EFFECT OF OCULAR HIGHER ORDER ABERRATIONS INDUCED FROM ORTHOKERATOLOGY LENSES WITH DIFFERENT COMPRESSION FACTORS ON AXIAL ELONGATION

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PhD

The Hong Kong Polytechnic University

2021

The Hong Kong Polytechnic University

School of Optometry

Effect of Ocular Higher Order Aberrations Induced from Orthokeratology Lenses with Different Compression Factors on Axial Elongation

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A thesis submitted in partial fulfilment of the requirements

for the degree of Doctor of Philosophy

June 2020

Certificate of originality

I hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, it produces no material previously published or written, nor material that has been accepted for the award of any other degree or diploma, except where due acknowledgement has been made in the text.

Jason Ki-kit LAU

This book is dedicated to my family.

The fear of the Lord is the beginning of wisdom, and the knowledge of the Holy One is understanding.

Proverbs 9:10 (KJV)

Abstract

Higher order aberrations (HOAs), optical imperfections that persist despite traditional spherocylindrical refractive correction, contribute to approximately 10% of the total ocular aberrations and vary with numerous factors, including, but not limited to, age, refractive error, pupil size, and accommodation. Changes in the HOA profile can improve or deteriorate retinal image quality, and potentially affect the vision dependent emmetropisation process.

While orthokeratology (ortho-k) is one of the most effective myopia control interventions, the mechanism by which it slows axial elongation remains unclear. Since HOAs are substantially elevated following ortho-k treatment, investigating the association between ocular HOAs and axial elongation in paediatric ortho-k may provide new insights into its mechanism of action. This study aimed to investigate this association in normal (untreated, spectacle-wearing) children and ortho-k-treated children using retrospective and prospective data. Modifications to ortho-k lenses by adjusting the compression factor were performed in order to manipulate the levels of induced HOAs. The short-term (one month) and long-term (two years) effects were examined using the changes in choroidal thickness and axial length, respectively. The predictive

value of induced ocular HOAs after one month of treatment for axial elongation across all study visits in the two-year period was also investigated.

In the retrospective analysis, the association between ocular HOAs and axial elongation measured annually over a two-year period in 137 children was analysed. Using a 6-mm pupil size and a sixth order Zernike polynomials expansion, it was shown that higher levels of ocular HOAs, particularly spherical aberration, were associated with longer axial length and slower axial elongation, after adjusting for other known confounding factors such as age, sex, and refractive error.

In the analysis of another 103 ortho-k-treated subjects, as expected, there were approximately three- to nine-time increases in HOAs after treatment. Adjusting for the influence of baseline ocular HOAs on axial elongation, similar associations were observed between HOAs and axial elongation as reported for spectacle-wearing children. Higher levels of HOAs and spherical aberration were associated with slower elongation. Based on statistical modelling, every micron increase in spherical aberration was associated with 0.46 mm slower axial elongation per year.

A contralateral eye, self-controlled study of 28 children was performed to investigate the effect of modifying the ortho-k lens compression factor on ocular HOAs. Ortho-k lenses of different compression factors (0.75 and 1.75 D) were randomly fitted on the fellow eyes of each subject and monitored weekly for one month. It was shown that increasing the compression factor by 1.00 D induced approximately 40% more ocular HOAs, without significantly altering the refractive correction of the subjects. There was no significant difference between the changes in choroidal thickness between the two eyes. Considering paired-eye data, the subfoveal choroidal thickness transiently increased in early lens wear (mean change at week 1: +9.1 ± 12.6 μm), but gradually regressed to the baseline level at the end of the study. However, on average this change approached the coefficient of repeatability of the instrument and analysis procedure (8.0 – 9.0 μm). Measuring the choroidal thickness in early ortho-k lens wear may not provide sufficient information to inform future axial elongation in eyes fitted with different compression factors.

A two-year longitudinal, randomised (using different compression factors of ortho-k lenses) study was conducted to examine the influence of different compression factors (0.75 and 1.75 D) on axial elongation. A total of 75 subjects (control: 11; ortho-k [0.75 D]: 29; ortho-k [1.75 D]: 35) completed the study. However, the high dropout rate (63%) and potentially biased control group was not suitable to include in between-group comparisons. Increasing the compression factor improved the myopia control effectiveness by about 30%, compared with the conventional compression factor. In addition, increasing the compression factor of ortho-k lenses significantly increased the induced HOAs, particularly spherical aberration, which was associated with slower axial elongation. It was therefore speculated that the myopia control effect of ortho-k treatment in Chinese children may be improved by increasing the compression factor of ortho-k lenses by 1.00 D.

