearman r=0.292, p=0.014).

The myopic group revealed higher total RMS (Mann-Whitney p<0.001) because of the higher LOA RMS (Mann-Whitney p<0.001). Indeed, LOA RMS had a relationship with the sphere (Spearman r=-0.927, p<0.001) cylinder (Spearman r=-0.483, p<0.001) and VCD (Spearman r=0.677, p<0.001). Table 8.20 presents the different calculated RMS for both refractive groups. HOA RMS were similar between refractive groups as well as the RMS for each high order separately (Mann-Whitney p>0.05). Low order astigmatism RMS was also greater in myopes (Mann-Whitney p=0.021) while the high order astigmatism RMS did not differ. Accordingly, the RMS of low order astigmatism correlated with the sphere (Spearman r=-0.397, p<0.001), cylinder (Spearman r=-0.801, p<0.001) and VCD

(Spearman r=0.292, p=0.013). Despite no significant differences in spherical aberration RMS, longer VCD associated with lower spherical RMS (Spearman r=-0.298, p=0.012). Meantime, the RMS of coma- and trefoil-like had a similar distribution among myopes and emmetropes (Mann-Whitney p>0.05).

Table 8.19. Ocular HOA for the emmetropic and myopic group (5 mm).

Order	Coefficient	Emmetropic (n=27)	Myopic (n=44)	p-value
3rd	Z_3^{-3} (µm)	-0.057 ± 0.093	-0.056 ± 0.081	0.973
	Z_3^{-1} (µm)	-0.022 ± 0.088	0.042 ± 0.085	0.004*
	Z_3^{1} (µm)	0.041 ± 0.066	0.045 ± 0.070	0.779
	Z_3^{3} (µm)	0.013 ± 0.053	0.021 ± 0.056	0.575
4th	Z_4^{-4} (µm)	0.012 ± 0.026	0.009 ± 0.028	0.654
	Z_4^{-2} (µm)	-0.007 ± 0.023	-0.008 ± 0.024	0.851
	Z_4^{0} (µm)	0.066 ± 0.083	0.047 ± 0.067	0.274
	Z_4^{2} (µm)	-0.006 ± 0.031	-0.008 ± 0.036	0.843
	Z_4^{4} (µm)	0.008 ± 0.030	0.000 ± 0.031	0.282
5th	Z_5^{-5} (µm)	-0.004 ± 0.014	-0.004 ± 0.025	0.894
	Z_5^{-3} (µm)	0.006 ± 0.015	0.009 ± 0.014	0.343
	Z_5^{-1} (µm)	-0.006 ± 0.015	-0.003 ± 0.017	0.406
	Z_5^{1} (µm)	-0.001 ± 0.016	-0.002 ± 0.015	0.967
	Z_5^{3} (µm)	-0.004 ± 0.012	-0.008 ± 0.012	0.142
	Z_5^{5} (µm)	-0.007 ± 0.014	-0.008 ± 0.017	0.833
6th	Z_6^{-6} (µm)	0.000 ± 0.010	0.001 ± 0.008	0.437
	Z_6^{-4} (µm)	-0.001 ± 0.009	0.002 ± 0.006	0.252
	Z_6^{-2}(µm)	-0.001 ± 0.005	-0.001 ± 0.006	0.517
	Z_6^{0} (µm)	-0.005 ± 0.011	-0.002 ± 0.014	0.138
	Z_6^{2} (µm)	0.003 ± 0.010	0.001 ± 0.010	0.817
	Z_6^{4} (µm)	0.003 ± 0.006	0.000 ± 0.008	0.060
	Z_6^{6} (µm)	-0.001 ± 0.007	-0.004 ± 0.010	0.090
7th	Z_7^{-7} (µm)	0.000 ± 0.006	0.000 ± 0.009	0.939
	Z_7^{-5} (µm)	0.000 ± 0.005	0.001 ± 0.008	0.721
	Z_7^{-3} (µm)	-0.002 ± 0.005	-0.002 ± 0.005	0.976
	Z_7^{-1} (µm)	0.001 ± 0.008	0.000 ± 0.005	0.230
	Z_7^{1} (µm)	-0.001 ± 0.006	-0.001 ± 0.006	0.399
	Z_7^{3} (µm)	0.002 ± 0.004	0.001 ± 0.005	0.453
	Z_7^{5} (µm)	0.001 ± 0.005	0.002 ± 0.005	0.363
	Z_7^{7} (µm)	0.000 ± 0.006	0.003 ± 0.007	0.197

*p-value<0.05

Table 8.20. Calculated ocular RMS for the myopic and emmetropic group (5 mm).

RMS (μm)	Emmetropic (n=27)	Myopic (n=44)	p-value
LOA (2nd)	0.607 ± 0.028	3.947 ± 2.639	<0.001*
HOA (3rd to 7th)	0.203 ± 0.063	0.197 ± 0.058	0.601
Total	0.650 ± 0.268	3.954 ± 2.634	<0.001*
3rd order	0.156 ± 0.064	0.159 ± 0.057	0.722
4th order	0.108 ± 0.051	0.092 ± 0.044	0.159
5th order	0.035 ± 0.012	0.040 ± 0.019	0.678
6th order	0.020 ± 0.013	0.021 ± 0.012	0.519
7th order	0.014 ± 0.009	0.015 ± 0.011	0.962
Low order astigmatism (2nd)	0.271 ± 0.190	0.458 ± 0.384	0.021*
High order astigmatism (4th and 6th)	0.037 ± 0.019	0.039 ± 0.024	0.934
Spherical aberration (4th and 6th)	0.091 ± 0.054	0.069 ± 0.046	0.066
Coma-like (3rd to 7th)	0.103 ± 0.062	0.113 ± 0.060	0.463
Trefoil-like (3rd to 7th)	0.104 ± 0.065	0.105 ± 0.050	0.696

*p-value<0.05

Simple linear regression revealed 97.7% and 63.7% of the defocus Z_2^0 variance was explained by the sphere and VCD, respectively. The vertical coma Z_3^{-1} was also predicted in part by the sphere (6.7%) and VCD (7.5%). The sphere predicted 7% of the WTR/ATR astigmatism Z_2^2 variability. The VCD accounted for 6.9% of the tretrafoil Z_4^4 variance, 3.7% of the spherical aberration Z_4^0 and 7.6% of the hexafoil Z_6^{-6}. LOA RMS was explained by the sphere (97.2%), cylinder (34.5%) and VCD (62.3%). Likewise, the sphere, cylinder and VCD accounted for 15.8%, 82.2% and 8.6% of the low astigmatism RMS variance, respectively. Furthermore, the VCD predicted 10.5% variability of the spherical aberration RMS.

The multiple regression analysis manifested that the SE was predicted including all Zernike coefficients (99.1%) but no significant model resulted including only HOA. Myopic SE was related to greater positive defocus Z_2^0, third-order trefoil Z_3^{-3} and horizontal coma Z_3^1 while more negative spherical aberration Z_4^0 and coma Z_5^{-1} (Table 8.21). The 74.4% of the VCD variance was explained by the defocus Z_2^0, spherical aberration Z_4^0 and Z_6^0 as well as the tetrafoil Z_4^6 (Table 8.22). Thus, longer VCD was related to greater positive defocus Z_2^0 and tetrafoil Z_4^6 while more negative spherical aberration Z_4^0 and Z_6^0.

Table 8.21. Multiple linear regression model for the SE (5 mm).

	R	R^2	R^2 adjusted	Error	Durbin-Watson
SE (D)	0.995	0.991	0.990	0.328	1.850

	β	SE	Sβ	p-value	Tolerance	VIF
Constant	0.362	0.070	-	<0.001	-	-
Z_2^0 (µm)	-1.208	0.015	-0.981	<0.001	0.949	1.053
Z_3^{-3} (µm)	-1.774	0.469	-0.045	<0.001	0.970	1.031
Z_4^0 (µm)	2.116	0.553	0.047	<0.001	0.928	1.078
Z_3^1 (µm)	-1.527	0.590	-0.031	0.012	0.956	1.046
Z_5^{-1} (µm)	5.905	2.556	0.028	0.024	0.919	1.088

Table 8.22. Multiple linear regression model for VCD (5 mm).

	R	R^2	R^2 adjusted	Error	Durbin-Watson
VCD (mm)	0.862	0.744	0.728	0.719	1.794

	β	SE	Sβ	p-value	Tolerance	VIF
Constant	16.151	0.138	-	<0.001	-	-
Z_2^0 (µm)	0.428	0.032	0.838	<0.001	0.974	1.027
Z_4^0 (µm)	-4.788	1.230	-0.256	<0.001	0.898	1.113
Z_6^0 (µm)	-33.172	7.685	-0.306	<0.001	0.772	1.296
Z_4^6 (µm)	31.477	12.335	0.172	0.013	0.858	1.166

8.3.2.4 The balance between corneal and internal wavefront.

Cornea manifested significantly greater values than the internal optics for: HOA RMS (Wilcoxon p<0.001), fourth-order RMS (Wilcoxon p<0.001), fifth-order RMS (Wilcoxon p<0.001), sixth-order RMS (Wilcoxon p=0.007), low order astigmatism RMS (Wilcoxon p<0.001), spherical RMS (Wilcoxon p<0.001) and trefoil-like RMS (Wilcoxon p<0.001). Meanwhile, internal wavefront had a bit higher fifth-order RMS (Wilcoxon p<0.001) and sixth order-RMS (Wilcoxon p<0.001) than corneal. Table 8.23 contains each RMS for ocular, corneal and internal wavefront in the whole sample.

Table 8.23. RMS for ocular, corneal and internal wavefront in the entire sample.

RMS (µm)	Ocular (n=71)	Corneal (n=71)	Internal (n=71)
HOA (3rd to 7th)	0.199 ± 0.060	0.232 ± 0.060	0.189 ± 0.062
3rd order	0.158 ± 0.060	0.161 ±0.062	0.129 ± 0.045
4th order	0.098 ± 0.047	0.141 ± 0.037	0.104 ±0.050
5th order	0.038 ± 0.017	0.042 ± 0.028	0.051 ± 0.030
6th order	0.021 ± 0.012	0.040 ± 0.026	0.042 ± 0.022
7th order	0.014 ± 0.010	0.036 ± 0.019	0.034 ± 0.019
Low order astigmatism (2nd)	0.387 ± 0.034	0.596 ± 0.039	0.384 ± 0.187
High order astigmatism (4th and 6th)	0.038 ± 0.022	0.043 ± 0.021	0.039 ± 0.019
Spherical aberration (4th and 6th)	0.078 ± 0.050	0.127 ± 0.036	0.086 ± 0.053
Coma-like (3rd to 7th)	0.141 ± 0.061	0.115 ± 0.061	0.103 ± 0.042
Trefoil-like (3rd to 7th)	0.105 ± 0.056	0.109 ± 0.055	0.085 ± 0.045

In general, ocular RMS reduced significantly in comparison to the corneal for HOA RMS (Wilcoxon $p<0.001$), low order astigmatism RMS (Wilcoxon $p<0.001$), fourth-order RMS (Wilcoxon $p<0.001$), sixth-order RMS (Wilcoxon $p<0.001$), seventh-order RMS (Wilcoxon $p<0.001$) and spherical RMS (Wilcoxon $p<0.001$). Thereby, most of the RMS were greater for the corneal wavefront demonstrating the cornea as the most contributor to the total wavefront. Moreover, the lower ocular RMS in comparison to the corneal pointed out the presence of a balance between corneal and internal wavefront to reduce even HOA ocular aberrations.

For both groups, the CF was significantly different from zero (Student t-test $p<0.001$) in fourth-order RMS, sixth-order RMS, seventh-order RMS and spherical aberrations RMS. The reduction of the fourth-order RMS (mixed ANOVA $p=0.016$) and spherical RMS (mixed ANOVA $p=0.031$) were significantly greater for the myopic group. Indeed, the CF of both fourth-order and spherical RMS was greater in myopes (Table 8.24), which indicated more compensation by the internal optics. The CF for sixth- and seventh-order RMS showed similar values between groups. Internal optics added third- and fifth-order RMS since the CF was negative for both emmetropic and myopic subjects. Similarly, coma- and trefoil-like CFs were more negative in the myopic group.

Additionally, the CF of low order astigmatism RMS was significant in emmetropes (Student t-test p=0.016) whereas for myopes was the CF of HOA RMS (Student t-test p<0.001). The low order astigmatism RMS had better compensation in emmetropes, however, the reduction did not differ significantly among groups (mixed ANOVA p=0.761). Meantime, the CF of the high order astigmatism RMS was similar among groups. The CF of HOA RMS resulted higher in myopia probably because of the greater compensation of the fourth-order aberrations.

Table 8.24. CF of each RMS for the emmetropic and myopic group.

CF	Emmetropic (n=27)	Myopic (n=44)
HOA (3rd to 7th)	0.07 ± 0.28	0.15 ± 0.22**
3rd order	-0.06 ± 0.45	-0.08 ± 0.44
4th order	0.19 ± 0.35**	0.32 ± 0.43**
5th order	-0.13 ± 0.81	-0.17 ± 0.68
6th order	0.38 ± 0.41**	0.29 ± 0.58**
7th order	0.52 ± 0.35**	0.50 ± 0.42**
Low order astigmatism (2nd)	0.31 ± 0.62*	0.18 ± 0.80
High order astigmatism (4th and 6th)	0.02 ± 0.59	0.04 ± 0.56
Spherical aberration (4th and 6th)	0.27 ± 0.41**	0.40 ± 0.54**
Coma-like (3rd to 7th)	-0.13 ± 0.78	-0.22 ± 1.02
Trefoil-like (3rd to 7th)	0.08 ± 0.38	-0.12 ± 0.54

*p-value<0.05; **p-value<0.001.

The differences in CF among refractive groups were further assessed in the individual Zernike coefficients (Table 8.25 and Table 8.26). The CF for seventh-order coefficients is not enclosed in Table 8.26 since the CF of almost all coefficients was near 1 in both refractive groups.

Table 8.25. CF of low order astigmatic coefficients for the emmetropic and myopic group.

Coefficient	Emmetropic (n=27)	Myopic (n=44)
Z_2^{-2} (µm)	-0.10 ± 4.91	0.73 ± 4.37*
Z_2^2 (µm)	0.63 ± 0.89**	1.26 ± 3.70**

*p-value<0.05; **p-value<0.001

Table 8.26. CF of the individual HOA coefficients for the emmetropic and myopic group.

Order	Coefficient	Emmetropic (n=27)	Myopic (n=44)
3rd	Z_3^{-3} (µm)	0.86 ± 2.31*	0.00 ± 2.43
	Z_3^{-1} (µm)	-0.03 ± 1.33	0.10 ± 1.92
	Z_3^{1} (µm)	3.30 ± 8.58**	0.67 ± 5.58**
	Z_3^{3} (µm)	0.09 ± 2.19	0.39 ± 6.48*
4th	Z_4^{-4} (µm)	0.81 ± 3.84	-0.56 ± 4.36
	Z_4^{-2} (µm)	0.35 ± 2.21	0.39 ± 3.06
	Z_4^{0} (µm)	0.46 ± 0.65**	0.76 ± 0.78**
	Z_4^{2} (µm)	-0.28 ± 2.56	-0.06 ± 4.49
	Z_4^{4} (µm)	-0.22 ± 5.58	0.23 ± 3.24
5th	Z_5^{-5} (µm)	1.13 ± 2.43*	1.00 ± 5.33*
	Z_5^{-3} (µm)	2.62 ± 5.26**	0.27 ± 4.82*
	Z_5^{-1} (µm)	0.85 ± 3.80*	0.95 ± 3.92
	Z_5^{1} (µm)	0.81 ± 1.63*	-1.07 ± 4.47
	Z_5^{3} (µm)	0.72 ± 2.49*	0.37 ± 3.31*
	Z_5^{5} (µm)	1.40 ± 3.10*	1.06 ± 3.14*
6th	Z_6^{-6} (µm)	0.21 ± 2.33**	0.86 ± 2.93**
	Z_6^{-4} (µm)	-0.12 ± 7.18**	0.45 ± 2.36**
	Z_6^{-2} (µm)	0.62 ± 1.45**	1.20 ± 1.00**
	Z_6^{0} (µm)	0.07 ± 2.56	0.98 ± 2.29**
	Z_6^{2} (µm)	0.87±0.85**	0.65 ± 1.11**
	Z_6^{4} (µm)	1.09 ± 1.62**	1.16 ± 1.45**
	Z_6^{6} (µm)	1.27 ± 2.18**	0.79 ± 3.60**

*p-value<0.05; ** p <0.001

As shown in Table 8.25, oblique astigmatism Z_2^{-2} had significant compensation in myopes (Wilcoxon p= 0.009) while the WTR/ATR astigmatism Z_2^2 did in both myopes and emmetropes (Wilcoxon p<0.001). The corneal oblique astigmatism Z_2^{-2} took values near to zero in most of the cases and only 39.43% of the subjects had a CF between 0 and 1. The myopic group presented more proportion of partial compensation for oblique astigmatism Z_2^{-2} (Table 8.27) as also can be seen in Figure 8.2. CF proportion tables show the predominant CF proportion highlighted in grey. The emmetropic group mostly exhibited lower values of corneal oblique astigmatism Z_2^{-2} which was either augmented and overcompensated (Figure 8.2).

Table 8.27. Proportion of the CF types for second-order astigmatism.

Coefficient	CF type	Emmetropic (n=27)	Myopic (n=44)
Z_2^{-2} (µm)	**Augmentation**	9 (33.33%)	12 (27.27%)
	Undercompensation	6 (22.22%)	22 (50%)
	Overcompensation	12 (44.44%)	10 (22.72%)
Z_2^2 (µm)	**Augmentation**	3 (11.11%)	7 (15.91%)
	Undercompensation	18 (66.67%)	25 (56.82%)
	Overcompensation	6 (22.22%)	12 (27.27%)

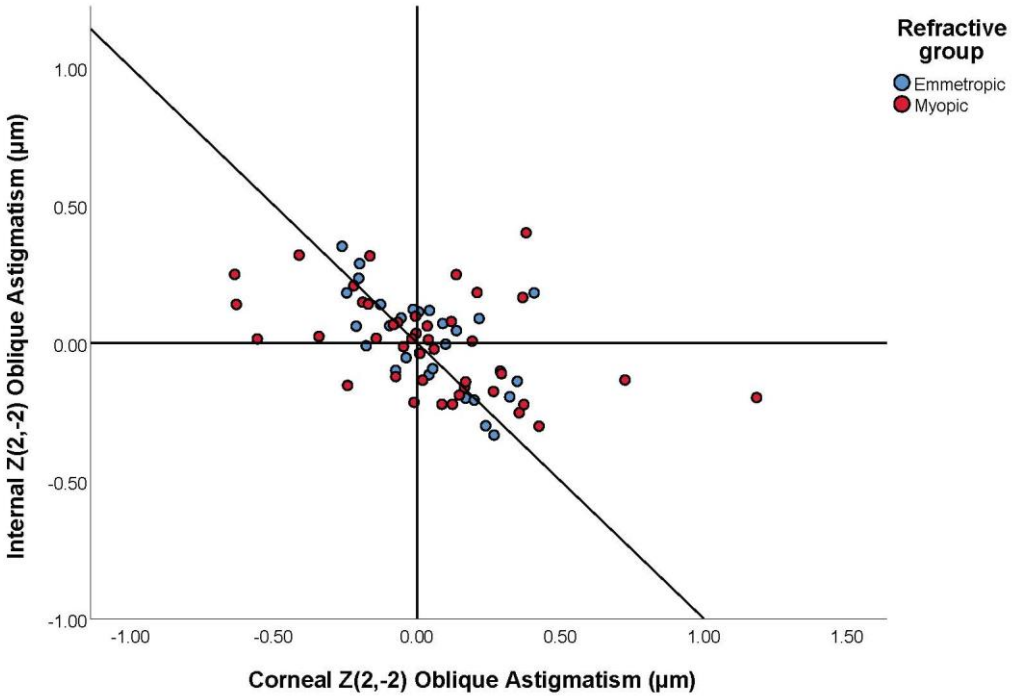

Figure 8.2. Relationship between corneal and internal oblique astigmatism Z(2,-2).

More effective compensation was found for the WTR/ATR astigmatism Z_2^2 compared to the oblique, 60% of the subjects did have partial compensation. Myopic group manifested an average CF above 1 because more proportion of myopes underwent augmentation of WTR/ATR astigmatism Z_2^2 (Table 8.27). The partial compensation of WTR/ATR astigmatism Z_2^2 by the internal wavefront was better for emmetropes (Table 8.27) since more proportion of them were clustered in the undercompensation (Figure 8.3).

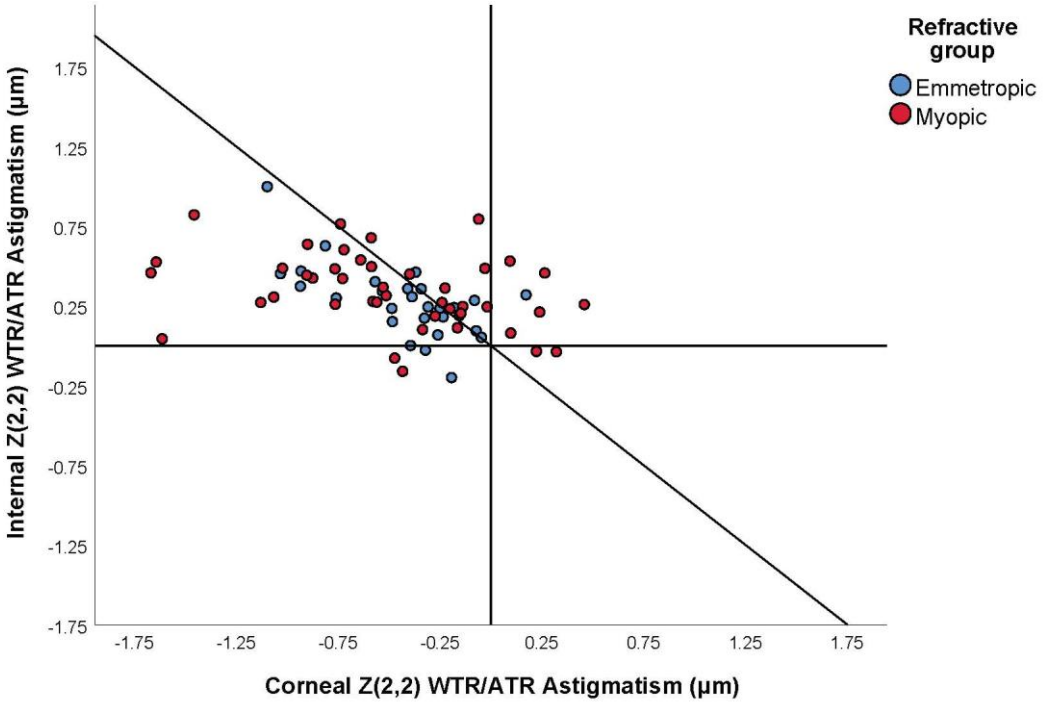

Figure 8.3. Relationship between corneal and internal WTR/ATR astigmatism Z(2,2).

Despite some significant CF in the third-order (Table 8.26), greater average ocular third-order coefficients were seen in both refractive groups compared to the corresponding corneal ones. Emmetropes manifested significant compensation for the trefoil Z_3^{-3} (Wilcoxon p= 0.005) whereas the myopes did for the trefoil Z_3^3 (Wilcoxon p= 0.025). The emmetropic group obtained more significant compensation than the myopic subjects for trefoil Z_3^{-3} (Table 8.28). Meantime, almost 60% of myopes experimented augmentation (Table 8.28 and Figure 8.4). Even though the CF was significant in myopes for trefoil Z_3^3, some compensation was seen in less than 30% of the myopic subjects and, therefore, it can be considered as negligible. The augmentation and overcompensation were seen in most of the subjects for trefoil Z_3^3 (Table 8.28 and Figure 8.5).

Table 8.28. Proportion of the CF types for third-order trefoil.