In conclusion, higher levels of ocular HOAs were associated with slower axial elongation in both spectacle-wearing and ortho-k treated children.

Increasing the compression factor of ortho-k lenses by 1.00 D induced more ocular HOAs without adversely affecting visual performance and improved the myopia control effect of the ortho-k treatment.

Publications arising from the thesis

Peer reviewed publications:

- Wan K, **Lau JK**, Cheung SW, P Cho. (2020) Orthokeratology with increased compression factor (OKIC): study design and preliminary results. BMJ Open Ophthalmol 5:e000345.

Contribution	**Author(s)**
Conceptualization	CP, CSW
Data analysis	WK, LJK
Funding acquisition	CP
Investigation	WK, LJK
Methodology	WK, LJK, CP, CSW
Project administration	CP, CSW
Supervision	CP
Visualization	WK, LJK
Writing - first draft	WK
Writing - review & editing	WK, LJK, CSW, CP

- **Lau JK**, Vincent SJ, Cheung SW, Cho P. (2020). Higher-order aberrations and axial elongation in myopic children treated with orthokeratology. Invest Ophthalmol Vis Sci 61:22.

Contribution	**Author(s)**
Conceptualization	CP, CSW, VSJ
Data analysis	LJK, VSJ
Funding acquisition	CP
Investigation	LJK
Methodology	LJK, VSJ, CP, CSW
Project administration	CP, CSW
Supervision	CP, VSJ
Visualization	LJK, VSJ
Writing - first draft	LJK
Writing - review & editing	LJK, VSJ, CSW, CP

- Wan K, **Lau JK**, Cheung SW, Cho P. (2020). Refractive and corneal responses of young myopic children to short-term orthokeratology treatment with different compression factors. Cont Lens Anterior Eye 43:65-72.

Contribution	**Author(s)**
Conceptualization	CP, CSW
Data analysis	WK, LJK
Funding acquisition	CP
Investigation	WK, LJK
Methodology	WK, LJK, CP, CSW
Project administration	CP, CSW
Supervision	CP
Visualization	WK, LJK
Writing - first draft	WK
Writing - review & editing	WK, LJK, CSW, CP

- **Lau JK**, Vincent SJ, Cheung SW, Cho P. (2020). The influence of orthokeratology compression factor on ocular higher-order aberrations. Clin Exp Optom 103:123-8.

Contribution	Author(s)
Conceptualization	CP, CSW, VSJ
Data analysis	LJK, VSJ
Funding acquisition	CP
Investigation	LJK
Methodology	LJK, VSJ, CP, CSW
Project administration	CP, CSW
Supervision	CP, VSJ
Visualization	LJK, VSJ
Writing - first draft	LJK
Writing - review & editing	LJK, VSJ, CSW, CP

- **Lau JK**, Wan K, Cheung S-W, Vincent SJ, Cho P. (2019). Weekly changes in axial length and choroidal thickness in children during and following orthokeratology treatment with different compression factors. Transl Vis Sci Technol 8:9.

Contribution	Author(s)
Conceptualization	CP, CSW, VSJ
Data analysis	LJK, VSJ
Funding acquisition	CP
Investigation	LJK, WK
Methodology	LJK, WK, VSJ, CP, CSW
Project administration	CP, CSW
Supervision	CP, VSJ
Visualization	LJK, WK, VSJ
Writing - first draft	LJK
Writing - review & editing	LJK, VSJ, WK, CSW, CP

- **Lau JK**, Cheung SW, Collins MJ, Cho P. (2019). Repeatability of choroidal thickness measurements with Spectralis OCT images. BMJ Open Ophthalmol 4:e000237.

Contribution	Author(s)
Conceptualization	CP, CSW, CMJ
Data analysis	LJK
Funding acquisition	CP
Investigation	LJK
Methodology	LJK, CP, CSW
Project administration	CP, CSW
Supervision	CP
Visualization	LJK
Writing - first draft	LJK
Writing - review & editing	LJK, CMJ, CSW, CP

- **Lau JK**, Vincent SJ, Collins MJ, Cheung SW, Cho P. (2018). Ocular higher-order aberrations and axial eye growth in young Hong Kong children. Sci Rep 8:6726.

Contribution	Author(s)
Conceptualization	CP, CSW, CMJ, VSJ
Data analysis	LJK, VSJ
Funding acquisition	CP
Investigation	LJK
Methodology	LJK, VSJ, CP, CSW
Project administration	CP, CSW
Supervision	CP, VSJ
Visualization	LJK, VSJ
Writing - first draft	LJK
Writing - review & editing	LJK, VSJ, CMJ, CSW, CP

Referred abstracts:

- **Lau JK**, Vincent SJ, Cheung SW & Cho P. The effect of orthokeratology compression factor on ocular higher-order aberrations. The 17th International Myopia Conference, 12-15 September, Tokyo, Japan.
- **Lau JK**, Vincent SJ, Cheung SW & Cho P. Higher-order aberrations and axial elongation in young myopic children undergoing orthokeratology treatment. The 22nd Asia Pacific Optometry Congress, 17-20 June, Manila, The Philippines.
- Wan K, **Lau JK**, Cheung SW & Cho P. First month preliminary results of orthokeratology lens wear with increased compression factor. The 2019 British Contact Lens Association Clinical Conference and Exhibition, 30 May - 1 June, 2019, Manchester Central, The United Kingdom.
- Wan K, **Lau JK**, Cheung SW & Cho P. Does increased compression factor in orthokeratology affect refractive and ocular responses? The 2018 British Contact Lens Association Asia Conference and Exhibition, 18-19 September, 2018, Singapore
- **Lau JK**, Cheung SW, Collins MJ & Cho P. Short-term changes in choroidal thickness and axial length in children fitted with orthokeratology lenses of different compression factors. The 2018 Association for Research in Vision and Ophthalmology Annual Meeting, 29 April - 3 May, 2018, Honolulu, Hawaii, United States.

- **Lau JK**, Vincent SJ, Collins MJ, Cheung SW & Cho P. Optical effects of orthokeratology on eye growth. The 11th Eye Research Day, 13 June, 2015, Hong Kong, China.
- **Lau JK**, Vincent SJ, Collins MJ, Cheung SW & Cho P. Optical effects of orthokeratology on eye growth. The 15th International Cornea and Contact Lens Congress, 22-24 May, 2015, Gold Coast, Australia.

Acknowledgements

First of all, I would like to thank my chief supervisor Prof Pauline Cho. She led me to the way when I was a lost sheep. I was very fortunate to have her guidance throughout these years. She also shared her invaluable experience and vast knowledge when I faced any difficulties. I have benefited so much from her positive encouragement, massive support, and expert advice that brought me to this stage.

I am thankful to have my co-supervisors Prof Michael Collins and Dr Stephen Vincent as well. Despite the geographical distance between Hong Kong and Australia, their selfless help and constructive feedback never come with time lag. Their visionary insights to the research field also open my eyes to the complex mechanism of optical influences for refractive development. I am also grateful to have Dr Maureen Boost for her help in revising this thesis and corresponding manuscripts.

Many thanks to all my colleagues and friends who interacted and discussed with me on the path of this scientific adventure. Thanks to Dr Peggy Cheung, Ms Kiki Tan, Ms Ella Guo, and Ms Grace Yang as being my strongest "the twelve man". I would like to thank Mr Jimmy Tse as my clinical mentor who gave me unreserved directions and helping hands in my residency work and advanced cases during the study period. Special thanks to Mr Ken Wan, Mr Kai-yip Choi, Mr Horace Wong, and Dr Jeffrey Leung, as being my greatest and strongest companions in optometry, work, and life. Thanks to Dr Ka-yin Chan and Dr Shanica Hon for their constructive comments when I failed to identify a clear road to the future.

Special thanks to all the subjects and their parents for devoting their valuable time in participating in our research and following our instructions. Their contribution was countless.

I would like to express my sincere gratitude to The Hong Kong Polytechnic University (PolyU) and Menicon Co., Ltd. (Collaborative Research Agreement [ZG3Z]), and the Research Residency Scheme of the School of Optometry, PolyU, for their generous support of my work. The studies could not have been completed without the kind support of solutions from Ophtecs Corp. (Ophtecs cleadew, TearW) and Precilens (Aquadrop+).