Coefficient	CF type	Emmetropic (n=27)	Myopic (n=44)
Z_3^{-3} (µm)	Augmentation	8 (29.63%)	26 (59.09%)
	Undercompensation	16 (59.26%)	12 (27.27%)
	Overcompensation	3 (11.11%)	6 (13.64%)
Z_3^3 (µm)	Augmentation	9 (33.33%)	14 (31.82%)
	Undercompensation	11 (40.74%)	13 (29.54%)
	Overcompensation	7 (25.93%)	17 (38.64%)

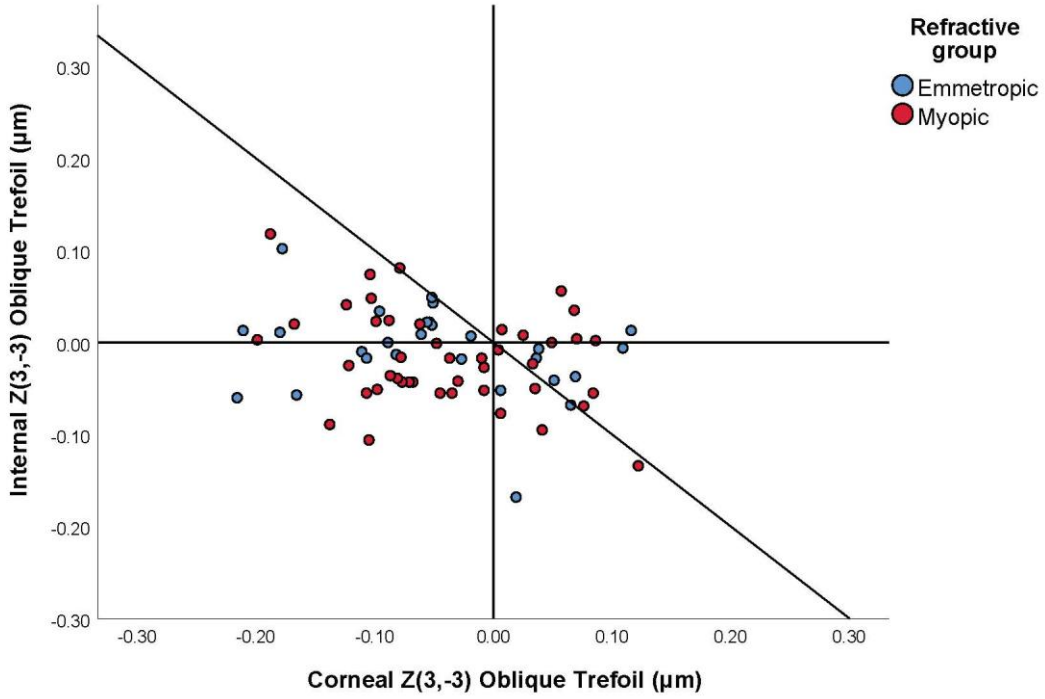

Figure 8.4. Relationship between corneal and internal trefoil Z(3,-3).

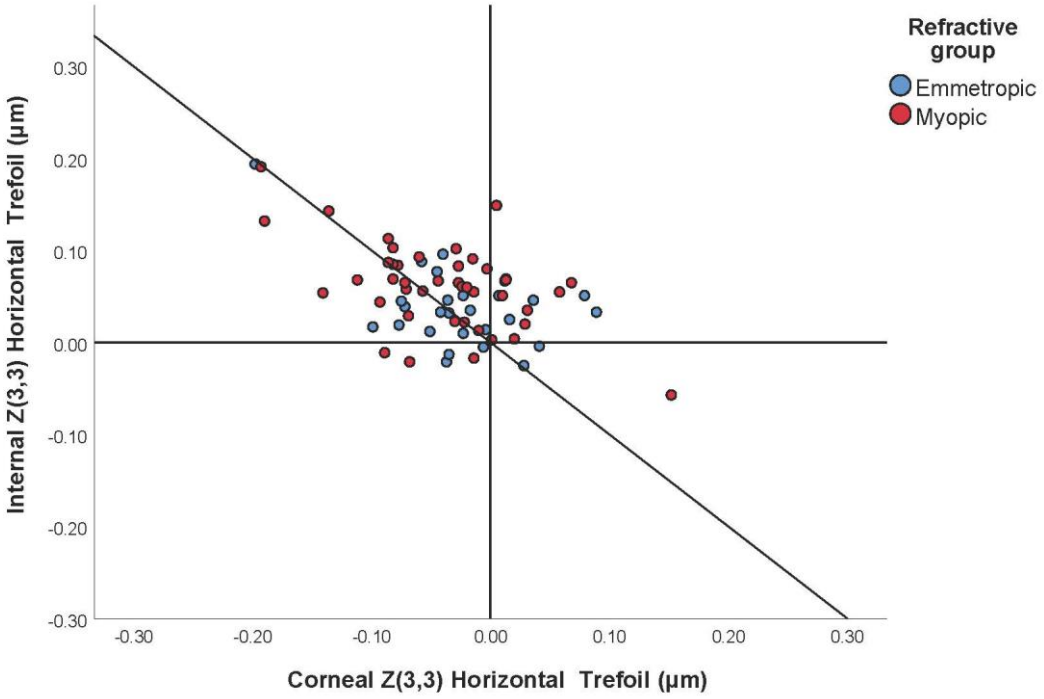

Figure 8.5. Relationship between corneal and internal trefoil Z(3,3).

The vertical coma Z_3^{-1} CF did not result significant in any refractive group (Wilcoxon p>0.05, Table 8.26). However, the myopic group acquired a bit greater proportion of subjects with partial compensation than emmetropes (Table 8.29), Augmentation and overcompensation were also quite present in both refractive groups (Figure 8.6).

Table 8.29. Proportion of the CF types for third-order coma.

Coefficient	CF type	Emmetropic (n=27)	Myopic (n=44)
Z_3^{-1} (µm)	Augmentation	13 (48.15%)	14 (31.82%)
	Undercompensation	9 (33.33%)	21 (47.73%)
	Overcompensation	5 (18.52%)	9 (20.45%)
Z_3^1 (µm)	Augmentation	6 (22.22%)	14 (31.82%)
	Undercompensation	7 (25.93%)	12 (27.27%)
	Overcompensation	14 (51.85%)	18 (40.91%)

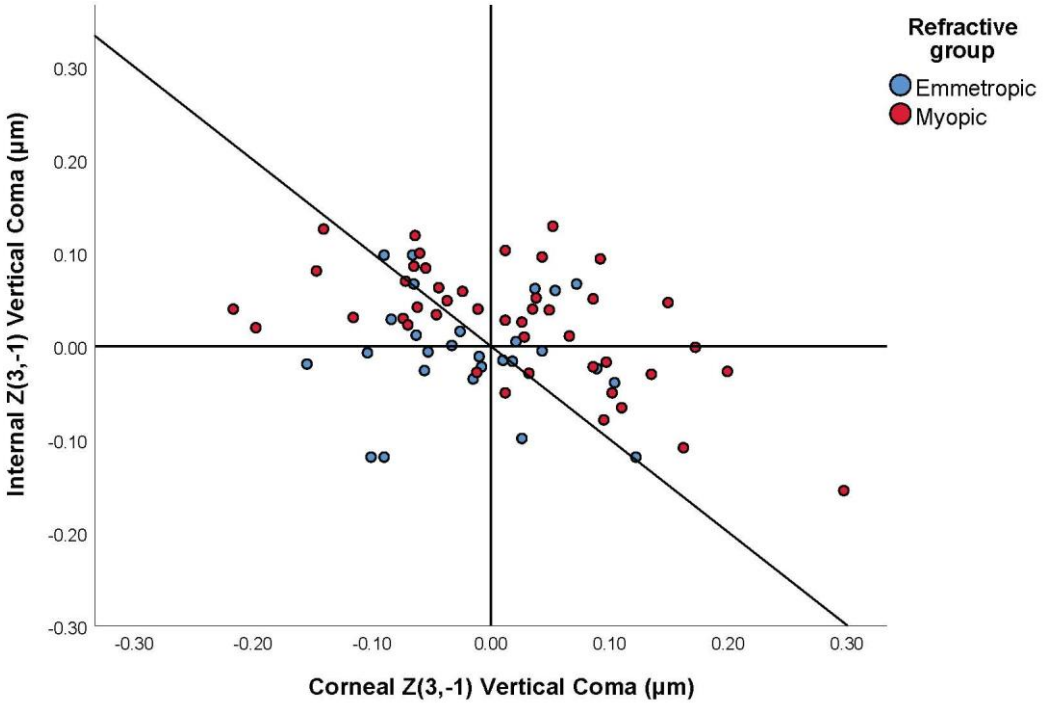

Figure 8.6. Relationship between corneal and internal vertical coma Z(3,-1).

On the other hand, CF of the horizontal coma Z_3^1 did reveal to be significant for both emmetropic and myopic group (Wilcoxon p<0.001 and p=0.029, respectively, Table 8.26), though the average CF was far above 1 for emmetropes. The relationship between corneal and internal horizontal coma Z_3^1 is shown in Figure 8.7. There was a presence of some

partial compensation but most of the subjects underwent overcompensation and even augmentation (Figure 8.7). The overcompensation by the internal optics was the most predominant in both refractive groups (Table 8.29).

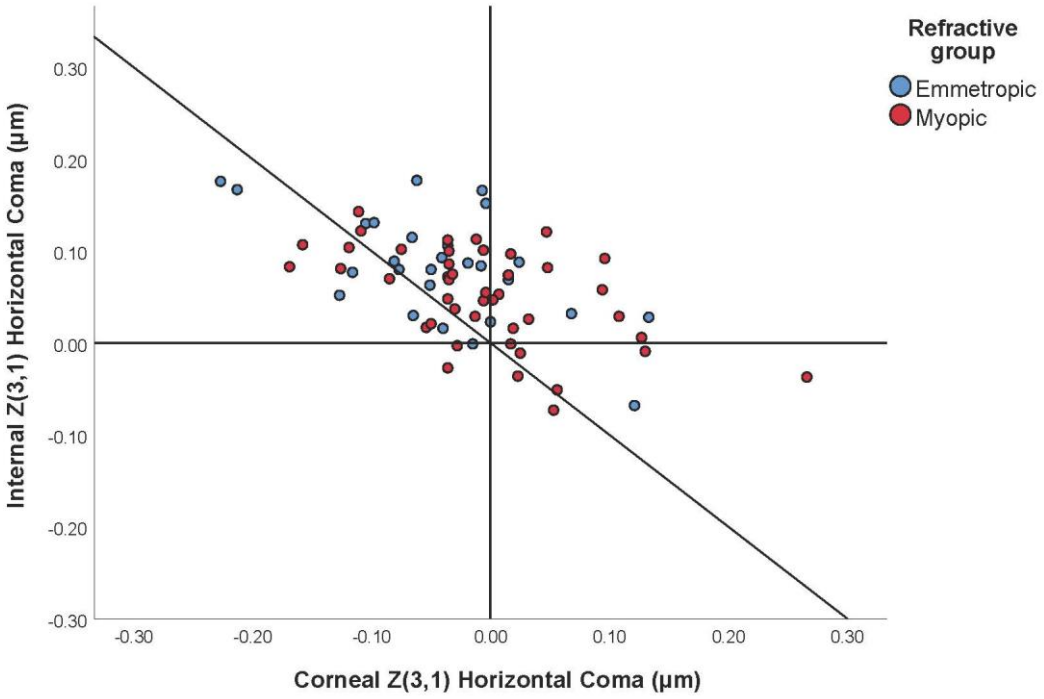

Figure 8.7. Relationship between corneal and internal horizontal coma Z(3,1).

Secondary astigmatism (Z_4^{-2} and Z_4^2) did not obtain significant CF in any refractive group (Table 8.26). Partial compensation was found in some part of the subjects for oblique astigmatism Z_4^{-2} and WTR/ATR astigmatism Z_4^2 (Figure 8.8 and Figure 8.9) but the augmentation was the pattern that most occurred in both refractive groups (Table 8.30).

Table 8.30. Proportion of the CF types for fourth-order astigmatism.

Coefficient	CF type	Emmetropic (n=27)	Myopic (n=44)
Z_4^{-2} (µm)	**Augmentation**	15 (55.56%)	22 (50%)
	Undercompensation	4 (14.81%)	12 (27.27%)
	Overcompensation	8 (29.63%)	10 (22.73%)
Z_4^2 (µm)	**Augmentation**	13 (48.15%)	18 (40.91%)
	Undercompensation	10 (37.04%)	16 (36.36%)
	Overcompensation	4 (14.81%)	10 (22.73%)

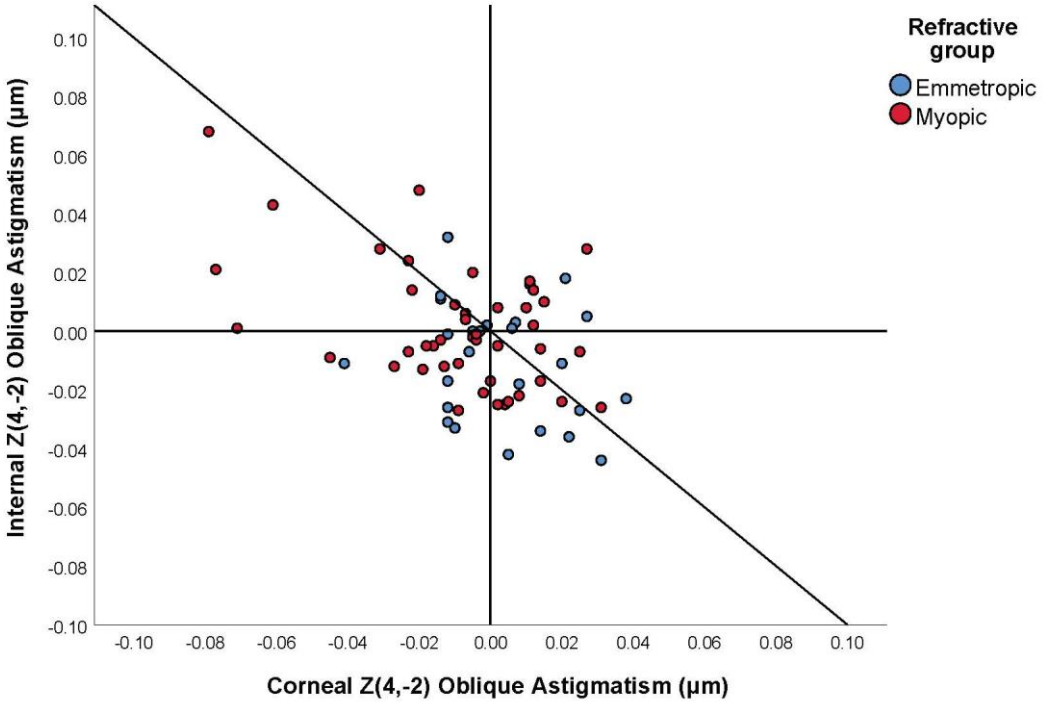

Figure 8.8. Relationship between corneal and internal oblique astigmatism Z(4,-2).

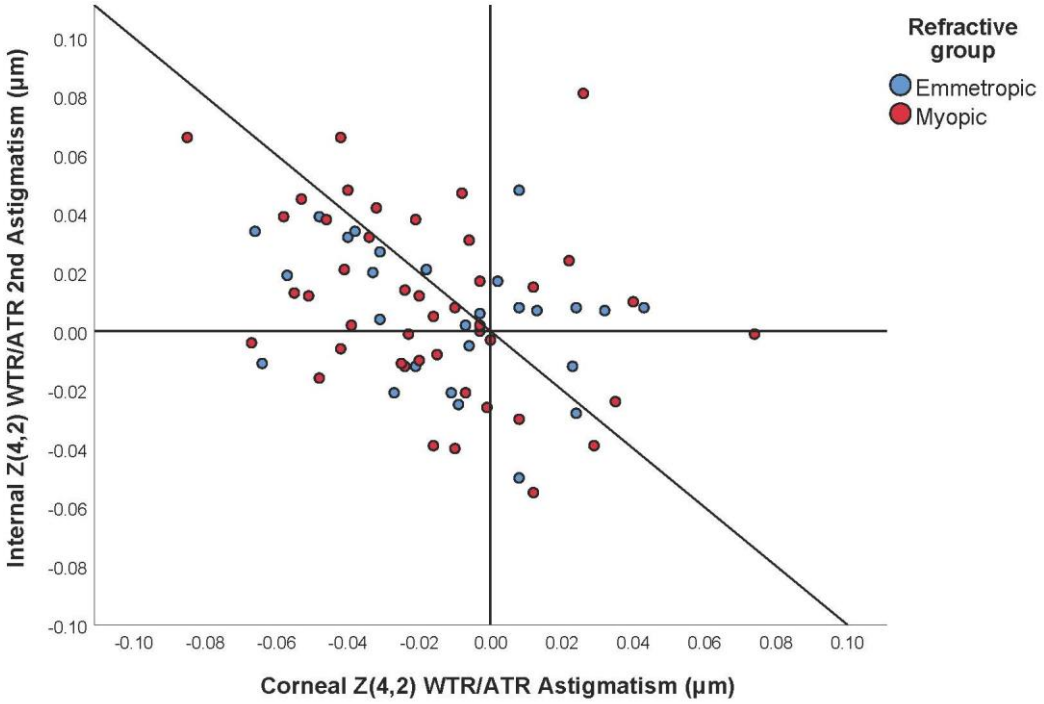

Figure 8.9. Relationship between corneal and internal WTR/ATR astigmatism Z(4,2).

The spherical aberration Z_4^0 was the only coefficient significantly compensated in the fourth-order for both emmetropic and myopic group (Wilcoxon p<0.001, Table 8.26). As seen in Figure 8.10, there was a general pattern for most of the cases (66.20%) whereby corneal spherical aberration was always positive and compensated by a negative internal spherical aberration. More proportion of myopes (70.45%) than emmetropes (59.26%) experienced undercompernsation. Moreover, some part of emmetropes (22.22%) had augmentation for the spherical aberration Z_4^0 while the overcompensation was quite similar among groups (Table 8.31).

Table 8.31. Proportion of the CF types for fourth-order spherical aberration.

Coefficient	CF type	Emmetropic (n=27)	Myopic (n=44)
Z_4^0 (µm)	**Augmentation**	6 (22.22%)	3 (6.82%)
	Undercompensation	16 (59.26%)	31 (70.45%)
	Overcompensation	5 (18.52%)	10 (22.73%)

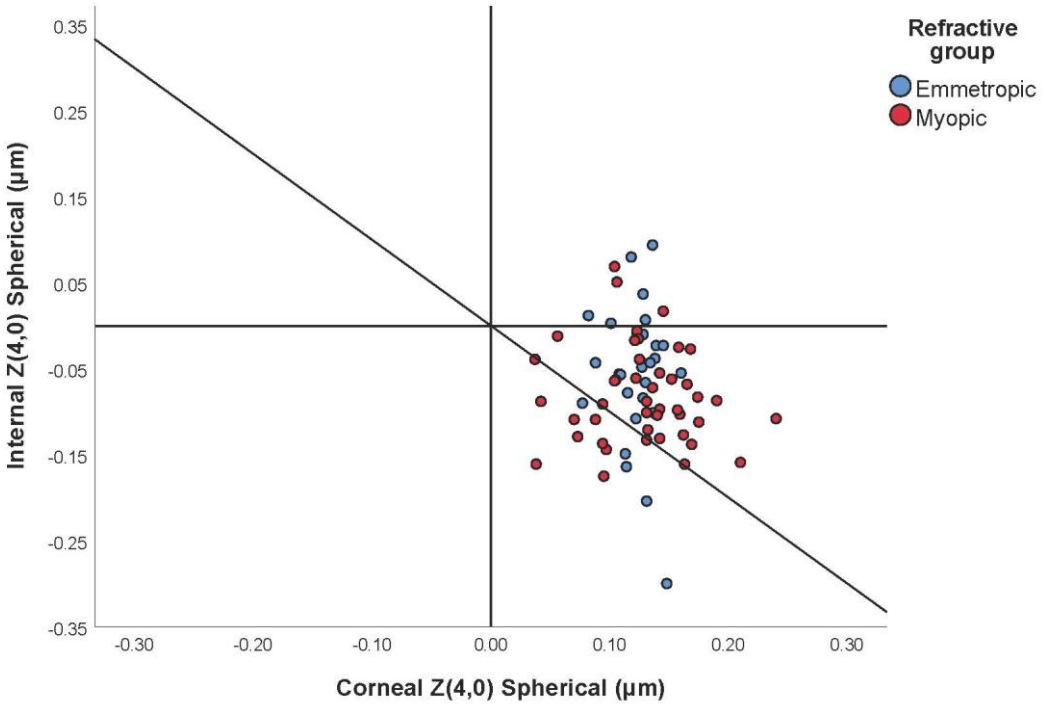

Figure 8.10. Relationship between corneal and internal spherical aberration Z(4,0).

All fifth-order coefficients showed a significant CF in emmetropes: pentafoil Z_5^{-5} (Wilcoxon p=0.002), trefoil Z_5^{-3} (Wilcoxon p<0.001), coma Z_5^{-1} (Wilcoxon p=0.006), coma Z_5^{1} (Wilcoxon p=0.010), trefoil Z_5^{3} (Wilcoxon p=0.001), pentafoil Z_5^{5} (Wilcoxon p=0.013). Meanwhile, the CF in the myopic group was significant for all fifth-order coefficients except for coma coefficients (Z_5^{-1}, Z_5^{1}): pentafoil Z_5^{-5} (Wilcoxon p=0.005), trefoil Z_5^{-3} (Wilcoxon p=0.001), trefoil Z_5^{3} (Wilcoxon p=0.019), pentafoil Z_5^{5} (Wilcoxon p=0.001). In general terms, compensation of pentafoil Z_5^{-5} and Z_5^{5} was closer to 1, that means good compensation. All of this can be seen in Table 8.26.

Both refractive groups had a significant CF for trefoil Z_5^{-3} and Z_5^{3} (Table 8.26) but the CF pattern was diverse among groups (Figure 8.11 and Figure 8.12). A bit more undercompensation was present in myopes for trefoil Z_5^{-3} although there was also some proportion of augmentation and overcompensation in the myopic group. Meantime, more than a half of the emmetropic underwent overcompensation (Table 8.32, Figure 8.11).

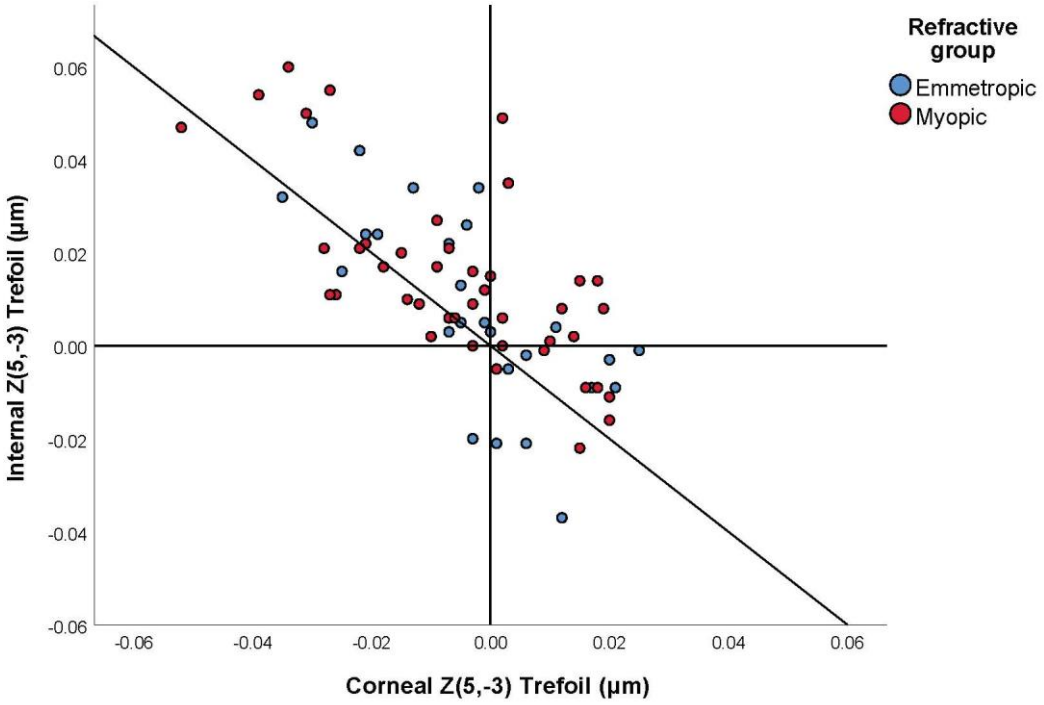

Figure 8.11. Relationship between corneal and internal trefoil Z(5,-3).