Finally, I would like to salute my family and my fiancée Zoey, for their endless patience, tolerance, and love. Their joy and smiles are a tremendous motivation to me always. There would be no accomplishment of this thesis without any of them.

Thank you all for accompanying me in this journey. Thank you all from the bottom of my heart.

Table of contents

List of figures

List of tables

List of abbreviations

ANOVA	analysis of variance
CI	confidence interval
D	dioptre
HOAs	higher order aberrations
LogMAR	logarithm of the minimum angle of resolution
OCT	optical coherence tomography
OR	odds ratio
Ortho-k	orthokeratology
RMS	root-mean-square
SD	standard deviation
SE	standard error
SER	spherical equivalent refraction

Chapter 1

Introduction

The human eye like any optical system, is frequently disturbed by optical imperfections, termed ocular aberrations. Ocular aberrations can be described using Zernike polynomials and the individual terms within the polynomial can be classified as corresponding to lower or higher order aberrations (HOAs). In the field of ophthalmology and optometry, lower order aberrations, known as defocus and astigmatism, can be corrected by conventional spherocylindrical spectacles or contact lenses. However, residual uncorrected HOAs can still alter the retinal image quality and therefore can potentially play a role in the visually-guided development of the eye.

While orthokeratology (ortho-k) treatment, using a reverse geometry overnight rigid contact lens, has been shown to effectively retard myopia progression by slowing axial elongation in children, little is known about the underlying mechanism. The aim of this post-graduate research was to examine the relationship between the optical changes induced by ortho-k (including changes in ocular aberrations) and axial elongation. The effect of increasing the compression factor of ortho-k lenses on ocular HOAs was also examined as a potential method of increasing myopia control effectiveness. In this chapter the synopsis of the thesis is presented.

Chapter 2 provides an overview of the structure of the human eye and its basic optics. The definition of monochromatic ocular aberrations, their mathematical presentation using Zernike polynomials, and measurement of HOAs are also described. In addition, the effects of age, refractive error, and accommodation on ocular HOAs are described. Finally, the influence of ocular HOAs on visual development is discussed. **Chapter 3** describes the need for myopia control, provides the definition of ortho-k, and discusses its effectiveness for myopia control, as well as refractive correction and the incorporation of compression factor for ortho-k lenses. Changes in HOAs associated with ortho-k treatment are described and compared with other myopia control interventions. **Chapter 4** describes the niche area and research objectives of the studies performed.

Chapter 5 details a retrospective analysis of a two-year longitudinal investigation of HOAs and axial elongation in young Hong Kong children, who previously participated in ortho-k clinical trials as spectacle-wearing control subjects. **Chapter 6** focuses on a retrospective analysis of the association between induced HOAs from ortho-k treatment and axial elongation over a two-year period. Experimental modifications to ortho-k lenses with different compression factors and the short-term (one month, **Chapter 7**) and long-term (two years, **Chapter 8**) effects on eye growth, including choroidal and axial length responses.

The effectiveness of using ortho-k lenses of different compression factors is examined and discussed.

Chapter 9 concludes the thesis with a precis of the work performed and the key results. Possible further investigations and improvements to study the influence of HOAs on eye growth in eyes treated with ortho-k are discussed.

Chapter 2

Overview of ocular aberrations

2.1 Basic optics of the eye

When light passes through an optical medium, it is absorbed, reflected, or transmitted (refracted) by the object. Since absorbance and reflection are beyond the scope of this thesis, they are not considered here and only refraction is discussed. In a camera, visible light is captured onto a light sensitive film by means of a focusing system and an aperture. Likewise, three components, the cornea, the pupil, and the crystalline lens, form the optical refractive system of the human eye. The cornea and the crystalline lens are the two main optical elements that refract and focus light onto the retina, while the pupil controls and limits the amount of light entering the eye. The optical power P of a refractive surface is proportional to the change in refractive index $(n' - n)$ and inversely proportional to the radius of the curvature r, shown as

$$P = \frac{n' - n}{r} \tag{2.1}$$

where n and n' are the refractive indices of the first and the second optical media.