For trefoil Z_5^{3}, overcompensation was the most common pattern in both emmetropes and myopes followed by augmentation (Table 8.32). The pattern with less proportion of subjects was the undercompensation (Figure 8.12).

Table 8.32. Proportion of the CF types for fifth-order trefoil.

Coefficient	CF type	Emmetropic (n=27)	Myopic (n=44)
Z_5^{-3} (µm)	**Augmentation**	3 (11.11%)	14 (31.82%)
	Undercompensation	9 (33.33%)	16 (36.36%)
	Overcompensation	15 (55.56%)	14 (31.82%)
Z_5^{3} (µm)	**Augmentation**	7 (25.93%)	16 (36.36%)
	Undercompensation	5 (18.52%)	11 (25%)
	Overcompensation	15 (55.55%)	17 (38.64%)

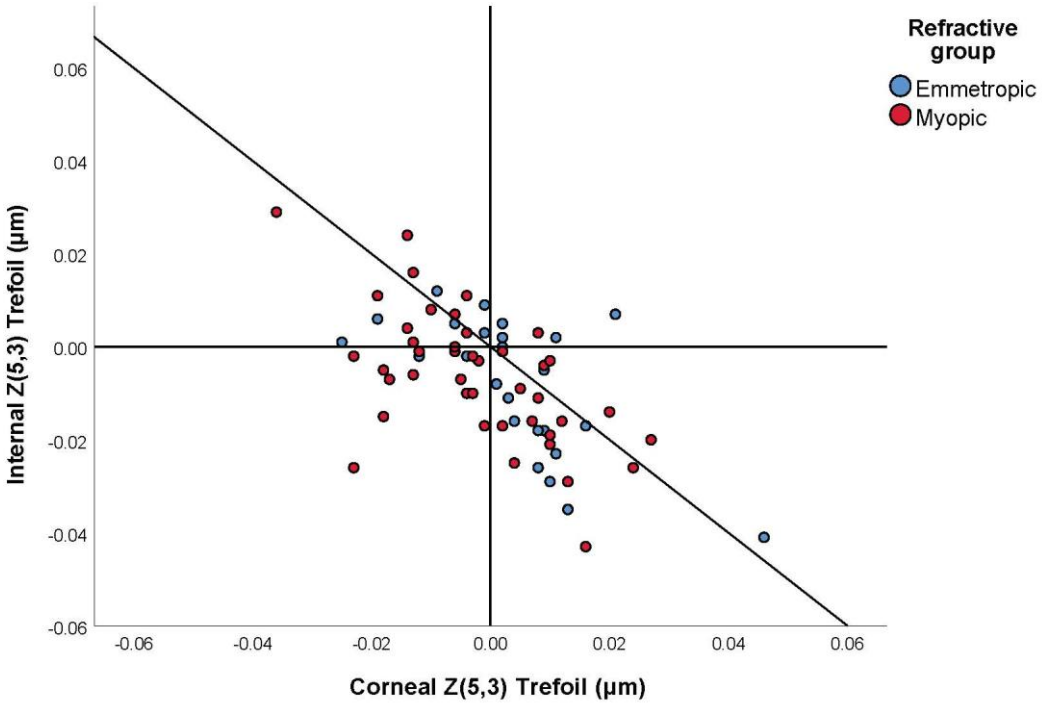

Figure 8.12. Relationship between corneal and internal trefoil Z(5,3).

For fifth-order coma, the CF was not significant in the myopic group (Table 8.26) since myopes tended to augment both vertical coma Z_5^{-1} and horizontal coma Z_5^{1} (Figure 8.13 and Figure 8.14), though also some part had partial compensation (around 35%; Table 8.33). Emmetropes mostly overcompensated the vertical coma Z_5^{-1} while experienced undercompensation for horizontal coma Z_5^{1} (Table 8.33).

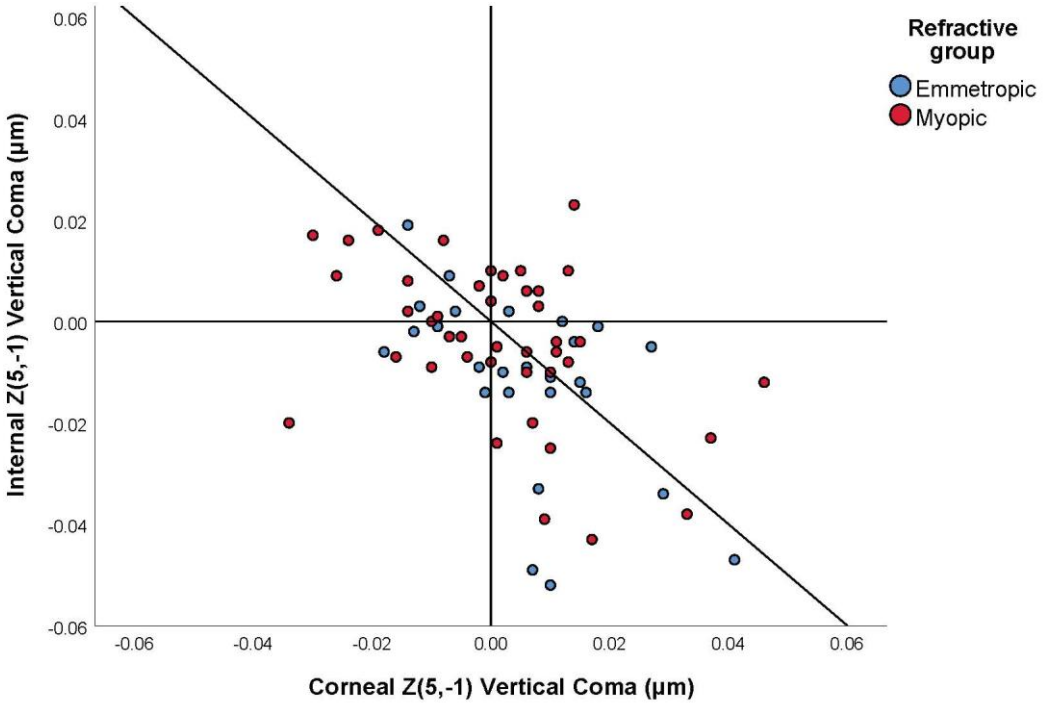

Figure 8.13. Relationship between corneal and internal vertical coma Z(5,-1).

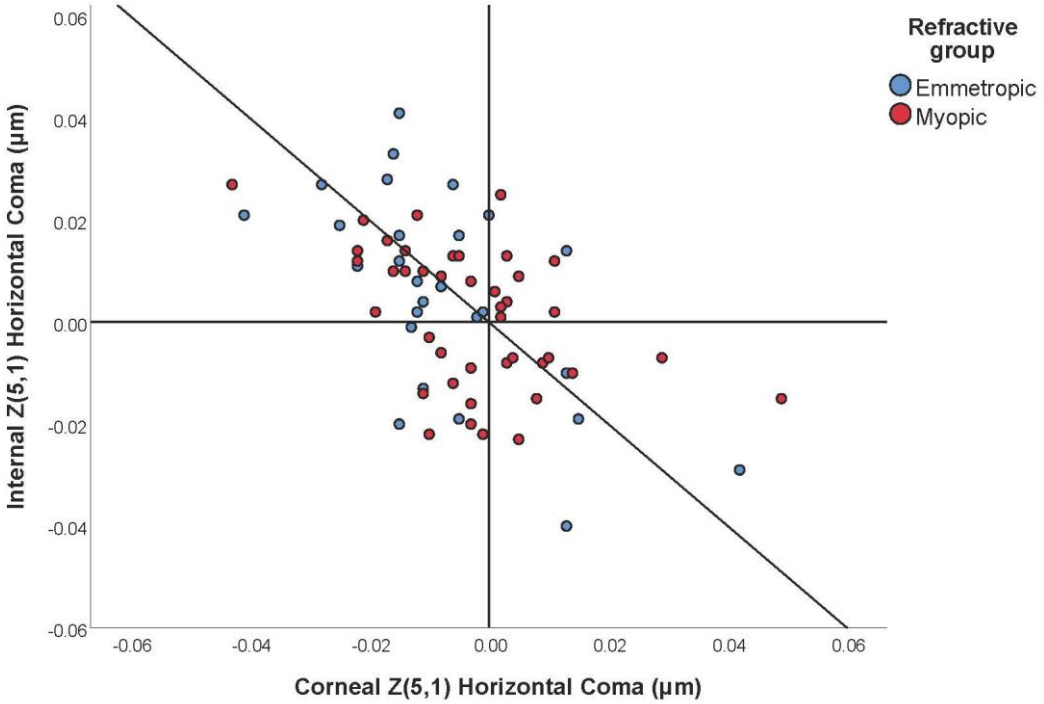

Figure 8.14. Relationship between corneal and internal horizontal coma Z(5,1).

Table 8.33. Proportion of the CF types for fifth-order coma.

Coefficient	CF type	Emmetropic (n=27)	Myopic (n=44)
Z_5^{-1} (µm)	**Augmentation**	7 (25.93%)	18 (40.91%)
	Undercompensation	7 (25.93%)	16 (36.36%)
	Overcompensation	13 (48.15%)	10 (22.73%
Z_5^{1} (µm)	**Augmentation**	6 (22.22%)	19 (43.18%)
	Undercompensation	12 (44.44%)	15 (34.09%)
	Overcompensation	9 (33.33%)	10 (22.73%)

The coefficients from sixth- and seventh- order revealed significant CF for both refractive groups (Wilcoxon p<0.001) excluding the spherical aberration Z_6^0 that was not significantly compensated in the emmetropic group (Wilcoxon p=0.304, Table 8.26). Emmetropes did compensate some part of spherical aberration Z_6^0 although in less number than myopes (Table 8.34). Nonetheless, the overcompensation was the most present type in the emmetropic and myopic subjects (Figure 8.15, Table 8.34).

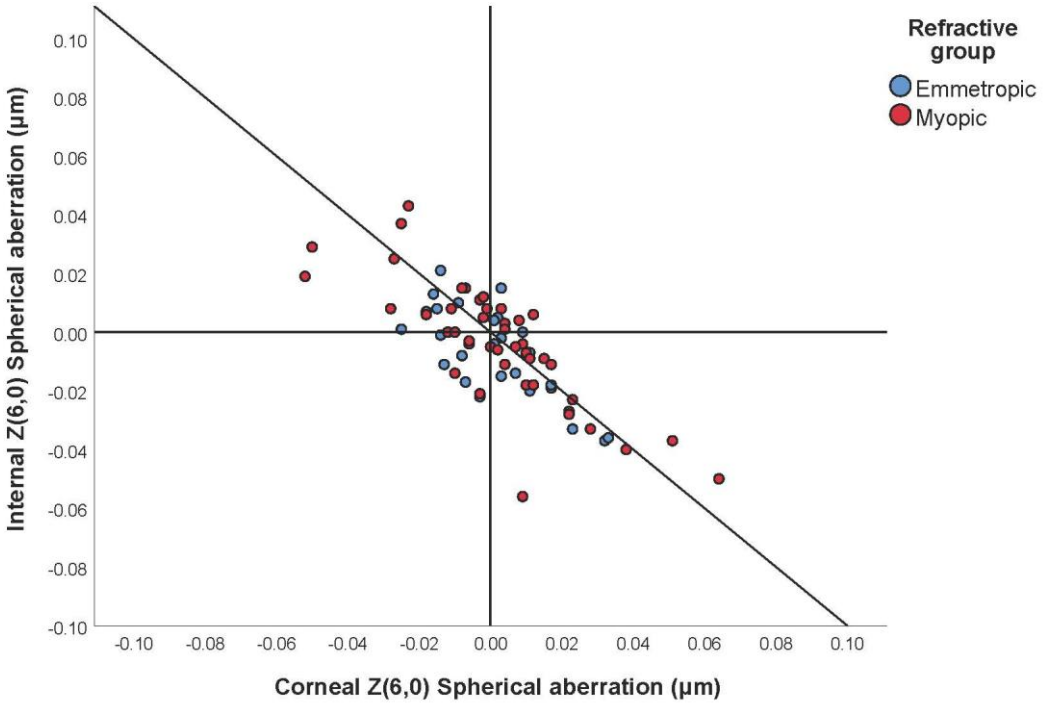

Figure 8.15. Relationship between corneal and internal spherical aberration Z(6,0).

Table 8.34. Proportion of the CF types for sixth-order spherical aberration.

Coefficient	CF type	Emmetropic (n=27)	Myopic (n=44)
Z_6^0 (µm)	**Augmentation**	9 (33.33%)	12 (27.27%)
	Undercompensation	7 (25.93%)	15 (34.09%)
	Overcompensation	11 (40.74%)	17 (38.64%)

Additionally, secondary astigmatism (Z_6^{-2} and Z_6^2) did result to be significantly compensated for both refractive groups in contrast to fourth-order astigmatism (Table 8.26). Undercompensation occurred in most of the emmetropic and myopic subjects for oblique astigmatism Z_6^{-2} (Figure 8.16 and Table 8.35).

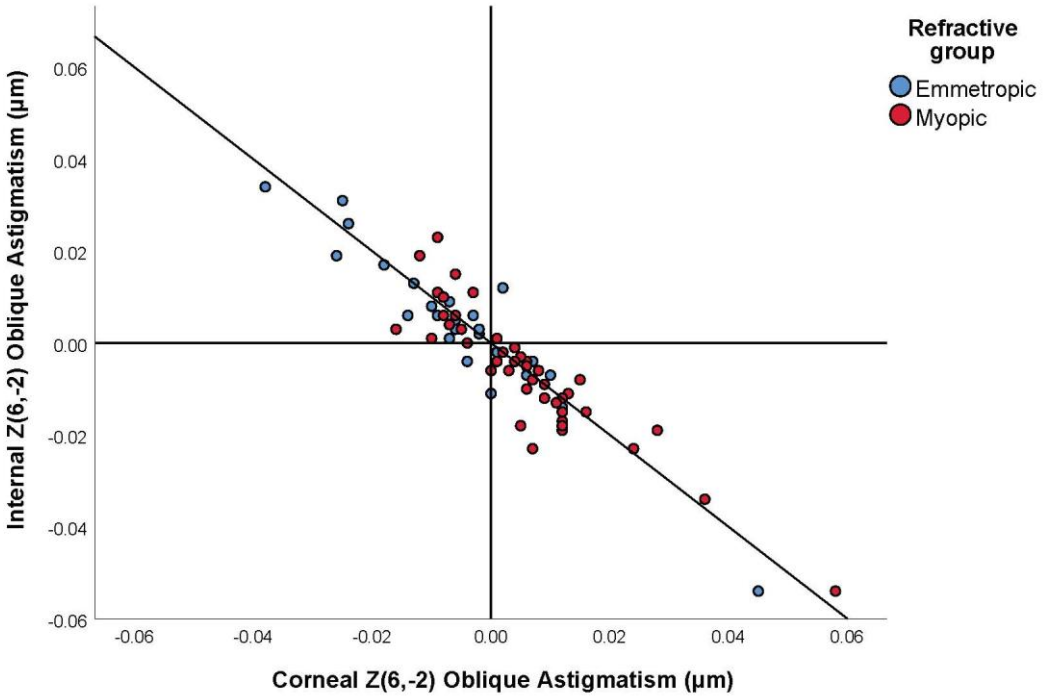

Figure 8.16. Relationship between corneal and internal oblique astigmatism Z(6,-2).

For WTR/ATR astigmatism Z_6^2, half of the myopic group had undercompensation whereas the emmetropic group had an almost similar proportion of undercompensation and overcompensation (Table 8.35 and Figure 8.17). Both astigmatism coefficients Z_6^{-2} and Z_6^2 showed clearly a compensation nearly the diagonal either in undecompensation or overcompensation zone (Figure 8.16 and Figure 8.17, respectively) and augmentation was unusual.

Table 8.35. Proportion of the CF types for sixth-order astigmatism.

Coefficient	CF type	Emmetropic (n=27)	Myopic (n=44)
Z_6^{-2} (µm)	**Augmentation**	3 (11.11%)	3 (6.82%)
	Undercompensation	15 (55.56%)	23 (52.27%)
	Overcompensation	9 (33.33%)	18 (40.91%)
Z_6^{2} (µm)	**Augmentation**	2 (7.41%)	7 (15.91%)
	Undercompensation	12 (44.44%)	22 (50%)
	Overcompensation	13 (48.15%)	15 (34.09%)

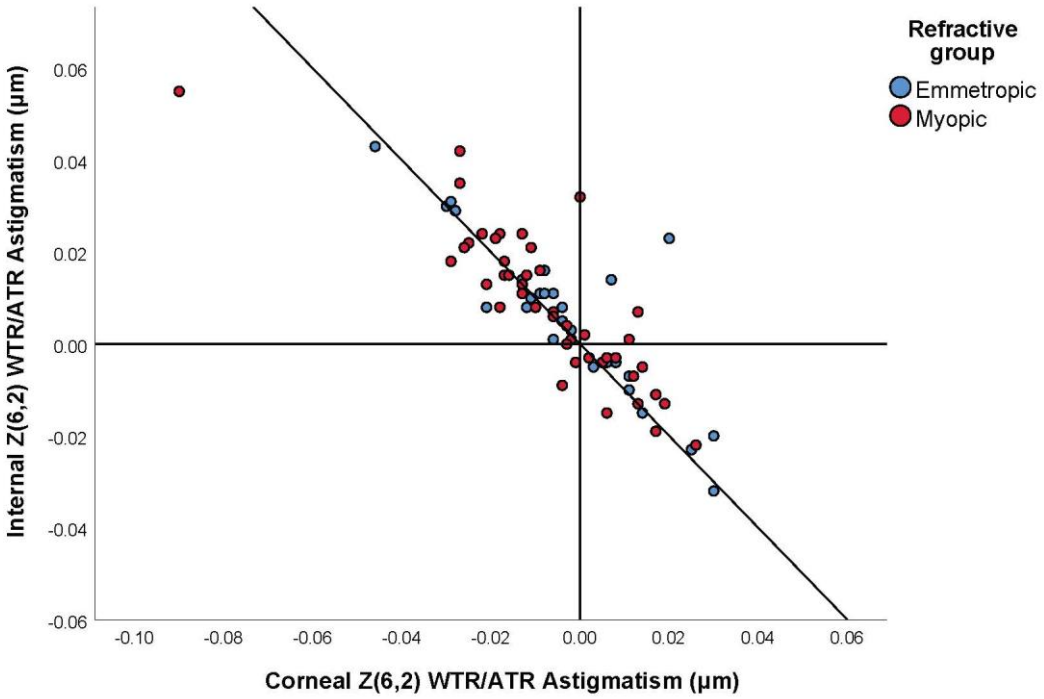

Figure 8.17. Relationship between corneal and internal WTR/ATR astigmatism Z(6,2).

8.4 Follow-up results

8.4.1 Corneal wavefront

Low-order astigmatism (Z_2^{-2} and Z_2^2) coefficients did not change significantly in the entire sample (Student t-test p>0.05) nor within the refractive groups (Student t-test p>0.05). WTR/ATR astigmatism presented a non-significant increase in both refractive groups (Table 8.36 and Table 8.37). Meantime, oblique astigmatism Z_2^{-2} had an increment in emmetropes while a reduction in myopes (Table 8.36 and Table 8.37). The change of the low-order astigmatism coefficients neither differed significantly between myopic and emmetropic subjects (mixed ANOVA p>0.05).

Table 8.36. Change of corneal LOA for the emmetropic group (3 mm).

Coefficient	Baseline (n=25)	One year (n=25)	Change (n=25)	p-value
Z_2^{-2} (µm)	0.008 ± 0.080	0.012 ± 0.081	0.004 ± 0.059	0.727
Z_2^2 (µm)	-0.144 ± 0.129	-0.133 ± 0.014	0.011 ± 0.071	0.451

Table 8.37. Change of corneal LOA for the myopic group (3 mm).

Coefficient	Baseline (n=40)	One year (n=40)	Change (n=40)	p-value
Z_2^{-2} (µm)	0.038 ± 0.125	0.021 ± 0.132	-0.016 ± 0.073	0.161
Z_2^2 (µm)	-0.196 ± 0.021	-0.183 ± 0.021	0.013 ± 0.087	0.353

Third-order trefoil Z_3^{-3} underwent a significant reduction toward negative values in the whole sample (Student t-test p=0.004). The change of each coefficient is shown in Table 8.38 and Table 8.39 for the emmetropic and myopic group, respectively. Seventh-order coefficients manifested non-significant variations of 0.001 µm or lower and were not included in Table 8.38 and Table 8.39. In the emmetropic group, the changes in the higher-order coefficients did not result statistically significant in any case (Table 8.38).

Table 8.38. Change of corneal HOA for the emmetropic group (3 mm).

Order	Coefficient	Baseline (n=25)	One year (n=25)	Change (n=25)	p-value
3rd	Z_3^{-3} (µm)	-0.007 ± 0.041	-0.016 ± 0.040	-0.008 ± 0.049	0.406
	Z_3^{-1} (µm)	0.001 ± 0.034	0.000 ± 0.040	-0.001 ± 0.043	0.905
	Z_3^{1} (µm)	-0.011 ± 0.032	-0.009 ± 0.039	0.003 ± 0.045	0.771
	Z_3^{3} (µm)	-0.010 ± 0.027	-0.003 ± 0.022	0.008 ± 0.036	0.287
4th	Z_4^{-4} (µm)	0.004 ± 0.016	-0.003 ± 0.021	-0.007 ± 0.026	0.173
	Z_4^{-2} (µm)	0.005 ± 0.016	0.000 ± 0.015	-0.005 ± 0.024	0.341
	Z_4^{0} (µm)	0.021 ± 0.021	0.021 ± 0.020	0.000 ± 0.032	0.990
	Z_4^{2} (µm)	0.002 ± 0.026	-0.002 ± 0.023	-0.004 ± 0.031	0.557
	Z_4^{4} (µm)	0.000 ± 0.019	0.010 ± 0.029	0.009 ± 0.032	0.287
5th	Z_5^{-5} (µm)	-0.003 ± 0.012	0.004 ± 0.025	0.007 ± 0.029	0.360
	Z_5^{-3} (µm)	0.005 ± 0.023	0.006 ± 0.021	0.001 ± 0.034	0.767
	Z_5^{-1} (µm)	0.001 ± 0.020	-0.001 ± 0.015	-0.001 ± 0.020	0.861
	Z_5^{1} (µm)	0.001 ± 0.016	0.006 ± 0.026	0.005 ± 0.030	0.628
	Z_5^{3} (µm)	0.005 ± 0.012	0.000 ± 0.014	-0.005 ± 0.020	0.201
	Z_5^{5} (µm)	-0.002 ± 0.012	0.007 ± 0.016	0.009 ± 0.021	0.068
6th	Z_6^{-6} (µm)	-0.005 ± 0.011	-0.005 ± 0.012	0.000 ± 0.018	0.956
	Z_6^{-4} (µm)	0.002 ± 0.012	-0.002 ± 0.013	-0.004 ± 0.018	0.293
	Z_6^{-2}(µm)	-0.001 ± 0.012	-0.003 ± 0.012	-0.002 ± 0.020	0.599
	Z_6^{0} (µm)	0.005 ± 0.036	-0.003 ± 0.020	-0.008 ± 0.041	0.344
	Z_6^{2} (µm)	-0.001 ± 0.016	0.005 ± 0.015	0.006 ± 0.023	0.214
	Z_6^{4} (µm)	-0.004 ± 0.014	-0.001 ± 0.022	0.003 ± 0.026	0.609
	Z_6^{6} (µm)	-0.004 ± 0.013	-0.001 ± 0.014	0.003 ± 0.020	0.476

Within the myopic group (Table 8.39), there was a significant shift after a year for trefoil Z_3^{-3} (Student t-test p=0.001), vertical coma Z_3^{-1} (Wilcoxon test p=0.047), oblique astigmatism Z_4^{-2} (Wilcoxon p=0.006) and Z_6^{-2} (Student t-test p=0.042). Compared to the emmetropes, myopes had a greater reduction of trefoil Z_3^{-3} and then both groups ended with a similar average magnitude in the one-year visit. In myopic eyes occurred an increase of vertical coma Z_3^{-1}, contrary to the emmetropic. Moreover, VCD elongation showed to correlate with the negative increase of horizontal coma Z_3^{1} (Spearman r=-0.280, p=0.024, Figure 8.18), which was seen in the myopic group (Table 8.39). In spite of this, the refractive group did not influence significantly in the change of trefoil Z_3^{-3} (mixed ANOVA p=0.248), vertical coma Z_3^{-1} (mixed ANOVA p=0.257), horizontal coma Z_3^{1} (mixed ANOVA p=0.538) nor trefoil Z_3^{3} (mixed ANOVA p=0.614).

Table 8.39. Change of corneal HOA for the myopic group (3 mm).

Order	Coefficient	Baseline (n=40)	One year (n=40)	Change (n=40)	p-value
3rd	Z_3^{-3} (µm)	0.007 ± 0.033	-0.015 ± 0.036	-0.021 ± 0.039	0.001*
	Z_3^{-1} (µm)	0.001 ± 0.030	0.010 ± 0.032	0.010 ± 0.031	0.047*
	Z_3^{1} (µm)	-0.002 ± 0.021	-0.005 ± 0.034	-0.003 ± 0.033	0.204
	Z_3^{3} (µm)	-0.009 ± 0.027	-0.006 ± 0.033	0.002 ± 0.041	0.882
4th	Z_4^{-4} (µm)	-0.005 ± 0.022	-0.003 ± 0.013	0.002 ± 0.026	0.925
	Z_4^{-2} (µm)	-0.005 ± 0.014	0.004 ± 0.014	0.009 ± 0.020	0.006*
	Z_4^{0} (µm)	0.013 ± 0.027	0.021 ± 0.022	0.008 ± 0.032	0.350
	Z_4^{2} (µm)	0.004 ± 0.020	0.001 ± 0.021	-0.003 ± 0.030	0.482
	Z_4^{4} (µm)	0.004 ± 0.022	0.005 ± 0.024	0.002 ± 0.033	0.783
5th	Z_5^{-5} (µm)	-0.008 ± 0.020	-0.005 ± 0.014	0.003 ± 0.024	0.764
	Z_5^{-3} (µm)	-0.001 ± 0.014	0.004 ± 0.013	0.006 ± 0.021	0.094
	Z_5^{-1} (µm)	-0.004 ± 0.014	0.001 ± 0.016	0.005 ± 0.024	0.416
	Z_5^{1} (µm)	-0.001 ± 0.020	0.003 ± 0.013	0.004 ± 0.020	0.194
	Z_5^{3} (µm)	0.003 ± 0.019	0.005 ± 0.016	0.002 ± 0.019	0.476
	Z_5^{5} (µm)	0.000 ± 0.017	0.002 ± 0.014	0.002 ± 0.024	0.173
6th	Z_6^{-6} (µm)	-0.002 ± 0.013	0.001 ± 0.010	0.004 ± 0.015	0.129
	Z_6^{-4} (µm)	0.001 ± 0.015	0.001 ± 0.010	0.000 ± 0.017	0.978
	Z_6^{-2}(µm)	-0.002 ± 0.014	0.004 ± 0.015	0.006 ± 0.019	0.042*
	Z_6^{0} (µm)	-0.001 ± 0.027	0.005 ± 0.023	0.005 ± 0.035	0.335
	Z_6^{2} (µm)	-0.002 ± 0.016	0.001 ± 0.016	0.003 ± 0.022	0.377
	Z_6^{4} (µm)	-0.005 ± 0.017	-0.003 ± 0.016	0.002 ± 0.020	0.471
	Z_6^{6} (µm)	-0.002 ± 0.025	0.000 ± 0.009	0.002 ± 0.026	0.586

*p-value<0.05

The differences between refractive groups did result significant for oblique astigmatism Z_4^{-2} (mixed ANOVA p=0.016) but not for Z_6^{-2} (mixed ANOVA p=0.093). As seen in Table 8.38 and Table 8.39, the emmetropic group experienced a reduction of positive values whereas the myopic group had an increase towards positive values. Meantime, the changes in secondary WTR/ATR astigmatism (Z_4^2, Z_6^2) were quite similar among refractive groups (mixed ANOVA p>0.05). The changes in secondary astigmatism coefficients did not manifest a significant association with other biometric or refractive change.

Spherical aberration Z_4^0 and Z_6^0 experienced a non-significant increase in myopes while in emmetropes remained stable and reduced, respectively, though it did not differ significantly between groups in any case (mixed ANOVA p=0.359 and p=0.167 for Z_4^0 and

Z_6^0, respectively). No other higher-order coefficient presented a different change between refractive groups (mixed ANOVA p>0.05).

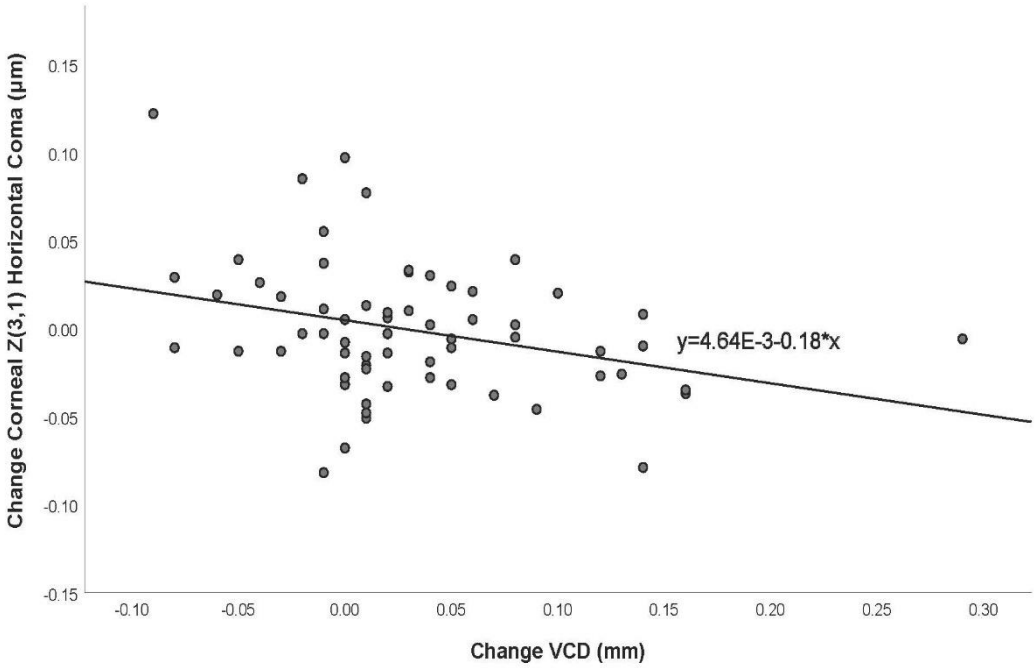

Figure 8.18. Linear relationship between the changes of corneal coma Z(3,1) and VCD.

Furthermore, the change of each RMS was obtained for the emmetropic (Table 8.40) and myopic group (Table 8.41). As a result of the changes in the coefficients, third-order RMS increased significantly in the myopic group (Wilcoxon p=0.010) while in the emmetropic was non-significant (Wilcoxon p=0.989). In comparison with myopes, the spherical aberration RMS had a greater reduction and HOA RMS had a greater increase in emmetropes although it was not significant in any group (Table 8.40 and Table 8.41). The change was not statistically different between groups in any of them: third-order RMS (mixed ANOVA p=0.401), spherical aberration RMS (mixed ANOVA p=0.233) and HOA RMS (mixed ANOVA p=0.803). Coma-like RMS increased in a similar way for both refractive groups but it did not reach the significance within any group (Wilcoxon p=0.563 and p=0.058 for the myopic and emmetropic group, respectively). Generally, the refractive error did not exhibit to have a significant influence in any RMS shift (mixed ANOVA p>0.05). No change in RMS was associated with the change of the sphere nor the VCD elongation.

Table 8.40. Change of corneal RMS for the emmetropic group (3 mm).

RMS (µm)	Baseline (n=25)	One year (n=25)	Change (n=25)	p-value
HOA (3rd to 7th)	0.104 ± 0.036	0.110 ± 0045	0.006 ± 0.058	0.820
Total	0.211 ± 0.105	0.215 ± 0.104	0.004 ± 0.077	0.444
3rd order	0.063 ± 0.027	0.066 ± 0.032	0.003 ± 0.047	0.989
4th order	0.044 ± 0.022	0.048 ± 0.025	0.004 ± 0.036	0.716
5th order	0.034 ± 0.022	0.041 ± 0.029	0.007 ± 0.029	0.638
6th order	0.044 ± 0.021	0.039 ± 0.016	-0.005 ± 0.022	0.183
7th order	0.032 ± 0.013	0.038 ± 0.016	0.006 ± 0.016	0.078
Low order astigmatism (2nd)	0.170 ± 0.121	0.173 ± 0.111	0.003 ± 0.069	0.946
High order astigmatism (4th and 6th)	0.030 ± 0.020	0.031 ± 0.013	0.000 ± 0.022	0.253
Spherical aberration (4th and 6th)	0.040 ± 0.024	0.030 ± 0.019	-0.010 ±0.035	0.115
Coma-like (3rd to 7th)	0.050 ± 0.027	0.058 ± 0.032	0.008 ± 0.040	0.563
Trefoil-like (3rd to 7th)	0.053 ± 0.026	0.052 ± 0.028	-0.001 ± 0.039	0.339

Table 8.41. Change of corneal RMS for the myopic group (3 mm).

RMS (µm)	Baseline (n=40)	One year (n=40)	Change (n=40)	p-value
HOA (3rd to 7th)	0.097 ± 0.048	0.100 ± 0.033	0.003 ± 0.039	0.251
Total	0.289 ± 0.139	0.293 ± 0.134	0.005 ± 0.074	0.327
3rd order	0.051 ± 0.026	0.062 ± 0.032	0.011 ± 0.029	0.010*
4th order	0.042 ± 0.027	0.043 ± 0.022	0.000 ± 0.031	0.925
5th order	0.037 ± 0.023	0.033 ± 0.015	-0.003 ± 0.016	0.270
6th order	0.043 ± 0.025	0.038 ± 0.012	-0.005 ± 0.021	0.436
7th order	0.036 ± 0.024	0.031 ± 0.012	-0.005 ± 0.021	0.188
Low order astigmatism (2nd)	0.266 ± 0.017	0.266 ± 0.151	0.000 ± 0.083	0.382
High order astigmatism (4th and 6th)	0.030 ± 0.014	0.031 ± 0.013	0.001 ± 0.018	0.788
Spherical aberration (4th and 6th)	0.036 ± 0.024	0.034 ± 0.018	-0.002 ± 0.020	0.648
Coma-like (3rd to 7th)	0.042 ± 0.019	0.049 ± 0.024	0.007 ± 0.025	0.058
Trefoil-like (3rd to 7th)	0.047 ± 0.028	0.052 ± 0.027	0.004 ± 0.028	0.188

*p-value<0.05

8.4.2 Internal wavefront

In the general sample, defocus Z_2^0 experienced a significant increase (Wilcoxon p<0.001) of 0.048 ± 0.092 μm on average. The defocus Z_2^0 increment was significant within the myopic group (Wilcoxon p<0.001, Table 8.43) but not within the emmetropic (Student t-test p=0.070, Table 8.42). This defocus Z_2^0 change was mainly related to the VCD enlargement (Spearman r=0.424, p<0.001). The differences in the increase of defocus Z_2^0 between groups were not statistically significant (mixed ANOVA p=0.666).

Table 8.42. Change of internal LOA for the emmetropic group (3 mm).

Coefficient	Baseline (n=25)	One year (n=25)	Change (n=25)	p-value
Z_2^{-2} (μm)	0.011 ± 0.078	-0.003 ± 0.071	-0.015 ± 0.053	0.177
Z_2^0 (μm)	0.097 ± 0.011	0.139 ± 0.163	0.042 ± 0.111	0.070
Z_2^2 (μm)	0.101 ± 0.106	0.091 ± 0.104	-0.010 ± 0.061	0.264

Table 8.43. Change of internal LOA for the myopic group (3 mm).

Coefficient	Baseline (n=40)	One year (n=40)	Change (n=40)	p-value
Z_2^{-2} (μm)	-0.019 ± 0.096	0.006 ± 0.068	0.024 ± 0.073	0.067
Z_2^0 (μm)	1.515 ± 0.958	1.567 ± 0.977	0.052 ± 0.078	<0.001*
Z_2^2 (μm)	0.144 ± 0.093	0.115 ± 0.098	-0.030 ± 0.072	0.013*

*p-value<0.05

WTR/ATR astigmatism Z_2^2 experienced a significant decrease (Student t-test p=0.012) in the entire sample of -0.022 ± 0.068 μm. Both refractive groups had a WTR/ATR astigmatism Z_2^2 reduction of its positive values but it was significant only in myopes (Student t-test p=0.013, Table 8.43). Despite the greater reduction of WTR/ATR astigmatism Z_2^2 in myopes, the shift was not different between emmetropes and myopes (mixed ANOVA p=0.266). The change of oblique astigmatism Z_2^{-2} was not significant within any group, nonetheless, it did differ among refractive groups (mixed ANOVA p=0.025). This was produced because the opposite changes where myopes increased toward positive values and emmetropes decreased the positive values (Table 8.42 and Table 8.43). WTR/ATR astigmatism Z_2^2 reduced with the negative shift of the sphere (Spearman r=0.246, p=0.048) while oblique astigmatism Z_2^{-2} change was not related to any refractive or biometric variation.

From HOA, only pentafoil Z_5^5 had a significant decrease (Wilcoxon p=0.034) of -0.004 ± 0.026 μm considering the entire sample. When divided into refractive groups, the changes in HOA coefficients were not significant within the emmetropic group (Table 8.44) whereas the myopic group did exhibit some significant changes (Table 8.45). Seventh-order coefficients manifested non-significant changes of 0.001 μm or lower and were not included in Table 8.44 and Table 8.45.

Myopic subjects underwent a significant reduction of negative trefoil Z_3^{-3} values (Student t-test p=0.022) but the change did not differ significantly between refractive groups (mixed ANOVA= 0.160). Vertical coma Z_3^{-1} tended to reduce the positive values in myopes (Student t-test p=0.194) whereas in emmetropes increased positively (Wilcoxon p=0.184). The positive increment of horizontal coma Z_3^1 resulted non-significant within myopes (Student t-test p=0.094), however, this tendency of positive Z_3^1 increase was related to the VCD elongation (Spearman r=0.278, p=0.025, Figure 8.19). The differences between groups did not reach the significance for vertical coma Z_3^{-1} (mixed ANOVA p=0.063) nor for horizontal coma Z_3^1 (mixed ANOVA=0.228).

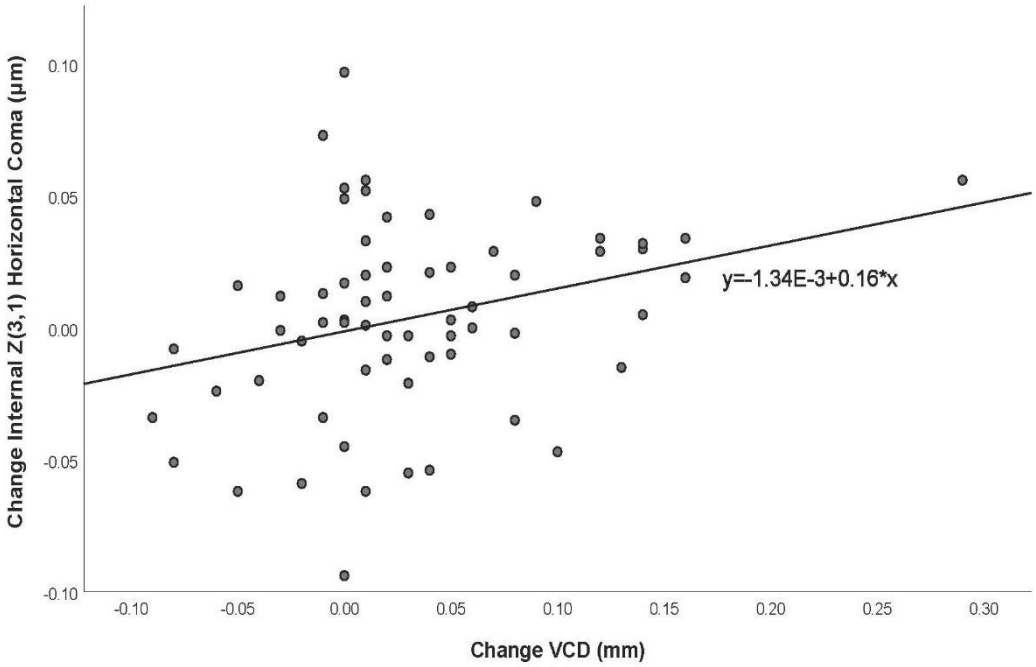

Figure 8.19. Linear relationship between the changes of internal coma Z(3,1) and VCD.

Table 8.44. Change of internal HOA for the emmetropic group (3 mm).

Order	Coefficient	Baseline (n=25)	One year (n=25)	Change (n=25)	p-value
3rd	Z_3^{-3} (µm)	-0.007 ± 0.029	-0.007 ± 0.035	-0.001 ± 0.045	0.545
	Z_3^{-1} (µm)	-0.002 ± 0.030	0.008 ± 0.032	0.010 ± 0.039	0.184
	Z_3^{1} (µm)	0.023 ± 0.027	0.019 ± 0.037	-0.003 ± 0.044	0.731
	Z_3^{3} (µm)	0.019 ± 0.028	0.012 ± 0.023	-0.007 ± 0.034	0.361
4th	Z_4^{-4} (µm)	-0.003 ± 0.015	0.004 ± 0.022	0.007 ± 0.027	0.231
	Z_4^{-2} (µm)	-0.006 ± 0.017	0.001 ± 0.015	0.007 ± 0.026	0.225
	Z_4^{0} (µm)	-0.009 ± 0.023	-0.010 ± 0.021	-0.001 ± 0.030	0.937
	Z_4^{2} (µm)	-0.004 ± 0.023	-0.001 ± 0.021	0.003 ± 0.029	0.435
	Z_4^{4} (µm)	-0.002 ± 0.019	-0.011 ± 0.030	-0.009 ± 0.032	0.287
5th	Z_5^{-5} (µm)	0.003 ± 0.013	-0.003 ± 0.026	-0.006 ± 0.030	0.638
	Z_5^{-3} (µm)	-0.004 ± 0.023	-0.004 ± 0.021	0.000 ± 0.035	0.484
	Z_5^{-1} (µm)	-0.001 ± 0.020	-0.001 ± 0.015	0.000 ± 0.019	0.721
	Z_5^{1} (µm)	-0.002 ± 0.018	-0.006 ± 0.003	-0.005 ± 0.030	0.788
	Z_5^{3} (µm)	-0.007 ± 0.012	-0.002 ± 0.014	0.005 ± 0.019	0.170
	Z_5^{5} (µm)	0.002 ± 0.012	-0.007 ± 0.017	-0.009 ± 0.021	0.076
6th	Z_6^{-6} (µm)	0.005 ± 0.011	0.005 ± 0.012	0.000 ± 0.018	0.929
	Z_6^{-4} (µm)	-0.002 ± 0.012	0.002 ± 0.013	0.004 ± 0.017	0.285
	Z_6^{-2}(µm)	0.001 ± 0.012	0.003 ± 0.012	0.002 ± 0.019	0.637
	Z_6^{0} (µm)	-0.005 ± 0.036	0.003 ± 0.020	0.008 ± 0.041	0.347
	Z_6^{2} (µm)	0.001 ± 0.016	-0.005 ± 0.014	-0.006 ± 0.023	0.210
	Z_6^{4} (µm)	0.004 ± 0.014	0.001 ± 0.022	-0.003 ± 0.026	0.581
	Z_6^{6} (µm)	0.004 ± 0.013	0.001 ± 0.015	-0.003 ± 0.020	0.483

*p-value<0.05

Secondary oblique astigmatism Z_4^{-2} (Student t-test p=0.014) and Z_6^{-2} (Student t-test p=0.039) changed significantly toward negative values in myopes (Table 8.45). The change was significantly different between the emmetropic and myopic group for oblique astigmatism Z_4^{-2} (mixed ANOVA p=0.013) but not for Z_6^{-2} (mixed ANOVA p=0.096). Besides, the spherical aberration Z_4^0 and Z_6^0 increased more their negative values in myopes (Table 8.45) while for emmetropes Z_4^0 remained almost stable and Z_6^0 increased toward positive values (Table 8.44). The differences were not significant between groups for Z_4^0 (mixed ANOVA p=0.263) nor Z_6^0 (mixed ANOVA p=0.165). For the rest HOA, there was no interaction between their change and the refractive group (mixed ANOVA p>0.05).

Table 8.45. Change of internal HOA for the myopic group (3 mm).

Order	Coefficient	Baseline (n=40)	One year (n=40)	Change (n=40)	p-value
3rd	Z_3^{-3} (µm)	-0.024 ± 0.031	-0.010 ± 0.029	0.014 ± 0.037	0.022*
	Z_3^{-1} (µm)	0.008 ± 0.022	0.002 ± 0.025	-0.006 ± 0.029	0.194
	Z_3^{1} (µm)	0.010 ± 0.022	0.018 ± 0.024	0.008 ± 0.030	0.094
	Z_3^{3} (µm)	0.020 ± 0.025	0.013 ± 0.029	-0.006 ± 0.041	0.489
4th	Z_4^{-4} (µm)	0.006 ± 0.023	0.003 ± 0.014	-0.003 ± 0.026	0.712
	Z_4^{-2} (µm)	0.004 ± 0.016	-0.004 ± 0.016	-0.009 ± 0.021	0.014*
	Z_4^{0} (µm)	-0.005 ± 0.025	-0.014 ± 0.024	-0.009 ± 0.030	0.061
	Z_4^{2} (µm)	-0.007 ± 0.022	-0.001 ± 0.020	0.006 ± 0.030	0.292
	Z_4^{4} (µm)	-0.004 ± 0.022	-0.007 ± 0.020	-0.003 ± 0.031	0.798
5th	Z_5^{-5} (µm)	0.007 ± 0.021	0.003 ± 0.015	-0.004 ± 0.024	0.620
	Z_5^{-3} (µm)	0.003 ± 0.015	-0.003 ± 0.011	-0.005 ± 0.019	0.072
	Z_5^{-1} (µm)	0.004 ± 0.014	-0.001 ± 0.016	-0.005 ± 0.024	0.324
	Z_5^{1} (µm)	0.001 ± 0.019	-0.004 ± 0.013	-0.005 ± 0.021	0.176
	Z_5^{3} (µm)	-0.004 ± 0.019	-0.005 ± 0.017	-0.001 ± 0.019	0.824
	Z_5^{5} (µm)	-0.002 ± 0.017	-0.003 ± 0.015	-0.001 ± 0.025	0.239
6th	Z_6^{-6} (µm)	0.002 ± 0.013	-0.001 ± 0.010	-0.004 ± 0.016	0.141
	Z_6^{-4} (µm)	-0.001 ± 0.015	-0.001 ± 0.010	0.000 ± 0.017	0.985
	Z_6^{-2}(µm)	0.002 ± 0.014	-0.004 ± 0.015	-0.006 ± 0.019	0.039*
	Z_6^{0} (µm)	0.000 ± 0.027	-0.005 ± 0.024	-0.006 ± 0.035	0.325
	Z_6^{2} (µm)	0.002 ± 0.016	-0.001 ± 0.016	-0.003 ± 0.022	0.355
	Z_6^{4} (µm)	0.005 ± 0.017	0.003 ± 0.016	-0.002 ± 0.020	0.494
	Z_6^{6} (µm)	0.002 ± 0.025	0.000 ± 0.009	-0.002 ± 0.026	0.617

*p-value<0.05

Including all subjects, LOA RMS and total RMS had a significant increment of 0.037 ± 0.087 µm (Wilcoxon p=0.002) and 0.036 ± 0.093 µm (Wilcoxon p=0.003), respectively, after one year. By contrast, low order astigmatism RMS experienced a significant decrease of -0.025 ± 0.076 µm (Wilcoxon p=0.013). Furthermore, the change of each RMS was obtained for the emmetropic (Table 8.46) and myopic group (Table 8.47). LOA increased in both refractive groups but ended up being significant only in the myopic group (Wilcoxon p=0.001, Table 8.47) and consistently the same occurred for total RMS change (Wilcoxon p=0.002, Table 8.47). Thereby, the VCD elongation was associated with the increase of LOA RMS (Spearman r=0.498, p<0.001) and total RMS (Spearman r=0.498, p<0.001).