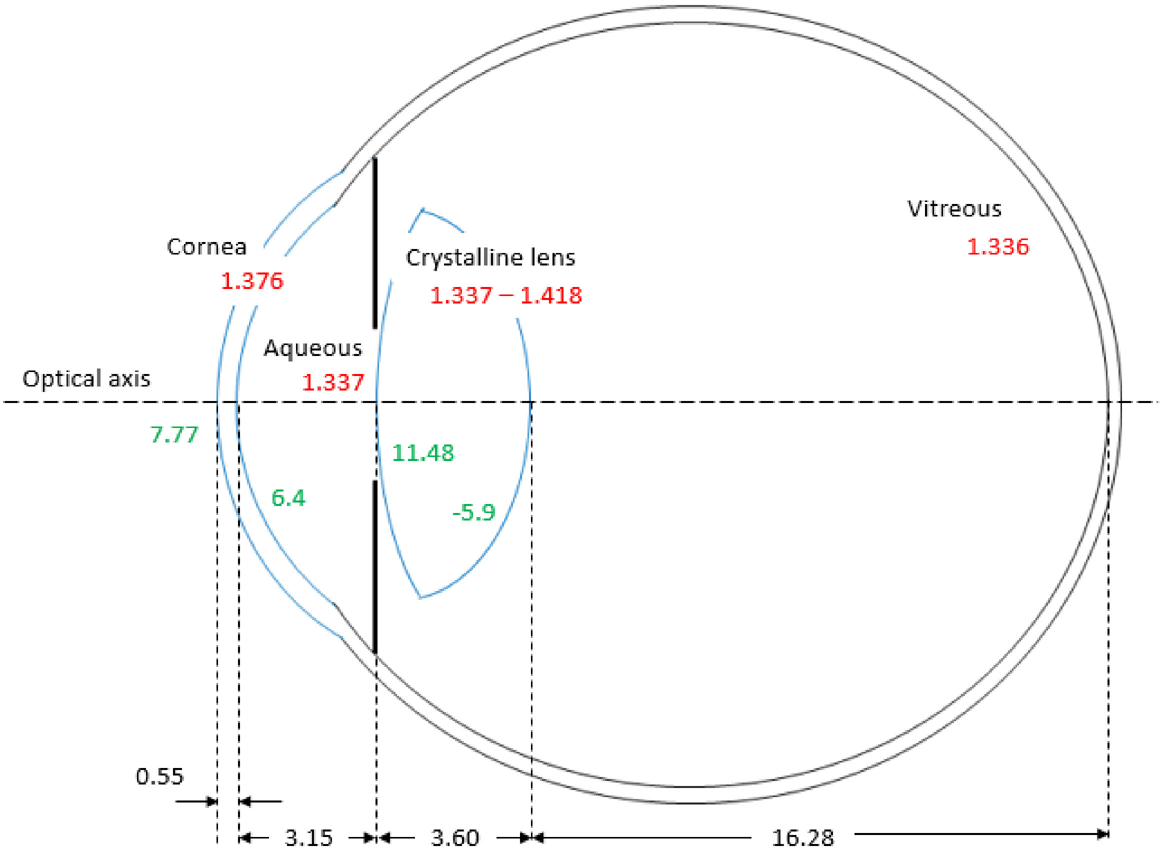


Figure 2.1 Schematic model of the human eye during relaxed accommodation. The model is calculated based on light of wavelength 555 nm. The red numbers represent the refractive indices of the optical media and the green numbers represent the radii of curvatures of the refractive surfaces (blue curves). The graph is not drawn to scale and the numbers (except those in red) presented are in mm. This illustration is re-constructed according to the optical model from Atchison and Thibos (2016).

Figure 2.1 demonstrates the physiological optical components of the eye and their refractive indices and dimensions. When light first enters the eye, it passes through the tear film and the cornea. The tear film is a thin layer of about 2 to 8 μm, consisting of lipid, water, mucins, and other substances, such as proteins and glycocalyx (King-Smith et al., 2000; Werkmeister et al., 2013; Bai and Nichols, 2019). It protects, lubricates, and provides nutrients and oxygen to the cornea, and smoothens the cornea to optimise retinal image quality (Tutt et al., 2000). In an optical system, the most refractive surface is situated between the media of the most dissimilar refractive indices (i.e. the air and the cornea). Hence, despite the thinness of the tear film, its coupling effect, together with the cornea, provides two thirds of the overall ocular refractive power of approximately 42.00 D (Albarran et al., 1997).

The cornea is a transparent avascular connective tissue, which is approximately 0.55 mm thick centrally (Scotto et al., 2017). It acts as the primary barrier to pathogens and provides the majority of refractive power for the eye (Ehlers and Hjortdal, 2004). In reality, the cornea is not perfectly spherical, but is rather aspheric and prolate in shape – steeper at the centre and flatter at the periphery (Davis et al., 2005). Its thickness also increases towards to the limbal region (Randleman et al., 2015).

The light then enters the 3-mm deep anterior chamber (Lam et al., 2001), containing aqueous humour, which is mainly composed of water, trace ions, and proteins (Greivenkamp et al., 1995) and provides nutrients to and removes metabolic wastes from the cornea, iris, and crystalline lens. The light then passes through the pupil, the aperture of the eye. The pupil is an opening of the iris and controls the amount of light entering the eye by varying its diameter from 2 to 7 mm under different lighting environments (Franssen et al., 2007; Guillon et al., 2016).

The crystalline lens is the next optical component encountered. It has a non-uniform gradient refractive index (Uhlhorn et al., 2008), meaning that the refractive index gradually decreases from the nucleus towards the peripheral cortex, and contributes one third of the overall refractive power of the eye of approximately 15.00 D (Borja et al., 2008), although its power gradually decreases with age (Glasser and Campbell, 1998). Its main function is to allow steepening of its curvature and increase in thickness upon the contraction of the ciliary muscles, providing accommodation, which helps to focus the image of near objects onto the retina.

The light eventually passes through the vitreous, the hydrated gel that supports the eye globe, and is focused on the retina. The photoreceptors of the retina are responsible for the detection of light and the image is converted and transmitted to the cortical cortex of the brain as electrical signals for further visual processing.

2.1.1 Reference axes of the eye

Two traditional axes of the eye centre at the fovea, the visual axis and the line of sight. The visual axis is the line passing through the fixation point and the nodal points of the optical system of the eye. However, it cannot be measured because the nodal points are not coincident. The line of sight is drawn from the fixation target, through the entrance pupil, to the fovea (Applegate et al., 2000). From the point of aberrometry, the line of sight is the path of the chief ray from the object of interest and, therefore, is appropriate as the reference line.

Misalignment of the line of sight may contribute to inaccurate estimation of the corneal and internal aberrations (Klein and Garcia, 2000; Salmon and Thibos, 2002). Aberrometers usually account for the use of the line of sight with respect to the pupil centre.

2.2 Monochromatic ocular aberrations

Three main factors contribute to image degradation:

1. Aberrations: variations in the geometrics of the optical components in the system, resulting in deviations of the incoming light rays,

2. Diffraction: limitation of the aperture stop and edge of the optical elements resulting in a bending of the light wave, and

3. Scattering: alterations in optical paths due to localised non-uniformities of the optical medium.

Aberrations can be further classified according to the involvement of wavelengths of the light (single: monochromatic; various: chromatic). This study focuses on the influence of monochromatic aberrations.

2.2.1 Definition

In an ideal optical system, all light rays focus at a single point (Figure 2.2A). However, with all the geometric deviations occurring in the human eye, including, but not limited to, rotational asymmetry, tilts, decentration, misalignment, and variations of curvatures, and refractive indices, a perfect image focusing only at a single point is almost impossible. Any misalignment of the light rays due to possible defects, resulting in a difference in vergence (the reciprocal of the distance between the reference plane and the focal point), is regarded as a wavefront error (Figure 2.2B) (Voke, 2010). The integration of all the differences between the ideal and actual wavefronts over a fixed pupil size determines the aberrations (Thibos, 2013).