Table 8.46. Change of internal RMS for the emmetropic group (3 mm).

RMS (µm)	Baseline (n=25)	One year (n=25)	Change (n=25)	p-value
LOA (2nd)	0.201 ± 0.087	0.223 ± 0.0139	0.023 ± 0.096	0.339
HOA (3rd to 7th)	0.098 ± 0.037	0.103 ± 0.046	0.005 ± 0.056	0.619
Total	0.227 ± 0.084	0.250 ± 0.138	0.023 ± 0.103	0.382
3rd order	0.057 ± 0.029	0.062 ± 0.028	0.005 ± 0.046	0.819
4th order	0.042 ± 0.019	0.044 ± 0.026	0.003 ± 0.031	0.968
5th order	0.035 ± 0.021	0.041 ± 0.029	0.006 ± 0.029	0.657
6th order	0.044 ± 0.021	0.039 ± 0.016	-0.005 ± 0.022	0.158
7th order	0.026 ± 0.010	0.033 ± 0.015	0.006 ± 0.014	0.058
Low order astigmatism (2nd)	0.143 ± 0.084	0.129 ± 0.084	-0.014 ± 0.055	0.093
High order astigmatism (4th and 6th)	0.029 ± 0.021	0.029 ± 0.014	0.000 ± 0.023	0.527
Spherical aberration (4th and 6th)	0.038 ± 0.022	0.027 ± 0.014	-0.011 ± 0.027	0.052
Coma-like (3rd to 7th)	0.050 ± 0.025	0.055 ± 0.030	0.005 ± 0.038	0.716
Trefoil-like (3rd to 7th)	0.052 ± 0.031	0.048 ± 0.021	0.002 ±0.039	0.778

Table 8.47. Change of internal RMS for the myopic group (3 mm).

RMS (µm)	Baseline (n=40)	One year (n=40)	Change (n=40)	p-value
LOA (2nd)	1.533 ± 0.950	1.580 ± 0.970	0.047 ± 0.081	0.001*
HOA (3rd to 7th)	0.098 ± 0.049	0.093 ± 0.023	-0.005 ± 0.041	0.798
Total	1.540 ± 0.944	1.584 ± 0.967	0.044 ± 0.087	0.002*
3rd order	0.053 ± 0.028	0.054 ± 0.023	0.001 ± 0.031	0.554
4th order	0.043 ± 0.024	0.042 ± 0.016	-0.001 ± 0.026	0.819
5th order	0.037 ± 0.024	0.034 ± 0.014	-0.004 ± 0.018	0.265
6th order	0.043 ± 0.025	0.038 ± 0.012	-0.005 ± 0.021	0.510
7th order	0.030 ± 0.024	0.025 ± 0.010	-0.005 ± 0.021	0.216
Low order astigmatism (2nd)	0.176 ± 0.088	0.143 ± 0.082	-0.033 ± 0.086	0.020
High order astigmatism (4th and 6th)	0.032 ± 0.014	0.032 ± 0.012	0.000 ± 0.018	0.767
Spherical aberration (4th and 6th)	0.033 ± 0.017	0.031 ± 0.019	-0.001 ± 0.019	0.830
Coma-like (3rd to 7th)	0.041 ± 0.017	0.042 ± 0.021	0.001 ± 0.026	0.707
Trefoil-like (3rd to 7th)	0.052 ± 0.031	0.048 ± 0.021	-0.003 ± 0.032	0.767

*p-value<0.05

Likewise, the decrease of the low order astigmatism RMS was significant for the myopic group (Student t-test p=0.020) but not for the emmetropic (Wilcoxon p=0.093). The change did not differ significantly between myopes and emmetropes for LOA RMS (mixed ANOVA p=0.279), total RMS (mixed ANOVA p=0.382) nor low order astigmatism RMS (mixed ANOVA p=0.321). The spherical RMS underwent a reduction almost significant in the emmetropic group (Wilcoxon p=0.052, Table 8.46) while for the myopic group remained quite stable (Wilcoxon p=0.830, Table 8.47). However, the spherical RMS change was not statistically different among groups (mixed ANOVA p=0.089). Even though it was non-significant, HOA RMS increased in emmetropic (Table 8.46) while it reduced in myopic subjects (Table 8.47). The change of HOA RMS, higher-order RMS (3rd to 7th), coma- and trefoil-like RMS did not result significant within any refractive group (Wilcoxon p>0.05) nor differed between groups (mixed ANOVA p>0.05).

8.4.3 Ocular wavefront

Defocus Z_2^0 had a significant increase of 0.048 ± 0.092 μm in the entire sample (Wilcoxon p<0.001). Meantime, the change of low order astigmatism coefficients was not significant (Wilcoxon p>0.05). The defocus Z_2^0 increment proved to be associated with the VCD enlargement over time (Spearman r=0.424, p<0.001). Thus, the change for defocus Z_2^0 was significant within myopes (Wilcoxon p<0.001) whereas it was not for emmetropes (Student t-test p=0.070). Despite the greater increase of defocus Z_2^0 in myopes, it did not differ significantly between groups (mixed ANOVA p=0.666).

Oblique astigmatism Z_2^{-2} experienced opposite changes between refractive groups but these were not significant (Table 8.48 and Table 8.49). Then, reduction of the WTR/ATR astigmatism Z_2^2 did not reach the significance in the myopic group (Wilcoxon p=0.077, Table 8.49). The refractive group did not manifest to influence significantly the change of oblique astigmatism Z_2^{-2} (mixed ANOVA p=0.120) nor WTR/ATR astigmatism Z_2^2 (mixed ANOVA p=0.223).

Table 8.48. Change of ocular LOA for the emmetropic group (3 mm).

Coefficient	Baseline (n=25)	One year (n=25)	Change (n=25)	p-value
Z_2^{-2} (μm)	0.019 ± 0.053	0.009 ± 0.052	-0.011 ± 0.048	0.282
Z_2^0 (μm)	0.097 ± 0.107	0.139 ± 0.163	0.042 ± 0.011	0.070
Z_2^2 (μm)	-0.043 ± 0.072	-0.042 ± 0.064	0.001 ± 0.048	0.932

Table 8.49. Change of ocular LOA for the myopic group (3 mm).

Coefficient	Baseline (n=40)	One year (n=40)	Change (n=40)	p-value
Z_2^{-2} (μm)	0.019 ± 0.120	0.027 ± 0.119	0.008 ± 0.043	0.274
Z_2^0 (μm)	1.515 ± 0.958	1.567 ± 0.977	0.052 ± 0.078	<0.001*
Z_2^2 (μm)	-0.052 ± 0.190	-0.068 ± 0.195	-0.017 ± 0.060	0.077

*p-value<0.05

From HOA, trefoil Z_3^{-3} underwent a significant negative increase of -0.008 ± 0.022 μm in the general sample after the follow-up (Student t-tets p=0.006). The changes of the HOA coefficients are presented for the emmetropic and myopic group in Table 8.50 and Table 8.51 respectively. Sixth- and seventh-order coefficients manifested non-significant changes of 0.001 μm or lower and were not included in Table 8.50 and Table 8.51

Table 8.50. Change of ocular HOA for the emmetropic group (3 mm).

Order	Coefficient	Baseline (n=25)	One year (n=25)	Change (n=25)	p-value
3rd	Z_3^{-3} (μm)	-0.014 ± 0.025	-0.023 ± 0.023	-0.009 ± 0.026	0.100
	Z_3^{-1} (μm)	-0.001 ± 0.025	0.008 ± 0.026	0.009 ± 0.028	0.124
	Z_3^1 (μm)	0.011 ± 0.019	0.011 ± 0.016	0.000 ± 0.021	0.927
	Z_3^3 (μm)	0.008 ± 0.016	0.009 ± 0.015	0.000 ± 0.017	0.909
4th	Z_4^{-4} (μm)	0.001 ± 0.006	0.000 ± 0.005	-0.001 ± 0.007	0.566
	Z_4^{-2} (μm)	-0.001 ± 0.006	0.001 ± 0.006	0.002 ± 0.009	0.352
	Z_4^0 (μm)	0.012 ± 0.014	0.011 ± 0.014	0.000 ± 0.012	0.872
	Z_4^2 (μm)	-0.002 ± 0.008	-0.003 ± 0.008	-0.001 ± 0.009	0.628
	Z_4^4 (μm)	-0.002 ± 0.007	-0.002 ± 0.007	0.000 ± 0.006	0.947
5th	Z_5^{-5} (μm)	0.000 ± 0.003	0.001 ± 0.004	0.001 ± 0.003	0.036*
	Z_5^{-3} (μm)	0.001 ± 0.004	0.002 ± 0.004	0.001 ± 0.005	0.102
	Z_5^{-1} (μm)	0.000 ± 0.006	-0.002 ± 0.004	-0.002 ± 0.005	0.186
	Z_5^1 (μm)	-0.001 ± 0.003	0.000 ± 0.003	0.000 ± 0.004	0.915
	Z_5^3 (μm)	-0.001 ± 0.002	-0.001 ± 0.003	0.000 ± 0.003	0.944
	Z_5^5 (μm)	0.000 ± 0.003	0.000 ± 0.004	0.000 ± 0.003	0.535

*p-value<0.05

Trefoil Z_3^{-3} increased significantly the negative values in myopes (Student t-test p=0.028, Table 8.51) while for emmetropes the change was not significant (Student t-test p=0.100, Table 8.50). Trefoil Z_3^3 decreased with the VCD elongation (Spearman r=-0.259, p=0.037, Figure 8.20). Horizontal coma Z_3^1 tended to increase in myopes although it was

non-significant (Student t-test p=0.223, Table 8.51). Meantime, trefoil Z_3^3 and horizontal coma Z_3^1 hardly change in emmetropes (Table 8.50). There were no significant differences between groups in the change of trefoil Z_3^{-3} and Z_3^3 (mixed ANOVA p= 0.771 and p=0.444, respectively) as well as for coma Z_3^{-1} and Z_3^1 (mixed ANOVA p=0.407 and p=0.388, respectively).

Table 8.51. Change of ocular HOA for the myopic group (3 mm).

Order	Coefficient	Baseline (n=40)	One year (n=40)	Change (n=40)	p-value
3rd	**Z_3^{-3} (µm)**	-0.017 ± 0.023	-0.025 ± 0.022	-0.007 ± 0.020	0.028*
	Z_3^{-1} (µm)	0.009 ± 0.026	0.012 ± 0.026	0.004 ± 0.024	0.359
	Z_3^1 (µm)	0.008 ± 0.021	0.013 ± 0.030	0.005 ± 0.024	0.223
	Z_3^3 (µm)	0.011 ± 0.017	0.007 ± 0.022	-0.004 ± 0.024	0.314
4th	**Z_4^{-4} (µm)**	0.001 ± 0.006	0.000 ± 0.007	-0.001 ± 0.008	0.413
	Z_4^{-2} (µm)	-0.001 ± 0.006	0.000 ± 0.007	0.000 ± 0.007	0.650
	Z_4^0 (µm)	0.008 ± 0.014	0.007 ± 0.015	-0.002 ± 0.012	0.423
	Z_4^2 (µm)	-0.003 ± 0.008	0.000 ± 0.010	0.003 ± 0.009	0.067
	Z_4^4 (µm)	0.000 ± 0.007	-0.002 ± 0.010	-0.001 ± 0.010	0.457
5th	**Z_5^{-5} (µm)**	0.000 ± 0.005	-0.001 ± 0.006	-0.001 ± 0.005	0.533
	Z_5^{-3} (µm)	0.001 ± 0.002	0.002 ± 0.005	0.000 ± 0.005	0.400
	Z_5^{-1} (µm)	0.000 ± 0.003	0.000 ± 0.003	0.000 ± 0.004	0.862
	Z_5^1 (µm)	0.000 ± 0.003	-0.001 ± 0.004	-0.001 ± 0.004	0.402
	Z_5^3 (µm)	-0.002 ± 0.003	0.000 ± 0.003	0.001 ± 0.004	0.056
	Z_5^5 (µm)	-0.002 ± 0.003	-0.001 ± 0.006	0.001 ± 0.006	0.271

*p-value<0.05

Even though the non-significance, oblique astigmatism Z_4^{-2} increased slightly in emmetropes (Table 8.50) while for myopes the WTR/ATR astigmatism Z_4^2 did (Table 8.51). The reduction of spherical aberration Z_4^0 within the myopic group resulted non-significant (Student t-test p=0.423). Thereby, the change was not different between emmetropes and myopes for oblique astigmatism Z_4^{-2} (mixed ANOVA p=0.516), WTR/ATR astigmatism Z_4^2 (mixed ANOVA p=0.126) and spherical aberration Z_4^0 (mixed ANOVA p=0.719). The influence of the refractive error was neither significant for the change of the rest of HOA coefficients (mixed ANOVA p<0.05).

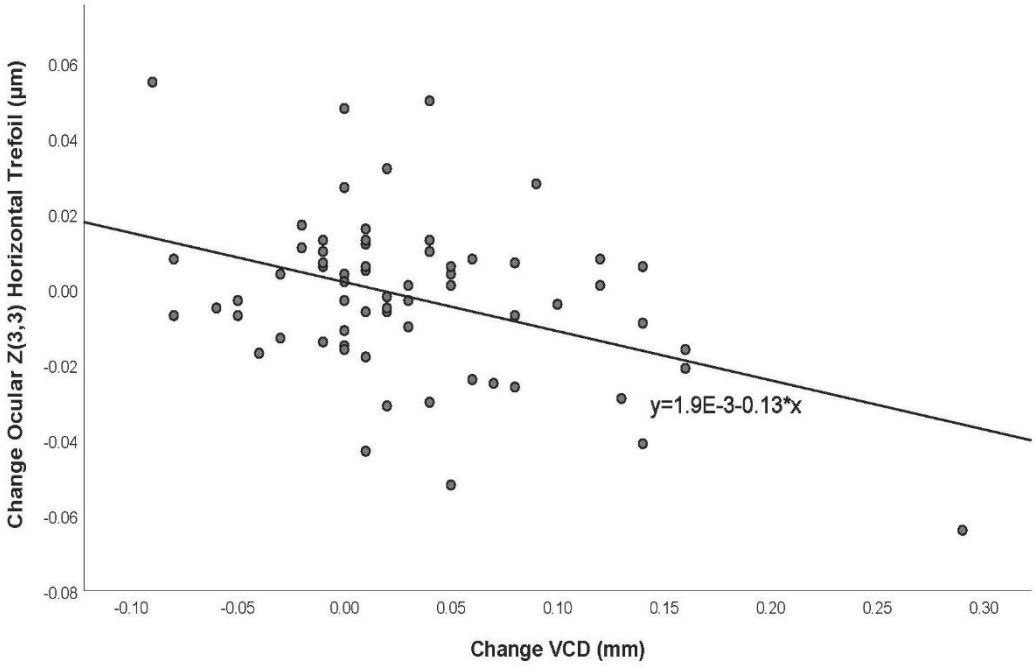

Figure 8.20. Linear relationship between the changes of internal trefoil Z(3,3) and VCD.

In general, LOA RMS increased after one year 0.047 ± 0.080 µm and consequently also the total RMS did 0.048 ± 0.078 µm (Wilcoxon p<0.001). LOA and total RMS increased significantly in both emmetropic group (Wilcoxon p=0.042 and p=0.026, respectively, Table 8.52) and myopic group (Wilcoxon test p<0.001, Table 8.53). LOA RMS increased with the negative shift of the sphere (Spearman r=-0.246, p=0.048) and the VCD enlargement (Spearman r=0.460, p<0.001). The change differences were not significant for LOA RMS change (mixed ANOVA p=0.496) nor total RMS change (mixed ANOVA p=0.425).

Low order astigmatism RMS manifested a slight reduction in emmetropes (Wilcoxon p=0.925, Table 8.52) whereas myopes experienced a non-significant raise (Wilcoxon p=0.129, Table 8.53). In this way, low order astigmatism RMS increased with the negative shift of the sphere (Spearman r=-0.367, p=0.003), whereby 10.5% of the SE change variance was explained by the change of low order astigmatism RMS. High order astigmatism RMS did result to vary significantly only in myopes (Wilcoxon p=0.029, Table 8.53). The change of astigmatism RMS did not differ between groups for low order (mixed ANOVA p=0.184) nor high order (mixed ANOVA p=0.394). Spherical aberration RMS exhibited low changes in both refractive groups not differing between them (mixed ANOVA p=0.145).

Table 8.52. Change of ocular RMS for the emmetropic group (3 mm).

RMS (μm)	Baseline (n=25)	One year (n=25)	Change (n=25)	p-value
LOA (2nd)	0.155 ± 0.082	0.193 ± 0.013	0.038 ± 0.086	0.042*
HOA (3rd to 7th)	0.050 ± 0.016	0.053 ± 0.015	0.003 ± 0.019	0.423
Total	0.166 ± 0.078	0.203 ± 0.121	0.038 ± 0.079	0.026*
3rd order	0.044 ± 0.015	0.047 ± 0.015	0.002 ± 0.018	0.511
4th order	0.020 ± 0.009	0.020 ± 0.010	0.000 ± 0.010	0.814
5th order	0.008 ± 0.005	0.008 ± 0.004	0.001 ± 0.006	0.037*
6th order	0.001 ± 0.001	0.001 ± 0.001	0.000 ± 0.002	0.896
7th order	0.000 ± 0.001	0.000 ± 0.001	0.000 ± 0.001	0.370
Low order astigmatism (2nd)	0.084 ± 0.054	0.082 ± 0.042	-0.002 ± 0.038	0.925
High order astigmatism (4th and 6th)	0.008 ± 0.005	0.009 ± 0.006	0.000 ± 0.008	0.778
Spherical aberration (4th and 6th)	0.016 ± 0.009	0.015 ± 0.011	-0.001 ± 0.009	0.294
Coma-like (3rd to 7th)	0.029 ± 0.017	0.030 ± 0.015	0.001 ± 0.017	0.619
Trefoil-like (3rd to 7th)	0.031 ± 0.013	0.033 ± 0.017	0.002 ± 0.015	0.638

*p-value<0.05

Table 8.53. Change of ocular RMS for the myopic group (3 mm).

RMS (μm)	Baseline (n=40)	One year (n=40)	Change (n=40)	p-value
LOA (2nd)	1.533 ± 0.958	1.585 ± 0.976	0.052 ± 0.077	<0.001*
HOA (3rd to 7th)	0.052 ± 0.017	0.059 ± 0.027	0.007 ± 0.025	0.097
Total	1.534 ± 0.957	1.588 ± 0.974	0.054 ± 0.077	<0.001*
3rd order	0.047 ± 0.017	0.053 ± 0.026	0.006 ± 0.025	0.139
4th order	0.019 ± 0.010	0.021 ± 0.011	0.002 ± 0.011	0.282
5th order	0.007 ± 0.004	0.010 ± 0.006	0.003 ± 0.006	0.002*
6th order	0.001 ± 0.002	0.002 ± 0.002	0.000 ± 0.002	0.056
7th order	0.000 ± 0.001	0.001 ± 0.001	0.000 ± 0.001	0.019*
Low order astigmatism (2nd)	0.182 ± 0.140	0.194 ± 0.138	0.012 ± 0.042	0.129
High order astigmatism (4th and 6th)	0.008 ± 0.006	0.010 ± 0.007	0.002 ± 0.008	0.029*
Spherical aberration (4th and 6th)	0.013 ± 0.011	0.014 ± 0.008	0.001 ± 0.009	0.424
Coma-like (3rd to 7th)	0.032 ± 0.016	0.036 ± 0.024	0.005 ± 0.023	0.226
Trefoil-like (3rd to 7th)	0.032 ± 0.015	0.037 ± 0.017	0.005 ± 0.019	0.237

*p-value<0.05

Fifth-order RMS changed in both emmetropic (Wilcoxon p=0.037) and myopic (Wilcoxon p=0.002) subjects and seventh-order RMS did only in the myopic group (Wilcoxon p=0.019). Some RMS showed a bit greater increase in myopes, such as for HOA, third-order, coma- and trefoil-like. However, there were no significant differences in the changes of these RMS because of the refractive error (mixed ANOVA p>0.05). The change of HOA RMS or other higher-order RMS did not correlate with any biometric or refractive parameter.

Multiple regression analysis demonstrated that 26.8% of the variance of the SE shift was explained by third-order coefficients (Table 8.54). Thus, negative SE shift was related to a negative change of trefoil Z_3^3 and Z_3^{-3} while a positive change of horizontal coma Z_3^1. Meanwhile, the model of the VCD change (Table 8.55) accounted for 27.2% of its variability including the defocus Z_2^0 alongside the trefoil Z_3^3. The VCD enlarged with the negative change of trefoil Z_3^3 and the positive increase of defocus Z_2^0.

Table 8.54. Multiple linear regression model for the SE change.

	R	R^2	R^2 adjusted	Error	Durbin-Watson
SE change (D)	0.518	0.268	0.232	0.151	1.588

	β	SE	Sβ	p-value	Tolerance	VIF
Constant	-0.068	0.020	-	0.002	-	-
Z_3^3 (µm)	3.388	0.890	0.422	<0.001	0.979	1.021
Z_3^1 (µm)	-2.099	0.826	-0.282	0.014	0.973	1.028
Z_3^{-3} (µm)	2.152	0.871	0.276	0.016	0.964	1.037

Table 8.55. Multiple linear regression model for VCD change.

	R	R^2	R^2 adjusted	Error	Durbin-Watson
VCD change (mm)	0.522	0.272	0.249	0.057	1.988

	β	SE	Sβ	p-value	Tolerance	VIF
Constant	0.017	0.008	-	0.035	-	-
Z_3^3 (µm)	-1.074	0.337	-0.350	0.002	0.977	1.023
Z_2^0 (µm)	0.244	0.079	0.338	0.003	0.977	1.023

8.5 Discussion

In this chapter, the aberrations' distribution for corneal, internal and ocular wavefront was evaluated among emmetropic and myopic university students. The combination of the topography and aberrometry in a single device allowed to obtain accurate measurements of the corneal and internal wavefront with the same reference point. Ignoring the corneal data decentration with respect to the pupil centre of the ocular aberrometry has been previously proved to produce significant changes in several Zernike coefficients (Atchison et al., 2016). Furthermore, the contribution of the different eye components (cornea and internal optics) to the total ocular wavefront was analysed. Finally, the change of the aberrometry data after the one-year period was assessed concerning the refractive error.

8.5.1 Aberrometry differences related to myopia

8.5.1.1 Corneal wavefront

The HOA from the anterior corneal surface have presented high variability among subjects in previous studies (Wang et al., 2003). Aligned with our results, the spherical aberration has been described to be positive for all corneas (Artal et al., 2002; Wang et al., 2003) without significant differences due to the refractive error (Artal, Benito and Tabernero, 2006; Tabernero et al., 2007).

In the study by Bao et al. (2009), corneal and ocular aberrations were assessed in emmetropic and myopic young adults (18 to 38 years). Corneal trefoil Z_3^{-3} and Z_5^3, horizontal coma Z_3^1 and Z_5^1, spherical aberration Z_4^0, and WTR/ATR astigmatism Z_4^2 were significantly different from zero in emmetropes. Whereas the myopes obtained more significant corneal coefficients: trefoil Z_3^{-3}, Z_5^{-3} and Z_5^3, coma Z_3^{-1}, Z_3^1, Z_5^{-1} and Z_5^1, spherical aberration Z_4^0, oblique astigmatism Z_4^{-2}, tetrafoil Z_4^{-4} and Z_4^4 and pentafoil Z_5^5. In comparison, our emmetropic and myopic group exhibited lower values for most of these corneal coefficients on account of the larger pupil size (6 mm) in this research (Bao et al., 2009).

The present work did not find differences in low order corneal astigmatism coefficients (Z_2^{-2} and Z_2^2). However, there was a significant tendency of the WTR/ATR astigmatism Z_2^2 to be more negative with more myopic sphere (around 7% variance).

Secondary oblique astigmatism Z_4^{-2} (3 and 5 mm) and Z_6^{-2} (5 mm) did differ between refractive groups. Accordingly, more negative oblique astigmatism Z_4^{-2} and more positive oblique astigmatism Z_6^{-2} were related to more myopic sphere (4.6% and 3.7% of variance, respectively) and longer VCD (13.2% and 6.2% of variance, respectively). On the other side, horizontal coma Z_3^1 revealed significantly more positive values in myopes (5 mm) and so 12.8% and 7.7% of its variance was explained by the sphere and VCD, respectively. Other coefficients from seventh-order (Z_7^{-3} and Z_7^5) and sixth-order (Z_6^4) differed between groups but these denoted low contribution.

The findings by Zhu, Collins and Yeo (2013) in young Singaporeans (18-24 years) are similar to ours (5 mm pupil). Despite being non-significant, WTR/ATR astigmatism Z_2^2 was slightly larger in myopes (SE < -1.50 D) compared to emmetropes (SE from+0.50 to -0.25 D). While our myopic group presented less negative horizontal coma Z_3^1 than emmetropes, their myopic subjects exhibited positive values and there were almost significant differences when divided into stable (SE progression ≥ -0.25 D within previous 12 months) and progressing (SE progression ≤ -0.50 D within previous 12 months) myopia. Thus, horizontal coma Z_3^1 took more positive values in progressing myopes than the stables.

In adolescents (16-19 years), Philip et al. (2012) obtained significant differences among refractive groups for WTR/ATR astigmatism Z_4^2 and tetrafoil Z_6^{-4} at a 5 mm pupil. Emmetropes had lower WTR/ATR astigmatism Z_4^2 than hyperopia and myopia but only the difference was significant compared to the hyperopes. Although it was not significant, horizontal coma Z_3^1 revealed less negative values and oblique astigmatism Z_4^{-2} tended to be a bit more negative with greater myopia as it occurred in our investigation. Besides, the tetrafoil Z_6^{-4} was greater in myopes than hyperopes though the authors considered it as negligible.

In the study by Leung, Lam and Kee (2015) in Chinese adults (50-70 years), myopes with compound ATR astigmatism had more corneal negative trefoil Z_3^{-3} and more positive vertical coma Z_3^{-1} considering a pupil size of 5 mm. In our case for young adults, the myopic group tended to have more positive vertical coma Z_3^{-1} but less negative trefoil Z_3^{-3} than emmetropes, non-significant in any case. Leung, Lam and Kee (2015) attributed the variation of the corneal trefoil Z_3^{-3} (21%) and vertical coma Z_3^{-1} (47%) to the corneal asymmetry along the vertical principal meridian. Some authors (Mohammadpour et al.,

2016; Yousif et al., 2020) found a positive relationship between corneal astigmatism and corneal HOA RMS. Further, larger corneal astigmatism associated with larger corneal coma- and trefoil-like RMS (Yousif et al., 2020). These findings suggest that the values of third-order coma and trefoil are dependent on the corneal astigmatism level.

In this study, myopic subjects manifested significantly greater low order astigmatism RMS in central cornea (3 mm) while it did not reach the significance for 5 mm. In both cases, primary astigmatism RMS was shown to increase with the myopic sphere (11-12% variance) and VCD elongation (7-7.2%). There were no significant differences for HOA RMS nor for any individual higher-order RMS, which agrees with former studies (Philip et al., 2012; Zhu, Collins and Yeo, 2013) except for the fourth-order. Fourth-order RMS resulted to be marginally higher in the myopic group (5 mm), increasing with the myopic sphere. Thereby, the sphere predicted 4.3% of the fourth-order RMS variability.

Recently, one research in young adults (Anbar et al., 2019) determined the differences in corneal HOA among different refractive groups. The spherical aberration RMS resulted larger in myopia compared to hyperopia while coma RMS was lower with high myopia. Compared to our emmetropic group, both spherical aberration and coma-like RMS had a non-significant tendency to be slightly greater with myopia. Like us, trefoil-like RMS was similar among refractive groups in the study by Anbar et al. (2019).

8.5.1.2 Internal wavefront

The defocus Z_2^0 was larger in myopes, increasing with more negative sphere (98% variance) and longer VCD (64-65% variance). The WTR/ATR astigmatism Z_2^2 showed higher values in the myopic group but only resulted to be significant with the smaller pupil size (3 mm). The myopic group had significantly more negative values of trefoil Z_3^{-3} (3 mm) and more positive values of trefoil Z_3^3 (5 mm). Only for 5 mm pupil, vertical coma Z_3^{-1} presented more positive values while horizontal coma Z_3^1 less positive values in myopes. Consistently, the sphere accounted for the variability of vertical coma Z_3^{-1} (5.4-7.7%), horizontal coma Z_3^1 (2.3-5.2%) and trefoil Z_3^3(3%). The VCD also explained the variance of vertical coma Z_3^{-1} (13.5%) and horizontal coma Z_3^1 (4.9%).

Moreover, both oblique astigmatism Z_4^{-2} and WTR/ATR Z_4^2 astigmatism differed between our refractive groups for 3 mm pupil. Whereas only oblique astigmatism Z_4^{-2} and

Z_6^{-2} resulted significantly different with 5 mm. The sphere accounted for 3.7% of oblique astigmatism Z_4^{-2} , 1.4 % of WTR/ATR astigmatism Z_4^2 and 5.8% of oblique astigmatism Z_6^{-2} . The VCD explained 6% of the WTR/ATR astigmatism Z_4^2 and 6.5% of oblique astigmatism Z_6^{-2}. Notwithstanding no significant differences between groups (5 mm), more negative spherical aberration Z_4^0 associated with more myopic sphere (3% variance). Furthermore, more positive tretrafoil Z_4^{-4} (3 mm) and coma Z_5^{-1} were detected in myopes (5 mm).

In a study with adolescents (16-19 years), several internal Zernike coefficients differed between hyperopes, emmetropes and myopes: vertical coma Z_3^{-1} and Z_5^{-1}, horizontal coma Z_3^1, trefoil Z_3^3, oblique astigmatism Z_4^{-2}, spherical aberration Z_4^0 and tretrafoil Z_6^{-4} (Philip et al., 2012). Contrary to our results, the differences in Z_3^{-1} and Z_3^1 were mainly between the emmetropic and hyperopic, with no differences with respect to the myopes. In comparison with the emmetropic group, the myopic group had greater positive values of trefoil Z_3^3 and oblique astigmatism Z_4^{-2} while more negative spherical aberration Z_4^0, which did agree with us. The differences in Z_5^{-1} and Z_6^{-4} were considered as negligible by the authors (Philip et al., 2012). Our coma Z_5^{-1} also differed between groups, however, we acquired negative values for both emmetropic and myopic group.

WTR/ATR astigmatism Z_2^2 was also more negative in myopes compared to emmetropes in a research with young Singaporeans (18-24 years) (Zhu, Collins and Yeo, 2013). Similar to us, the stable myopes in this study (Zhu, Collins and Yeo, 2013) obtained more positive horizontal coma Z_3^1 than emmetropes but it was not significant. Strikingly, internal horizontal coma Z_3^1 was significantly more negative in progressing myopes (SE progression ≤ -0.50 D within previous 12 months) than the stable ones (SE progression ≥ -0.25 D within previous 12 months). Besides, the spherical aberration Z_4^0 differed between emmetropes and progressing myopes, where the latter had more negative values. Our spherical aberration Z_4^0 tended to be more negative with more myopic sphere but did not result in significant differences between groups.

Higher LOA RMS was perceived in myopes, which was related to the sphere, cylinder and VCD. Meantime, HOA RMS was similar between refractive groups and only had a relationship with the cylinder power (1.9% variance). Likewise, the work by Zhu, Collins and Yeo (2013) reported differences in LOA RMS but similar HOA RMS. Our fourth-order RMS exhibited a significant tendency to increase with the myopic sphere (1.1% variance) and the difference between groups was almost significant for 5 mm pupil size.

Something similar occurred for the spherical aberration RMS that was slightly greater in myopes under 5 mm pupil size but it did not reach the significance. The study by Philip et al. (2012) did report significantly higher fourth-order RMS and spherical RMS in low and moderate myopes. Additionally, our trefoil-like RMS resulted to be greater in the myopic group with the larger pupil size (5 mm), increasing with the myopic sphere (1.3% variance).

8.5.1.3 Ocular wavefront

Generally, the ocular third-order aberrations presented greater magnitudes than the subsequent orders. Coma and spherical aberration have proved to be the most contributors to third- and fourth-order aberrations (Collins, Wildsoet and Atchison, 1995; He et al., 2002; Castejón-Mochón et al., 2002; Cheng et al., 2003). Plainis and Pallikaris (2008) informed the oblique trefoil Z_3^3 and spherical aberration Z_4^0 were the most prominent HOA coefficients in a sample of emmetropic subjects (-1.25 to 1.13 D) between 21-43 years. For a 5-mm pupil, WTR/ATR astigmatism Z_2^2, horizontal coma Z_3^1 and spherical aberration Z_4^0 were the most important ocular coefficients in the work by Atchison et al. (2016) in subjects between 20-55 years with different refractive errors. Similarly, our coefficients with larger values were second-order astigmatism, third-order coma and trefoil as well as the spherical aberration.

In the current investigation, ocular wavefront exhibited fewer significant differences between myopic and emmetropic compared to corneal or internal wavefront. The defocus Z_2^0 exhibited significantly higher values in the myopic group, increasing with more negative sphere (97-98%) and longer VCD (64-66%). Myopic sphere also associated with more negative WTR/ATR astigmatism Z_2^2 (7-7.4% variance) despite no significant differences among refractive groups. Conformed with other authors (Plainis and Pallikaris, 2008; Bao 2009), emmetropic subjects did not reveal to be free from ocular HOA. From HOA, only the primary vertical coma Z_3^{-1} resulted to differ between emmetropes and myopes (both 3 and 5 mm pupil). More positive values of Z_3^{-1} were seen with more myopic sphere (6.7% variance) and longer VCD (7.5% variance). Moreover, longer VCD was related to more negative spherical aberration Z_4^0 (3.7% variance) with larger pupil size (5 mm).

As expected, our LOA RMS was greater in the myopic group increasing with the negative sphere and longer VCD. The RMS of low order astigmatism took higher values in myopes compared to emmetropes (3 and 5 mm), having a relationship also with the sphere (15.8-21.6%) and VCD (8.6-14.5%). In young Singaporeans (18-24 years) (Zhu, Collins and Yeo, 2013), myopic eyes exhibited larger values of WTR/ATR astigmatism Z_2^2 compared to the emmetropic. In our case, the differences for WTR/ATR astigmatism Z_2^2 between groups did not reach the significance.

Coma and spherical aberration were the largest HOA saw in myopic eyes (-1.00 to -9.25 D) in the work by Paquin, Hamam and Simonet (2002) in young adults (18-26 years), where coma occurred more frequently increasing myopia. Like in the study by Karimian, Feizi and Doozande (2010), the primary trefoil Z_3^3, vertical coma Z_3^{-1} and spherical aberration Z_4^0 were the more predominant HOA coefficients. In our research, vertical coma Z_3^{-1} differed among refractive groups and horizontal coma Z_3^1 only resulted to be a significant predictor of the SE in multiple regression analysis. Horizontal coma Z_3^1 has also been previously associated with the refractive error (Karimian, Feizi and Doozande, 2010; Hartwig and Atchison, 2012) and AL (Cerviño et al., 2008).

Horizontal coma Z_3^1 presented differences even between stable (SE progression ≥ -0.25 D within previous 12 months) and progressing (SE progression ≤ -0.50 D within previous 12 months) myopes in a previous work in Singaporeans (Zhu, Collins and Yeo, 2013). On average, stable myopes had positive values while the progressing myopes had negative values for Z_3^1. On the other hand, third-order coma has not differed between pathologic myopes (SE< -8.00 D and AL≥26.5 mm) and emmetropes (-1.00 to +1.00 D) in Japanese adults (Kasahara et al., 2016). One investigation in Chinese young adults (Wei, Chan and Tan, 2006) reported the refractive astigmatism was correlated with the horizontal coma Z_3^1 and horizontal trefoil Z_3^3. Therefore, differences in refractive error classification and astigmatism inclusion between studies may explain the discrepancy of the results.

Myopic eyes manifested less positive spherical aberration Z_4^0 than emmetropes in the study by Zhu, Collins and Yeo (2013). In our study, the spherical aberration was lower in myopes but the difference did not result statistically significant. Spherical aberration Z_4^0 tended to be lower with the VCD elongation in our sample, conformed to preceding observations (Cerviño et al. 2008). Other authors (Karimian, Feizi and Doozande, 2010;

Hartwig and Atchison, 2012) have found a direct relationship between refractive error and spherical aberration. In adolescents (Philip et al., 2012), moderate myopes (-3.00 to -6.00 D) exhibited the least spherical aberration Z_4^0 compared to low myopes (-0.50 to -3.00 D) and emmetropes (-0.50 to +0.50 D). Besides, moderate myopic eyes revealed lower fourth-order and spherical RMS, which also agrees with our outcomes in young adults. In contrast, pathologic myopes manifested more positive ocular spherical aberration Z_4^0 than emmetropes in the research by Kasahara et al. (2016). Other fourth-order coefficients have been reported to differ in myopic eyes such as greater ocular tetrafoil Z_4^{-4} and more positive oblique astigmatism Z_4^{-2} (Yazar et al., 2014).

Our HOA RMS did not evidence differences between refractive groups nor did any individual higher-order RMS. Former studies did inform of larger ocular HOA RMS in myopic eyes (He et al., 2002; Paquin, Hamam and Simonet, 2002; Yazar et al., 2014). Whereas many others did not identify differences nor an association between HOA RMS and refractive error (Porter et al., 2001; Cheng et al., 2003; Netto et al., 2005; Zadok et al., 2005; Kwan, Yip and Yap, 2009; Karimian, Feizi and Doozande, 2010) which is aligned with our results. Highly astigmatism eyes (< -1.00 D) have formerly confirmed significantly higher levels of HOA compared to low astigmatic and non-astigmatic eyes regardless of the refractive error (Cheng et al., 2003).

He et al. (2002) obtained significant greater RMS in myopic adults (18-29 years) for every individual RMS from second to seventh-order (6 mm diameter). Similarly, coma- and trefoil-like RMS as well as third-, fourth and fifth-order RMS were greater in myopic eyes (SE ≤ -0.50 D) compared to emmetropic (SE -0.50 to +0.50) and hyperopic eyes (SE ≥ +0.50 D) in other work (Yazar et al., 2014) in young adults (18-22 years). On the contrary, young Chinese subjects (19-29 years) exhibited significantly lower fourth-order RMS and spherical RMS with more myopia in the study by Kwan, Yip and Yap (2009). Moreover, anisometropic subjects (≥2 D difference between eyes) were examined in this same research (Kwan, Yip and Yap, 2009). The more myopic eye of the anisometropes presented significantly lower HOA RMS, third-order RMS and spherical aberration RMS.

In accordance with Kwan, Yip and Yap (2009), our spherical aberration RMS was lower in myopes. However, it only was significant with the 3 mm pupil whereas in the study of Kwan, Yip and Yap (2009) the difference was still significant for 5 mm. Further,

some authors (Kwan, Yip and Yap, 2009; Karimian, Feizi and Doozande, 2010; Yazar et al., 2014) have acquired an association of lower spherical RMS when myopic SE increased. Aligned with former findings (Cheng et al., 2003; Zadok et al., 2005), we did not identify such a relationship. Instead, longer VCD correlated with lower spherical aberration RMS (5 mm) in our investigation. As seen above, these results contradict previous reports (He et al., 2002; Paquin, Hamam and Simonet, 2002; Yazar et al., 2014) of higher fourth-order or spherical RMS in myopes.

Multiple regression manifested that SE and VCD were explained by more high order coefficients with larger pupil size. Alongside the defocus Z_2^0, the spherical aberration Z_4^0, trefoil Z_3^{-3} and horizontal coma Z_3^1 were the most important higher-order predictors of the SE model (99.1% variance). Meanwhile, the VCD variability (68.4-74.4%) was explained mainly by the defocus Z_2^0, WTR/ATR astigmatism Z_4^2 and spherical aberration coefficients Z_4^0 and Z_6^0. HOA were not able to explain a significant variability of SE nor VCD by themselves. As shown in results, in spite of the significant association of some HOA with myopia, HOA only accounted for a small variability of SE or VCD.

Many researchers agree with the large variation subject to subject, particularly in HOA (Porter et al., 2001; Castejón-Mochón et al., 2002; Wang and Koch, 2003; Plainis and Pallikaris, 2008; Yazar 2014). Further, the direct comparison among studies is not easy because of the differences in methodology as well as the age, ethnicity and refractive error of the sample. For instance, some authors (McLellan, Marcos and Burns, 2001; Wang and Koch, 2003) have already demonstrated the aberrations increase with the age. Alike, Cerviño et al. (2008) reported differences in the relationship of aberrations with AL between Asian and Caucasian adults. And as exposed above, refractive astigmatism can influence the HOA levels (Cheng et al., 2003). Therefore, given the controversy among studies, there is little evidence that determines a systematic variation of the HOA in myopia up to now.

8.5.1.4 The balance between corneal and internal wavefront

Corneal and internal aberrations were predominantly larger than the ocular in the present study, pointing out that the internal optics compensated part of the corneal aberrations as demonstrated previously (Artal et al., 2001; Mrochen et al., 2003; Atchison et al., 2016). The cornea usually contributes to a greater extent the ocular wavefront

(Artal et al., 2001). However, He et al. (2003) have suggested the internal optics may play a more important role than the anterior cornea in the HOA. The crystalline lens is considered the main contributor to the internal aberrations although the posterior corneal surface and the ocular media are also included in the internal wavefront (Artal et al., 2001; Smith et al., 2001). This compensation mechanism between corneal and internal wavefront has shown to be disrupted in the older eye (Artal et al., 2002).

Our results revealed the ocular low order astigmatism RMS, fourth-order RMS, spherical RMS and HOA RMS were significantly reduced. Meanwhile, our ocular third-order RMS, fifth-order RMS, high order astigmatism RMS, coma-like RMS and trefoil-like RMS did not manifest a significant reduction. The observations of this study are aligned with former studies (Artal et al., 2001; Mrochen et al., 2003; Kelly, Mihashi and Howland 2004), which have informed the partial compensation of the WTR/ATR astigmatism Z_2^2 and the spherical aberration Z_4^0 by the internal optics. It is widely known that the anterior corneal surface provides most of total astigmatism (He et al., 2003; Leung, Lam and Kee, 2015). Spherical aberration is mainly negative for the crystalline lens, and thus, both anterior corneal and internal spherical aberration are partially balanced (Smith et al., 2001).

In young adults, Artal et al. (2001) perceived that internal optics compensated partially the vertical trefoil Z_3^{-3} as well as the WTR/ATR astigmatism Z_2^2 and spherical aberration Z_4^0. One study in myopic subjects (Mrochen et al., 2003) obtained significant correlation between corneal and ocular wavefront for WTR/ATR astigmatism Z_2^2 but also for oblique astigmatism Z_2^{-2}, and for both third-order coma coefficients (Z_3^{-1}, Z_3^1), whereas the spherical aberration Z_4^0 did not exhibit such an association. The work by Kelly, Mihashi and Howland (2004) reported the internal wavefront reduced 41% of WTR/ATR astigmatism Z_2^2, 51% of horizontal coma Z_3^1 and 36% of spherical aberration Z_4^0 considering a 6 mm pupil size. Further, half of the ocular HOA RMS reduction was produced by the compensation of the horizontal coma Z_3^1 and spherical aberration Z_4^0 between corneal and internal wavefront.

One study in young (18-24 years) Singaporeans (Zhu, Collins and Yeo, 2013) acquired differences in the compensation by the internal optics between emmetropic (+0.50 to -0.25 D) and myopic (SE < -1.50 D) subjects. The WTR/ATR astigmatism Z_2^2 compensation was lower in myopic eyes where most of corneal astigmatism remained in

the total ocular wavefront. Internal optics compensated part of the horizontal coma Z_3^1 in emmetropes, whereas it induced more horizontal coma Z_3^1 in myopes. Spherical aberration Z_4^0 was partially compensated in progressing myopes (SE progression ≤ -0.50 D within previous 12 months) while more ocular spherical aberration resulted in stable myopes (SE progression ≥ -0.25 D within previous 12 months) and emmetropes.

Broadly, the current research detected differences in the compensation by the internal optics between refractive groups aligned with Zhu, Collins and Yeo (2013). Emmetropes manifested better compensation for low order astigmatism while myopes for spherical aberration. Myopes compensated better the oblique astigmatism Z_2^{-2} coefficient whereas the emmetropic the WTR/ATR astigmatism Z_2^2, which was the higher component of corneal astigmatism. The high order astigmatism RMS presented lower compensation and was similar between groups. The compensation of astigmatism Z_4^{-2} and Z_4^2 was low and non-significant since the augmentation occurred more frequently in both emmetropic and myopic subjects. In contrast, astigmatism Z_6^{-2} and Z_6^2 showed in most of the cases undercompensation followed by overcompensation.

The only fourth-order coefficient experiencing significant compensation was the spherical aberration Z_4^0 and again in both refractive groups. More proportion of myopes (70.45%) revealed partial compensation of primary corneal spherical aberration Z_4^0 than emmetropes (59.26%). Something similar occurred for the secondary spherical aberration Z_6^0 even though the overcompensation was more commonly seen in both emmetropic and myopic subjects. Thereby, the myopic group ended up with greater compensation for the spherical aberration RMS. It also seems to be the main reason for the better compensation in the fourth-order RMS.

Contrary to Zhu, Collins and Yeo (2013), horizontal coma Z_3^1 exhibited similar compensation for the emmetropes and myopes, where the overcompensation was the predominant CF pattern. Our general compensation of third-order RMS and coma RMS was not effective in any refractive group. Nonetheless, there is still some controversy regarding the compensation of other aberrations beyond astigmatism and spherical aberration due to the high inter-subject variability. Two studies (Kelly, Mihashi and Howland, 2004; Lu et al., 2008) concluded that the compensation of the horizontal coma Z_3^1 by the internal optics had an individual dependency and was linked to the angle kappa (angle between the optical axial and the line of sight).

Some authors have found larger values in other third-order ocular aberrations such as vertical trefoil Z_3^{-3} (He et al., 2003; Kelly, Mihashi and Howland, 2004) and vertical coma Z_3^{-1} (Kelly, Mihashi and Howland, 2004). Similarly, our ocular coma-like RMS was a bit greater than the corneal, though it was not significant. We identified some differences between groups for the individual third-order coma and trefoil coefficients. Both trefoil Z_3^{-3} and Z_3^3 were compensated in more proportion for emmetropes, particularly significant for Z_3^{-3} (59.26%). The trefoil Z_3^{-3} was augmented by the internal optics in most of the myopes (59.09%). In contrast, more proportion of myopes (47.73%) had partial compensation than emmetropes (33.33%) for vertical coma Z_3^{-1} and the latter showed more augmentation (48.15%). And, as mentioned above, the horizontal coma Z_3^1 was mostly overcompensated in both groups.

Secondary trefoil (Z_5^{-3} and Z_5^3) was overcompensated in emmetropes. Meanwhile, the myopic group had a diverse distribution of CF patterns for both Z_5^{-3} and Z_5^3, predominating slightly the undercompensation and overcompensation, respectively. The augmentation was very usual among myopes for secondary coma (Z_5^{-1} and Z_5^1), whereas the emmetropes evidenced undercompensation or overcompensation. As it can be perceived, trefoil and coma have exhibited high individual variability in the compensation patterns, especially the secondary coefficients. These coefficients took either positive and negative values in the corneal and internal wavefront, and there was no fixed pattern.

The posterior corneal surface has demonstrated to contribute to total corneal astigmatism (Dubbelman, Sicam and Van der Heijde, 2006) and spherical aberration (Sicam, Dubbelman and van der Heijde, 2006). The anterior astigmatism compensation by the posterior cornea was reported between 12.9% to 31% among studies (Dubbelman, Sicam and Van der Heijde, 2006; Ho, Tsai and Liou, 2009; Koch et al., 2012; Nemeth et al., 2014). Spherical aberration of posterior corneal also reduces the total corneal spherical aberration at a young age because its negative sign but becomes positive at an older age (Sicam, Dubbelman and van der Heijde, 2006; Navarro, Rozema and Tassignon, 2013).

Furthermore, the posterior corneal surface has shown to compensate for a small part of the third-order coma aberration (Z_3^{-1}, Z_3^1) also with an age dependence (Dubbelman, Sicam and van der Heijde, 2007). This compensation was 6% of the coma at the age of 20, decreasing with the age and disappearing completely at the age of 60 in the study by Dubbelman, Sicam and van der Heijde (2007). The compensation by the

posterior cornea was 39% for WTR/ATR astigmatism Z_2^2, 28% for horizontal coma Z_3^1 and 43% for spherical aberration Z_4^0 in the work by Atchison et al. (2016). Generally, posterior cornea revealed to compensate the 17% of the total RMS and 10% of the corneal HOA RMS (Atchison et al., 2016). Thereby, the posterior has some compensatory role even though with a lower contribution to the total wavefront than the crystalline lens (Artal et al., 2001; He et al., 2003).

8.5.2 Aberrometry changes alongside myopia progression

The longitudinal assessment of the aberrometry in university students indicated that, generally, there were differences in some coefficients between emmetropic and myopic subjects. However, the differences obtained after a year were not big enough to become statistically significant. The ocular defocus Z_2^0 experienced a general increment after one-year of follow-up because of internal optics. This increase was a little higher in myopes but it did not differ significantly between refractive groups. Indeed, the defocus Z_2^0 increment was mainly related to the VCD elongation over time. LOA RMS also showed to increase with the negative shift of the sphere and the VCD enlargement.

Similarly, low order ocular astigmatism RMS increased with the myopic sphere. Corneal WTR/ATR astigmatism Z_2^2 tended to change to less negative values while the internal WTR/ATR astigmatism Z_2^2 reduced the positive values after one year. The variations in corneal and internal WTR/ATR astigmatism Z_2^2 were quite balanced in emmetropes. In contrast, the myopic group exhibited greater reduction in internal optics that lead to a negative increase in ocular WTR/ATR astigmatism Z_2^2. Thereby, the reduction of internal WTR/ATR astigmatism Z_2^2 was associated with the negative shift of the refractive sphere. On the other hand, oblique astigmatism Z_2^{-2} exhibited opposite changes between emmetropes and myopes for both corneal and internal wavefront. The change of internal oblique astigmatism Z_2^{-2} resulted to differ significantly between refractive groups, where myopic subjects had an increment toward positive values. As a result of these opposed changes, ocular oblique astigmatism Z_2^{-2} ended up in a reduction in emmetropes while in a positive increase for myopes.

In myopes, third-order RMS increased in the corneal and ocular wavefront. Ocular trefoil Z_3^{-3} and vertical coma Z_3^{-1} varied similarly in both emmetropic and myopic group although the changes of these coefficients had some slight difference between groups in

the corneal and internal wavefront. The corneal and internal changes of horizontal coma Z_3^1 and trefoil Z_3^3 were quite compensated on average for emmetropes. Meantime, ocular horizontal coma Z_3^1 increase its positive values in the myopic group. Both negative increase of corneal horizontal coma Z_3^1 and the positive increase of internal horizontal coma Z_3^1 were related to longer VCD. Then, ocular trefoil Z_3^3 reduced the positive values in myopes and this manifested a relationship with the VCD elongation. Multiple linear regression also pointed out the negative SE shift was related to a negative change of trefoil Z_3^3 and Z_3^{-3} while a positive change of horizontal coma Z_3^1.

Spherical aberration Z_4^0 did not exhibit significant changes in emmetropes because it remained quite stable in both corneal and internal wavefront. Myopic subjects did manifest a reduction, though small, in ocular spherical aberration Z_4^0. This occurred as a result of the corneal spherical aberration Z_4^0 positive increment was balanced with a greater reduction of the internal one. Moreover, ocular high order astigmatism RMS did result to vary significantly in myopes. The change of oblique astigmatism Z_4^{-2} proved to differ significantly between emmetropic and myopic subjects due to the opposite changes in both corneal and internal wavefront. Then, there was a positive increase of oblique astigmatism Z_4^{-2} in emmetropes while almost no change in myopes. Conversely, ocular WTR/ATR astigmatism Z_4^2 increased positively in the myopic group due to the higher increase in internal optics.

Up to now, the few longitudinal studies about aberrations and myopia progression have been mostly performed in children (Hiraoka et al., 2017; Lau et al. 2018) or adolescents (Philip et al., 2014). As far as we know, only one study (Vasudevan et al., 2015) have assessed the change of aberrations in young adults related to myopia and with which we can compare our results. The study by Vasudevan et al. (2015) was a 9-months follow-up that evaluated the aberrations change in myopic (SE ≤ -0.50 D) and non-myopic (-0.37 to +1.00 D) young adults (mean age 24.3±3.2 years). There were no significant changes of HOA RMS, coma RMS and spherical aberration RMS within myopes nor non-myopes. Contrary to us, both refractive groups even obtained similar spherical aberration on average in the initial and final visit. In our case, the changes of ocular HOA ad coma-like RMS did not differ significantly between groups but were a bit greater in myopes.

The 5-year follow-up in emmetropic (-0.50 D to +0.50 D) adolescents (16-19 years) performed by Philip et al. (2014) reported that those with a myopic change of the SE ≤ -0.50 D experienced a significant change in trefoil Z_3^3, spherical aberration Z_4^0, third-order RMS, coma RMS, fourth-order RMS and spherical RMS. Trefoil Z_3^3 and spherical aberration Z_4^0 became less positive in those with a myopic shift. Then, third-order and coma RMS increased while fourth-order and spherical RMS decreased. These results from the study by Philip et al. (2014) are quite similar to our results obtained in myopic university students, even though our changes were lower in magnitude and not always statistically significant.

Contrary to the lower spherical aberration seen in myopes, Cheng et al. (2003) predicted theoretically that the eye elongation would increase the spherical aberration positively. The spherical aberration changes can be produced by the asphericity or/and curvature changes of the corneal and crystalline lens. Myopic eyes have shown more negative internal spherical aberration in this study and previous ones (Philip et al., 2012; Zhu, Collins and Yeo, 2013). The thinning of the crystalline lens in myopia has been suggested as a possible reason for this negative increase of the internal spherical aberration (Philip et al., 2014). However, we have not observed an association between the changes of LT with the ones of the spherical aberration. Besides, coma coefficients may also occur because of the shape change of corneal and crystalline lens or ocular components tilt (Artal, Benito and Tabernero, 2006; Berrio, Tabernero and Artal, 2010).

In Japanese schoolchildren (6-12 years), one 2-year longitudinal study (Hiraoka et al., 2017) obtained that both myopia progression and axial elongation correlated more strongly with corneal aberrations than the ocular ones. Myopia progression and axial elongation associated with a negative change of vertical coma Z_3^{-1} and spherical aberration Z_4^0 while a positive change in horizontal coma Z_3^1 for both corneal and ocular wavefront. We also observed in university students the positive increase of horizontal coma Z_3^1 and reduction of spherical aberration Z_4^0 but not the negative change of vertical coma Z_3^{-1}. Interestingly, another 2-year follow-up study in Hong Kong children (6-12 years) by Lau et al. (2018) found that more positive Z_3^{-3}, more positive spherical aberration Z_4^0 and less positive trefoil Z_3^3 were related to slower axial elongation. Contrary, our myopic young subjects less positive trefoil Z_3^3 with the VCD increment.

8.6 Conclusion

8.6.1 Aberrometry differences related to myopia

Low order astigmatism manifested significant differences associated with the refractive error. More negative corneal and ocular WTR/ATR astigmatism Z_2^2 was associated with more myopic sphere. Internal WTR/ATR astigmatism Z_2^2 was significantly greater in myopes with 3 mm pupil size. Generally, low order astigmatism RMS tended to be higher in myopic eyes particularly significant for the ocular wavefront (3 and 5 mm). Compensation between corneal and internal low order astigmatism RMS ended up being more effective in emmetropes because the better compensation of WTR/ATR astigmatism Z_2^2, which is the most contributor to corneal astigmatism. Oblique astigmatism Z_2^{-2} was more compensated in myopic eyes because they tended to have slightly more oblique component in corneal wavefront.

Some high order astigmatism coefficients also manifested differences even though high order ocular astigmatism RMS resulted similar among groups. Secondary oblique astigmatism Z_4^{-2} and Z_6^{-2} differed for both corneal and internal wavefront. Internal secondary WTR/ATR astigmatism Z_4^2 also tended to be greater in myopes with smaller pupil size (3 mm). Considering the total high order astigmatism RMS, compensation between corneal and internal wavefront was quite similar between emmetropia and myopia. On the other side, more negative spherical aberration Z_4^0 was significantly related to more myopic sphere or longer VCD for internal and ocular wavefront (5 mm) despite the non-significant differences between groups. The more negative internal spherical aberration Z_4^0 led to more proportion of partial compensation in myopic eyes for this coefficient. Thereby, ocular spherical aberration RMS revealed lower values in myopic eyes.

Other HOA differences were found for coma and trefoil aberrations, especially with larger pupil size (5 mm). Third-order coma coefficients (Z_3^{-1}, Z_3^1) were related to both sphere and VCD. Vertical coma Z_3^{-1} was significantly more positive in myopes for internal wavefront (3 and 5 mm) and there was also this tendency in corneal wavefront. Meanwhile, emmetropic subjects tended to exhibit negative values of both corneal and internal vertical coma Z_3^{-1}, showing mostly an augmentation of this coefficient rather than compensation. Although myopic eyes had a larger proportion of undercompensation,

ocular vertical coma Z_3^{-1} still remained more positive in myopic eyes. Horizontal coma Z_3^1 revealed significantly less negative values for corneal wavefront while less positive values for internal wavefront (5 mm) in myopic subjects compared to emmetropes. Compensation between corneal and internal wavefront was similar among groups and ocular horizontal coma Z_3^1 did not differ. Secondary coma coefficients (Z_5^{-1}, Z_5^1) tended to be augmented by the internal optics in myopia, however, the wavefront differences (cornea, internal optics, ocular) between groups were not significant. Thus, coma-like RMS did not result to differ significantly, though myopes had slightly greater average values.

The multiple regression analysis manifested that the SE and VCD were predicted including all Zernike coefficients but no significant model resulted including only HOA. The most important predictors for the SE were defocus Z_2^0, trefoil Z_3^{-3}, spherical aberration Z_4^0 and horizontal coma Z_3^1. Meantime, the defocus Z_2^0 as well as the spherical aberration Z_4^0 and Z_6^0 were the most important for the VCD model.

8.6.2 Aberrometry changes alongside myopia progression

There were a general increment of ocular defocus Z_2^0 being a bit greater in myopic eyes. Thus, defocus Z_2^0 increase was related to the VCD elongation over time. While ocular WTR/ATR astigmatism Z_2^2 was stable in the emmetropic group, it increased negatively in myopes because of the internal optics. Indeed, internal WTR/ATR astigmatism Z_2^2 was associated with the negative change of the refractive sphere. Oblique astigmatism Z_2^{-2} manifested opposed changes between groups, however, it was not associated with any refractive or biometric change.

Regarding the HOA, the longitudinal data demonstrated that third-order trefoil, third-order coma and primary spherical aberration were the main coefficients that have some differences between the emmetropic and myopic group. However, the changes observed after one year were not different enough to obtain statistically differences between refractive groups in most of the cases.

Despite some differences in corneal and internal wavefront, ocular trefoil Z_3^{-3} and vertical coma Z_3^{-1} changed similarly in both refractive groups. Meantime, the myopic group tended to increase positively horizontal coma Z_3^1 and reduce the positive values of trefoil Z_3^3. The changes of some third-order coefficients also showed an association with the

myopic shift or/and the VCD enlargement. Besides, myopic eyes underwent a slight reduction of ocular spherical aberration Z_4^0 as a result of the greater negative increase of the internal one. Nonetheless, the changes in spherical aberration were not associated with the refractive nor biometric changes.

Broadly, the aberration changes experienced in our young sample were not strongly associated with the myopic shift or VCD elongation. Therefore, these changes may not be the trigger of myopic progression but rather a consequence of it.

CHAPTER 9. STUDY LIMITATIONS

In this study, cycloplegia was not used to obtain the refractive status. The non-use of cycloplegia might lead to an overestimation of myopia. But, on one hand, we believe the cut-off of -0.75 D applied in both meridians ensured to classify the myopic subjects correctly. On the other hand, the negative shift obtained in a part of our sample could be due to accommodative fluctuations between visits, particularly in the cases with small negative changes. However, this fact would not change the results of myopic subjects since most of them underwent shifts between -0.25 and -1.00 D, a thing that is unlikely to be only due to an accommodative effect.

Other limitations can be considered for the sample and follow-up. The sample size did not allow to achieve a power of 0.8 in some cases, such as for Chi-square test, or the power reached 0.8 with a large effect size. There was a different proportion between females and males as well as between emmetropic and myopic students. The more number of females in the sample could have led to a significant effect of sex in some multiple regression models. Moreover, a greater number of emmetropic participants would have been desirable in order to balance the refractive groups. The follow-up was only performed after a year and some part of the sample dropped-out. Therefore, our results should be confirmed by results obtained with a larger sample size, balanced between sexes and refractive groups, and with a longer follow-up.

Bonferroni correction for multiple testing was not applied in our analysis. This correction is recommended to reduce the type I error (Armstrong, 2014), that is to say, finding a significant difference when it is not significant. However, the reduction of type I error leads to an increase of type II error, so as significant differences may not be found (Armstrong, 2014). Therefore, even though this correction was not used, the differences detected were further judged by its clinical significance and were aligned with previous results in most of the cases.

Additionally, some measurements obtained during the data collection have not been analysed since the pandemic situation altered the established planning. In this way, ciliary muscle and posterior segment measurements were explained in the protocol section but not included among the results.

CHAPTER 10. GENERAL CONCLUSIONS

The main goal of the present thesis was to characterise the myopic eye by means of quantitative ocular descriptors and to analyse the change of them over time alongside myopia progression in a sample of young university students. The quantitative descriptors were obtained from ocular biometry, corneal topography and wavefront aberrometry in emmetropic and myopic students. From them, the quantitative descriptors that best represent the ocular features of myopic eyes and their progression were determined.

The main conclusions regarding the quantitative descriptors of myopic eyes are:

- Myopic students manifested significantly deeper ACD, longer VCD and tended to have slightly thinner LT. Further, deeper ACD and thinner LT associated with longer VCD, however, this linear relationship was not maintained when the VCD elongation exceeded 20 mm.

- Greater corneal curvature was found in the myopic group particularly for the steep meridian in central and paracentral cornea. Likewise, higher corneal astigmatism was also seen in myopic eyes overall in the central cornea. Consequently, the anterior and posterior BFS were also steeper for myopes. Both corneal curvature and elevation had a dichotomous relationship with the VCD whereby the eye elongation led the cornea to flatten until the VCD reached 19-19.5 mm, point from which the cornea could no longer compensate the eye enlargement and it even steepened. In this way, greater AL/CR was seen in myopes than in emmetropes, where myopes were mostly above 3.00 in this ratio.

- In myopic eyes, WTR/ATR astigmatism Z_2^2 was more negative in corneal and ocular wavefront whereas more positive for internal optics. Thereby, compensation between corneal and internal optics of WTR/ATR astigmatism Z_2^2 was better in emmetropic eyes. Secondary oblique astigmatism also manifested some differences between the emmetropic and myopic group. More negative spherical aberration Z_4^0 was significantly related to more myopic sphere or VCD for internal and ocular wavefront, despite the non-significant differences between groups. It also led to more proportion of partial compensation in myopic eyes for spherical aberration Z_4^0, resulting in lower ocular spherical aberration RMS. Third-order coma coefficients

were also related to the refractive error. Ocular vertical coma Z_3^{-1} was more positive in myopic eyes and was related to more myopic sphere and longer VCD. Horizontal coma Z_3^1 had differences in corneal and internal wavefront but ended up being similar in the ocular wavefront.

- Multiple linear regression proved that SE was better predicted when the corneal curvature was included with the ocular biometry. Thereby, 91.5% of the SE variability was explained by the VCD, CR and LT. Moreover, multiple regression analysis manifested that the SE and VCD were predicted including all Zernike coefficients but no significant model resulted including only HOA. The most important predictors for the SE were defocus Z_2^0, trefoil Z_3^{-3}, spherical aberration Z_4^0 and horizontal coma Z_3^1. Meantime, the defocus Z_2^0 as well as the spherical aberration Z_4^0 and Z_6^0 where the most important for the VCD model.

The main conclusions regarding the changes in the quantitative descriptors alongside myopia progression are:

- The refractive error experienced a negative shift that was greater in magnitude for myopic eyes. Despite this, refractive changes of this sample of young university students were mostly quite stable within a year since around 64% of them did not have any change. Therefore, myopic shifts did occur in some part of the initial myopic students, though small, demonstrating that myopia may keep progressing during this academic stage.

- The VCD, ACD and LT changed significantly but only the VCD change was related to the refractive changes. In fact, myopic students showed higher VCD elongation agreeing with their greater negative shift of the SE compared to the emmetropes.

- The curvature of the flat meridian as well as the anterior BFS experienced a decrease that was greater in emmetropes and not related to the SE change. These corneal changes may indicate that axial elongation still may be compensated by corneal flattening in young adults, particularly among emmetropic eyes. The change of the AL/CR ratio differed among refractive groups where the myopic group experienced

an increase whereas the emmetropic a reduction, though it was small in both cases and not related to the SE changes.

- There was an increment of ocular defocus Z_2^0, which was greater in the myopic group and related to the VCD elongation over time. WTR/ATR astigmatism Z_2^2 increased negatively in myopes because the internal optics whereas it remained stable in emmetropes. Besides, the myopic group tended to increase positively the ocular horizontal coma Z_3^1 and reduce the positive values of ocular trefoil Z_3^3. Ocular spherical aberration Z_4^0 underwent a slight reduction in the myopic group but this was not related with the refractive nor biometric changes.

- The VCD increment was the main responsible for the SE changes in both myopia and emmetropia. Further, the VCD change was the most significant contributor to the AL change followed by the LT and ACD changes. The corneal curvature changes did not result to predict the SE longitudinal changes. Thus, the AL/CR ratio was not considered useful to monitor or quantify myopia progression in young adults. Furthermore, only a small part of the variance of the SE and VCD changes were explained by HOA. The negative SE shift was related to the change of trefoil Z_3^3 and Z_3^{-3} and horizontal coma Z_3^1. The VCD enlarged with the change of trefoil Z_3^3 and defocus Z_2^0.

FUTURE WORK

As mentioned in the limitations, ciliary muscle and posterior segment measurements were not included in this document. The measurements are being assessed and will be used for further publications. For instance, it is intended to develop a custom-software to process the ciliary muscle scans to obtain metrics such as its thickness, length or area. Moreover, new future research lines have emerged as from the results already obtained, such as:

- Analysis of the corneal, internal and ocular astigmatism considering also the orientation and the association with myopia and its progression.

- The study of how the aberrometry differences related to myopia may influence the vision quality through the analyse of metrics such as the modulation transfer function and the Visual Strehl ratio.

- Impact assessment of the use of contact lens designed for myopia progression on the quantitative eye descriptors after a short and long term.

APPENDIX A. IOLMaster 700

Repeatability assessment of the biometric measurements with different refractive states and age using a swept-source biometer.

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Methodology

Sixty-one phakic volunteers, aged between 20 and 58 years old, were enrolled in this prospective observational study. The study protocol was approved by the Ethics Committee of the University of Valencia and was performed according to the tenets of the Declaration of Helsinki. Written informed consent was obtained from each subject after receiving an explanation of the study purpose. Subjects with ocular pathologies, cataract diagnosis, systemic diseases with ocular effects, previous ocular surgery, binocular vision problems or poor fixation were excluded. Previously to biometry examination, automatic refraction with the L67 Auto Kerato Refractometer (Luneau, France) was obtained for all subjects to assess their refractive status.

Measurements were acquired only in the right eye by one formed examiner using an SS-OCT optical biometer (IOLMaster 700). The following parameters were evaluated: CCT defined as the distance between corneal epithelium and endothelium, AQD defined as the distance between endothelium and anterior crystalline lens surface, LT defined as the distance between anterior and posterior surfaces of the crystalline lens in its centre, AL defined as the distance between corneal epithelium and fovea, WTW defined as the horizontal width of the visible iris, K readings for identifying the flat and the steep meridians (K1, K2), and corneal astigmatism. The latest measurement was converted to Jackson's cross-cylinder power vector components (J_0 and J_{45}), described by Thibos, Wheeler and Horner (1997).

Finally, the sample was classified by refractive error and age. The refractive groups were classified by means of the SE in three groups: myopic eyes (SE ≤ -0.50 D), emmetropic eyes (SE between -0.50 D and +0.50 D), and hyperopic eyes (SE ≥ +0.50 D). The age classification divided the sample in two groups: presbyopic and non-presbyopic

eyes. Subjects' eyes were included in the presbyopic group whether the age was higher or equal to 40 years, and in the non-presbyopic group when the age was lower than 40 years.

Acquisition process

Five consecutive measurements were taken for each subject in the same session using the IOLMaster 700 biometer. Subjects were instructed to place correctly the chin and forehead, and to focus their vision in the fixation light during the examination. They were asked to perform a complete blink prior to each scan in order to achieve an appropriate tear film, and to keep their eyes wide open during the measurement acquisition. In the short time between measurements, patients were asked to remove their heads from the chinrest and then, the quality of scans and proper patient's fixation along the visual axis was checked. The latter was done through the SD warnings and the fovea scan, respectively, in accordance with the manufacturer's recommendations. Calibration of the device was performed previously to each measurement session following the manufacturer's advice.

Statistical analysis

Statistical analysis was performed using SPSS v22.0 for Windows (IBM Corp, Armonk, New York, USA). Obtained results are shown as the mean ± SD. Normality distribution was checked by means of the Shapiro-Wilk test. Differences of age distribution among refractive groups were checked with Kruskal-Wallis test while differences of refractive distribution among age groups were assessed with Student's t-test. Statistically significant differences between the 5 measurements taken were evaluated with the ANOVA test for repeated measurements (r-ANOVA). Mauchly's sphericity test was used to evaluate if the variances of the differences between groups could be assumed as equal. In the case of nonsphericity, the Greenhouse-Geisser correction was used, which changes the freedom of the distribution of the F statistic. Besides, post hoc analysis was performed with the Bonferroni test in order to evaluate the differences between all pair group combinations. A p-value less than 0.05 was defined as statistically significant.

In order to assess the absolute repeatability of measurements, the S_w and CoR were calculated. The S_w was calculated as the square root of the mean within-subject variance (McAlinden, Khadka and Pesudovs, 2015). The CoR was expressed from SD of the

differences between measurements, which is calculated as $\sqrt{2} \times S_w$, in accordance with the definition of the British Standard Institution (Bland and Altman, 1986). If the differences between measurements are assumed as a normally distributed, the 95% CI of differences is obtained multiplying by 1.96. Thereby, the CoR was calculated as $1.96 \times \sqrt{2} \times S_w$, which can be approximated as $2.77 \times S_w$. Relative repeatability was assessed by the ICC that was evaluated as the absolute agreement through the two-way mixed effect model that considers the examiner effect as fixed and the subjects effects as random.

Results

This study included 61 right eyes of 61 subjects aged between 20 and 58 years. The myopic group had 27 eyes (11 females and 16 males) with a mean SE of -2.31 ± 1.68 D (ranging from -0.63 to -6.50 D) and a mean age of 32.70 ± 12.45 years (from 20 to 58 years). The emmetropic group had 15 eyes (9 females and 6 males) with a mean SE of 0.05 ± 0.26 D (ranging from -0.38 D to 0.38 D) and a mean age of 30.07 ± 12.09 years (from 20 to 55 years). And finally, the 19 hyperopic eyes (10 females and 9 males) had a mean SE of 1.76 ± 1.04 D (ranging from 0.63 to 4.38 D) and a mean age of 35.68 ± 12.51 years (from 20 to 54 years). The age distribution was not significantly different among these refractive groups (p=0.322). The non-presbyopic group had 41 eyes (20 females and 21 males), the mean age was 25.27 ± 5.43 years (ranging from 20 to 39 years) and the mean SE was -0.65 ± 2.29 D (from -6.50 to 4.38 D). The presbyopic group had 20 eyes (9 females and 11 males), a mean age of 48.80 ± 5.33 years (ranging from 40 to 58 years), and the mean SE was -0.08 ± 1.92 D (from -4.38 D to + 3.00 D). There were not significant differences in the refractive distribution among the age groups (p=0.339).

For the groups defined following the refractive criteria, there were no statistical differences between the 5 repeated measurements for any biometric parameter (p>0.05). Repeatability coefficients and mean values for each parameter are shown in Table 1. AL showed a S_w of 0.007 mm and a CoR around 0.019 mm among refractive groups. For AQD and LT the emmetropic group obtained the lowest S_w and CoR. For the WTW distance the emmetropic group showed the highest S_w and CoR values which could be because this is the refractive group with less subjects and thus, the statistical uncertainty might be affected. For K readings the S_w and CoR values for the emmetropic and hyperopic group were higher than the myopic. K1 for emmetropic and hyperopic group showed a CoR less

than 0.06 mm that means the 95% of the differences between measurements would be less than 0.3 D. While for K2 the hyperopic group showed the highest CoR (0.080 mm), which involves the differences between measurements in 95% of cases would be around 0.4 D at most. The emmetropic group had higher S_w and CoR for both J_0 and J_{45} because patients had lower astigmatism magnitudes, which is resulting in lower magnitudes for J_0 and J_{45}. Hyperopic group had the highest J_{45} component that seems to affect its repeatability, since it means this group had more magnitude of oblique astigmatism.

Table 1. Repeatability assessment of biometric parameters classified by refractive error.

Parameter	Group	Mean ± SD	S_w	CoR	ICC
AL (mm)	**Myopic**	24.47 ± 1.02	0.007	0.019	1.000
	Emmetropic	23.62 ± 0.81	0.007	0.019	1.000
	Hyperopic	22.54 ± 1.09	0.007	0.018	1.000
AQD (mm)	**Myopic**	3.07 ± 0.32	0.026	0.073	0.999
	Emmetropic	2.98 ± 0.29	0.016	0.044	0.999
	Hyperopic	2.69 ± 0.33	0.022	0.061	0.999
LT (mm)	**Myopic**	3.76 ± 0.32	0.026	0.071	0.998
	Emmetropic	3.84 ± 0.35	0.023	0.064	0.999
	Hyperopic	3.92 ± 0.33	0.029	0.079	0.999
CCT (µm)	**Myopic**	548.21 ± 30.82	2.156	5.972	0.999
	Emmetropic	546.88 ± 27.71	2.657	7.360	0.998
	Hyperopic	551.07 ± 27.29	2.723	7.543	0.998
WTW (mm)	**Myopic**	12.10 ± 0.32	0.071	0.197	0.990
	Emmetropic	12.23 ± 0.41	0.086	0.238	0.991
	Hyperopic	11.97 ± 0.47	0.066	0.184	0.996
K1 (mm)	**Myopic**	7.74 ± 0.27	0.014	0.038	0.999
	Emmetropic	7.85 ± 0.31	0.020	0.057	0.999
	Hyperopic	7.77 ± 0.34	0.020	0.055	0.999
K2 (mm)	**Myopic**	7.60 ± 0.26	0.016	0.046	0.999
	Emmetropic	7.74 ± 0.31	0.018	0.050	0.999
	Hyperopic	7.54 ± 0.31	0.029	0.080	0.998
J_0 (D)	**Myopic**	0.42 ± 0.50	0.066	0.183	0.996
	Emmetropic	0.15 ± 0.27	0.084	0.234	0.981
	Hyperopic	0.56 ± 0.45	0.065	0.181	0.996
J_{45} (D)	**Myopic**	-0.05 ± 0.28	0.051	0.141	0.993
	Emmetropic	0.02 ± 0.12	0.070	0.194	0.932
	Hyperopic	0.08 ± 0.41	0.085	0.236	0.991

When comparing the repeatability among groups, we found similar results for AL while some differences for AQD, LT, CCT, WTW, K readings, J_0 and J_{45}, although these differences between refractive groups were not clinically significant. This implies that the same precision is achieved in a large range of different biometric magnitudes, from long ALs (>27 mm) and wide AQDs (>3.5 mm) in myopic subjects to short ALs (<21 mm) and narrow AQDs (<3 mm) in hyperopic subjects. Furthermore, these results indicate that the small changes produced during the measurement acquisition due to the fluctuation of the accommodation state between refractive groups do not seem to affect the device repeatability. These results demonstrated good and comparable repeatability among the three refractive groups.

For the groups defined following the age criterion, no statistically significant differences between the 5 repeated measurements were obtained for any biometric parameter ($p>0.05$). Repeatability coefficients and mean values for each parameter are included in Table 2. AL had a S_w of 0.007 mm and a CoR around 0.019 mm for both groups. For AQD and LT the presbyopic group showed lower values of S_w and CoR than the non-presbyopic group. K2 did have differences, obtaining lower coefficients values the non-presbyopic group. The presbyopic group obtained for K2 a CoR of 0.086 mm that means the 95% of the differences between measurements would be less than around 0.4 D. And concerning corneal astigmatism, the S_w and CoR values of both J_0 and J_{45} for the non-presbyopic group were lower than the presbyopic group. That could be explained by two reasons: because of the small number of subjects in the presbyopic group, and because a higher component of oblique astigmatism might be affecting the repeatability values. Therefore, slight differences were found for CCT, WTW, K2, J_0 and J_{45}, where the presbyopic group showed higher repeatability coefficients. This may be due to the fact that this group had less number of subjects than the non-presbyopic group. Besides, AQD and LT repeatability comparison showed some differences, obtaining higher repeatability coefficients the non-presbyopic group. That can be explained by the fact that the subjects in the non-presbyopic group have good accommodation ability, and then accommodation can fluctuate during the measurement process.

Table 2. Repeatability assessment of biometric parameters classified by age.

Parameter	Group	Mean ± SD	S_w	CoR	ICC
AL (mm)	**Non-presbyopic**	23.65 ± 1.28	0.007	0.019	1.000
	Presbyopic	23.68 ± 1.34	0.007	0.019	1.000
AQD (mm)	**Non-presbyopic**	3.04 ± 0.30	0.025	0.071	0.999
	Presbyopic	2.71 ± 0.36	0.016	0.045	1.000
LT (mm)	**Non-presbyopic**	3.68 ± 0.27	0.029	0.080	0.998
	Presbyopic	4.14 ± 0.24	0.018	0.050	0.999
CCT (μm)	**Non-presbyopic**	548.04 ± 29.39	2.244	6.217	0.999
	Presbyopic	550.29 ± 27.54	2.879	7.975	0.998
WTW (mm)	**Non-presbyopic**	12.09 ± 0.41	0.069	0.192	0.994
	Presbyopic	12.08 ± 0.40	0.074	0.204	0.993
K1 (mm)	**Non-presbyopic**	7.77 ± 0.27	0.019	0.052	0.999
	Presbyopic	7.82 ± 0.37	0.018	0.050	1.000
K2 (mm)	**Non-presbyopic**	7.62 ± 0.27	0.014	0.037	1.000
	Presbyopic	7.61 ± 0.33	0.031	0.086	0.998
J_0 (D)	**Non-presbyopic**	0.34 ± 0.44	0.062	0.172	0.996
	Presbyopic	0.51 ± 0.49	0.086	0.238	0.994
J_{45} (D)	**Non-presbyopic**	-0.06 ± 0.24	0.058	0.160	0.988
	Presbyopic	0.15 ± 0.37	0.085	0.234	0.989

APPENDIX B. Visante Omni

Repeatability of whole-cornea measurements using an anterior segment imaging device based on OCT and Placido-disk.

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METHODS

Patients

In total, 30 right eyes of 30 patients (18 women and 12 men) aged between 20 and 30 years were included in this study. Exclusion criteria were ocular or systemic disease, previous ocular surgery or a visual acuity less than 20/25. This study was approved by the Ethics Committee of the University of Valencia and followed the principles of the Declaration of Helsinki. All patients gave their informed consent after verbal and written explanation of the nature and purpose of the study.

Acquisition process

The experimental procedure was performed in the same order during a single session, by the same observer and in the same time period (between 3:00 pm and 6:00 pm) to minimize the fluctuation of corneal morphological and biomechanical properties (Read and Collins, 2009). The instrument was calibrated previously to each session of measurements.

First, the patient was placed in the Atlas 9000 topographer to obtain measurements of the anterior surface. Each subject was instructed to focus on the vision target, to perform a complete blink and to keep their eyes wide open during scanning. After scanning, the patient information and anterior corneal topography data were automatically transferred to the Visante OCT station via a network link. Then, the subject was moved to the Visante OCT station to measure global pachymetry. In this procedure aligning the tomography corneal centre with the anterior corneal surface topography is necessary. The correct alignment is achieved when the corneal reflex appears as a vertical white line along the central cornea. The posterior corneal elevation and curvature

measurements were carried out by the system software. A total of 3 measurements with the Visante omni combined device (Atlas 9000 topographer and Visante OCT) were taken sequentially for each patient following the explained procedure.

Evaluated parameters were anterior simulated keratometry (steep K, flat K, astigmatism and mean K), asphericity at a 4.5 mm diameter zone, thinnest pachymetry, pupil diameter, primary spherical aberration Z_4^0 for a 6 mm pupil size and WTW distance. Standard anterior and posterior elevation was also assessed by the BFS at 9 mm diameter zone.

Statistical analysis

Statistical analysis was performed using SPSS software for Windows (22.0 version; SPSS Inc, Chicago, Illinois). Comparison of the three repeated measurements was assessed by a non-parametric Friedman test in all cases. Differences were considered to be statistically significant when the p-value was less than 0.05.

To determine repeatability, the following coefficients were calculated: S_w, CoR, CoV, and ICC. The CoR was expressed according to the definition of the British Standard Institution, as a result from SD of the difference between measurements (McAlinden, Khadka and Pesudovs, 2011). The SD of the difference between 2 measurements was calculated from the intra-subject SD expressed as $\sqrt{2}S_w$. If we assume that differences between measurements follow the normal distribution, the value t which establishes the CI of 95% is 1.96. Thus, the CoR was calculated as: $CoR = 1.96\sqrt{2} \cdot S_w$. It can be approximated as $2.77S_w$ and it represents the interval which contains 95% of the differences between measurements (Bland and Altman, 1999). The CoV was calculated as the ratio between S_w and average value: $CoV = \frac{S_w}{\overline{x}}$. The ICC indicates the correlation between measurements and was considered to be statistically significant when the p-value was less than 0.05.

Graphic analysis was also applied with the method suggested by Bland-Altman (Bland and Altman, 1986) analyzing the difference between the first and the last measurement. The average and the difference between both measurements were calculated for all parameters. Normal distribution of the differences was also checked ($p > 0.05$). Besides, the following aspects were represented on the plot: average

difference, 95% CI of the average difference and 95% LoA. The LoA were calculated as the mean difference ± 1.96 SD.

RESULTS

In total, 30 right eyes of 30 subjects were evaluated in this study. The mean age of the patients was 23.70 ± 2.28 years (range from 19 to 29 years). The mean refractive error, expressed as spherical equivalent, was -1.45 ± 2.47 D (from 4 to -6.25 D). There were no statistically significant differences (P > 0.05) for repeated measurements of simulated keratometry (steep K, flat K, mean K and astigmatism), asphericity, thinnest pachymetry, WTW, primary spherical aberration and corneal elevation (anterior and posterior). Table 1 summarizes the mean differences, 95%CI of the mean and LoA for each topographic parameter, which are illustrated in some Bland-Altman plots.

Table 1. Average differences of topographic parameters.

Parameter	Mean Difference ± SD	95% CI	95% LoA
Steep K (D)	-0.01±0.16	-0.06, 0.05	-0.31, 0.30
Flat K (D)	0.01±0.17	-0.06, 0.07	-0.33, 0.34
Astigmatism (D)	0.02±0.15	-0.04, 0.07	-0.28, 0.31
Mean K (D)	0,02±0.15	-0.04, 0.08	-0.28, 0.32
Asphericity Q	-0.01±0.02	-0.02, 0.00	-0.05, 0.03
Minimum pachymetry (µm)	-0.60±1.98	-1.34, 0.14	-4.47, 3.27
WTW (mm)	0.02±0.08	-0.01, 0.05	-0.15, 0.18
Spherical aberration Z_4^0 (µm) @ 6 mm	0.00±0.02	-0.01, 0.01	-0.04, 0.04
Anterior BFS (mm)	0.00±0.03	-0.01, 0.01	-0.04, 0,04
Anterior BFS (D)	0.00±0.13	-0.05, 0.05	-0.26, 0.26
Posterior BFS (mm)	0.01±0.03	0.00, 0.02	-0.05, 0.06
Posterior BFS (D)	0.00±0.02	-0.01, 0.01	-0.04, 0.05

Bland-Altman plots of simulated keratometry parameters (Figure 1 and 2) showed narrow LoA. Steep K and flat K showed a mean difference of 0.01 D and the LoA were around -0.30 to 0.30 D. For astigmatism and mean K, the mean difference was 0.02 D and LoA were about -0.28 to 0.30 D for both parameters. Similar results were obtained for the other parameters. Asphericity and spherical aberration (for 6-mm pupil) obtained a mean difference of -0.01 and 0.00 µm respectively and the LoA were -0.05 to 0.03 for asphericity and -0.04 to 0.04 µm for spherical aberration.

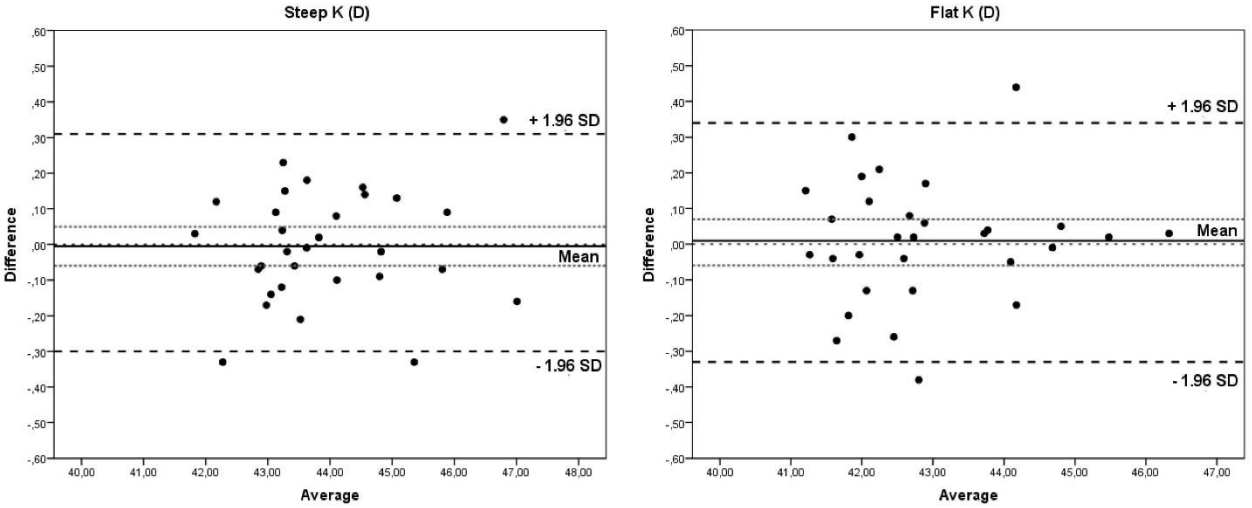

Figure 1. Bland-Altman plots of steep and flat keratometry.

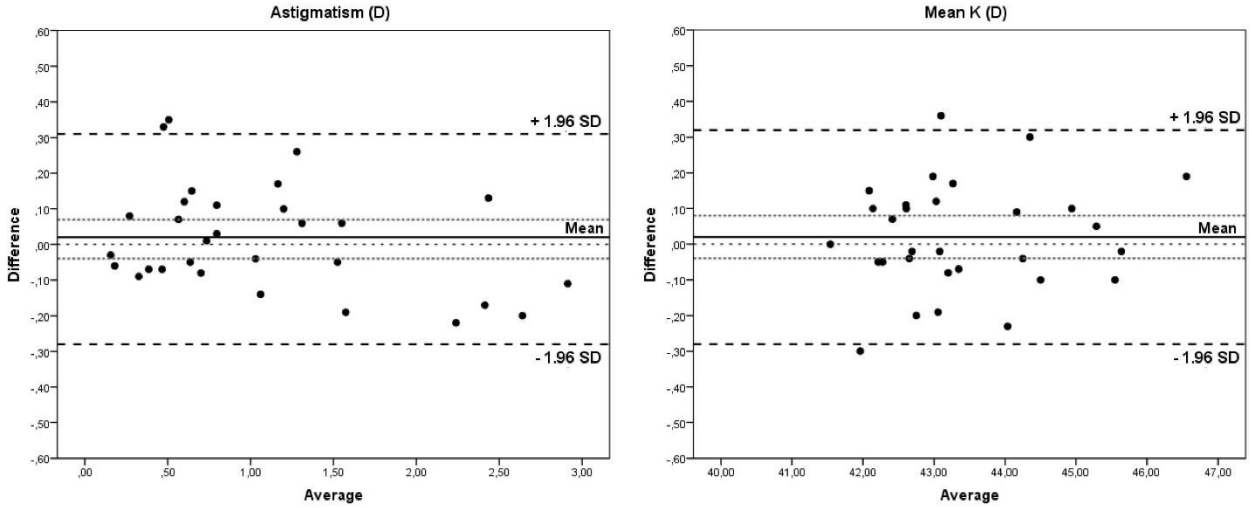

Figure 2. Bland-Altman plots of astigmatism and mean keratometry.

Minimum pachymetry and WTW showed a LoA of -4.47 to 3.27 µm and 0.15 to 0.18 mm for each parameter respectively (Table 1). The mean difference found for minimum pachymetry was -0.60 µm and 0.02 mm for WTW. And for corneal elevation (anterior and posterior) plots (Figure 3) showed a mean difference of 0.00 D and between 0.00 and 0.01 expressed in mm; LoA were -0.05 mm to 0.06 mm and -0.04 D to 0.05 D. For all parameters, the CI of 95% represented in Bland-Altman plots contained the value zero within its range.

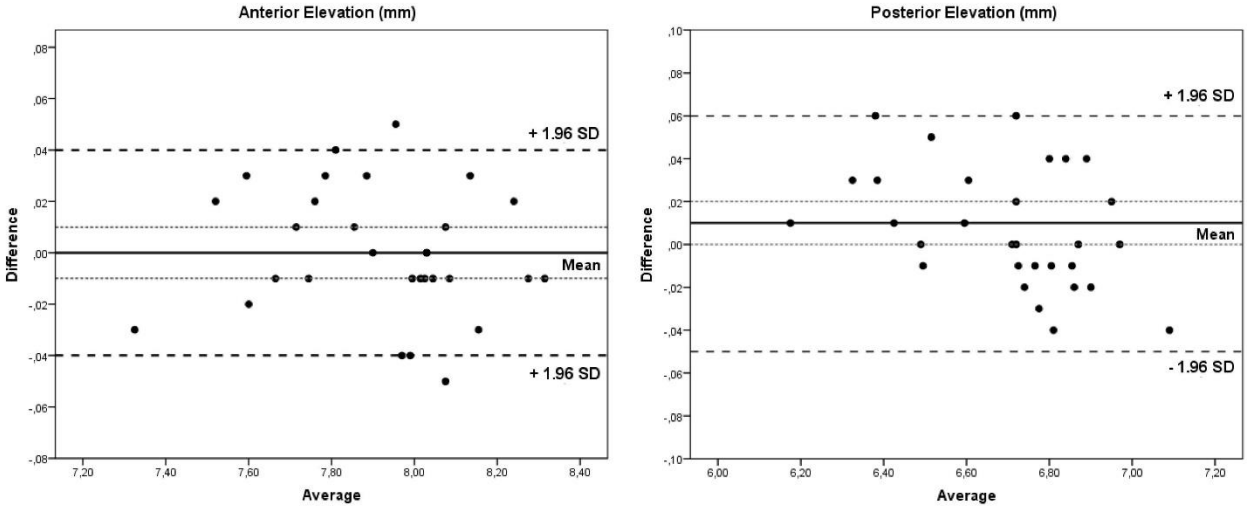

Figure 3. Bland-Altman plots of aanterior and posterior elevation.

The CoR for simulated keratometry parameters ranged between 0.22D and 0.28D. The CoV was less than 0.25% except for the astigmatism (7%) and the ICC was higher than 0.98. Asphericity obtained a CoR of 0.04 and for spherical aberration the CoR was also 0.04 mm. For minimum pachymetry the CoR was 3.76 µm and for WTW was 0.36 mm. The CoV was 4.43% for asphericity; 0.26% for minimum pachymetry; 0.36% for WTW and 7.11% for spherical aberration. For all of these previous parameters, the ICC was between 0.96 and 0.99. A CoR of 0.05 mm and 0.23 D was acquired for anterior elevation and for posterior elevation was 0.04 expressed in millimetres and diopters. The CoV ranged between 0.19% and 0.21% for anterior elevation and between 0.21% and 0.22% for posterior elevation. Table 2 summarizes the repeatability coefficients and the mean values for each topographic parameter.

Table 2. Repeatability of topographic parameters.

Parameter	Mean ± SD	P	S_w	CoV(%)	CoR	ICC
Steep K (D)	43.95±1.29	0.506	0.10	0.23	0.28	0.992
Flat K (D)	42.90±1.29	0.731	0.09	0.21	0.25	0.993
Astigmatism (D)	1.09±0.77	0.792	0.08	7.22	0.22	0.986
Mean K (D)	43.42±1.26	0.797	0.09	0.21	0.25	0.993
Asphericity Q	-0.36±0.13	0.071	0.01	4.3	0.04	0.982
Minimum pachymetry (µm)	516.78±28.68	0.123	1.36	0.26	3.76	0.998
WTW (mm)	12.43±0.39	0.280	0.04	0.36	0.13	0.979
Spherical aberration Z_4^0 (µm) @ 6 mm	0.23±0.06	0.497	0.02	7.11	0.04	0.968
Anterior BFS (mm)	7.92±0.23	0.857	0.02	0.21	0.05	0.993
Anterior BFS (D)	42.66±1.26	0.991	0.08	0.19	0.23	0.994
Posterior BFS (mm)	6.70±0.21	0.468	0.02	0.22	0.04	0.994
Posterior BFS (D)	-5.98±0.20	0.609	0.01	0.21	0.04	0.995

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PUBLICATIONS

JOURNAL PUBLICATIONS

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Martínez-Albert, N., García-Marqués, J., Bueno-Gimeno, I., Gené-Sampedro, A., and Montés-Micó, R., 2020. Elevación corneal y miopía. *26 Congreso Internacional de Optometría, Contactología y Óptica Oftálmica OPTOM.* Accepted

Martínez-Albert, N., García-Marqués, J., Talens-Estarelles, C., Bueno-Gimeno, I., Gené-Sampedro, A., and Montés-Micó, R., 2020. Contribución del frente de onda interno en función del error refractivo. 5º *Congreso Internacional de Jóvenes Optometristas, SIYO*. Accepted.

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