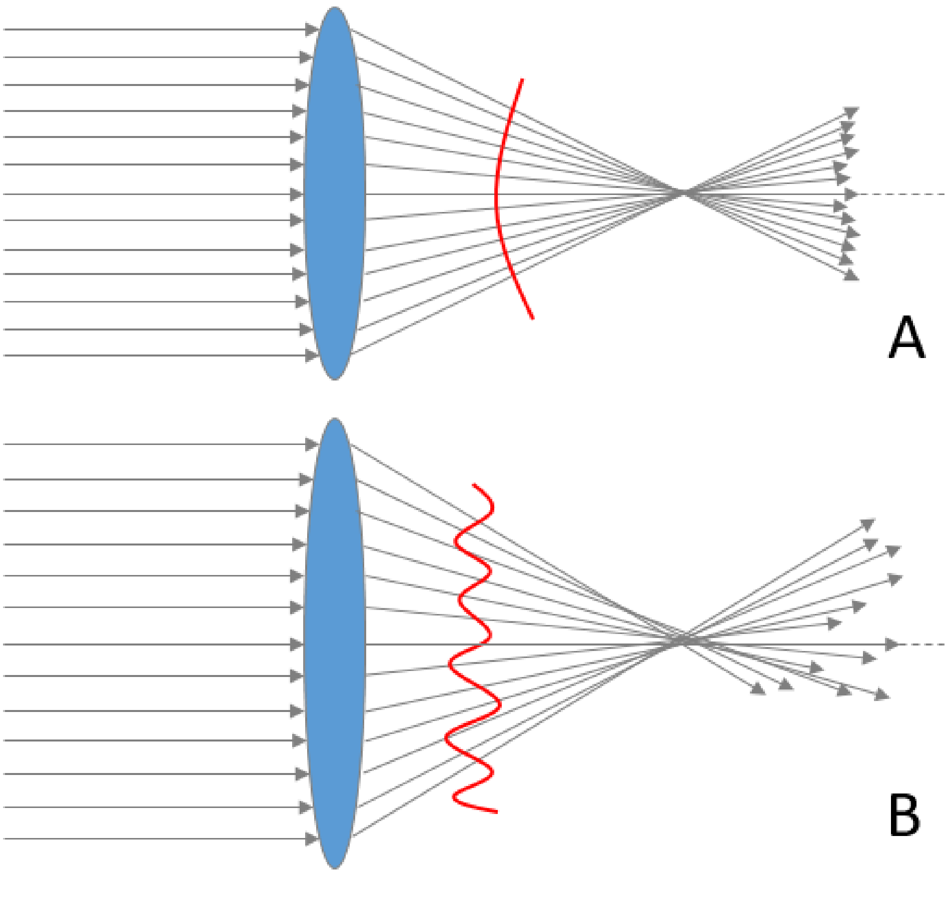


Figure 2.2 Illustration of aberration using light rays and wavefronts. The images formed from the light rays of a distant object passing through (A) a perfect (aberration-free) lens and (B) an aberrated lens. The red lines represent the wavefronts perpendicular to the direction of the light rays (not drawn to scale).

2.2.2 Polynomial representation

Wavefront aberrations can be expressed using Zernike polynomials (Atchison, 2004), which is a set of azimuthal and radial dependent functions orthogonal to the pupil. They can be expressed as a pyramid and remain the most commonly used presentation for aberrations in ophthalmology and optometry studies and are recommended by the Optical Society of America (OSA) (Thibos et al., 2002a). They can be applied to describe any continuous wavefront aberration over a circular area as

$$W(\rho,\theta) = \sum Z_n^m P_n^m(\rho,\theta) \qquad (2.2)$$

where W is a summation function of Zernike polynomials P of the product of Zernike coefficient Z, radial variable ρ, and angular variable θ; while m and n are the angular and radial orders, respectively. Table 2.1 shows the polynomial terms and aberration names of the Zernike polynomials up to the sixth order.

The zeroth and the first order aberrations in the pyramid, piston, and tilts, represent the mean value and the direction of the propagating wavefront. These are usually ignored as they describe the displacement, but not the quality of the image (Charman, 2005).

Table 2.1 Zernike coefficients and corresponding names, up to the sixth order.

j	n	m	Polynomial term	Aberration name
0	0	0	1	Piston
1	1	-1	$2\rho\sin\theta$	Vertical tilt
2	1	1	$2\rho\cos\theta$	Horizontal tilt
3	2	-2	$\sqrt{6}\rho^2\sin 2\theta$	Oblique astigmatism
4	2	0	$\sqrt{3}(2\rho^2-1)$	Defocus
5	2	2	$\sqrt{6}\rho^2\cos 2\theta$	Horizontal astigmatism
6	3	-3	$\sqrt{8}\rho^3\sin 3\theta$	Vertical trefoil
7	3	-1	$\sqrt{8}(3\rho^3-2\rho)\sin\theta$	Vertical coma
8	3	1	$\sqrt{8}(3\rho^3-2\rho)\cos\theta$	Horizontal coma
9	3	3	$\sqrt{8}\rho^3\cos 3\theta$	Horizontal trefoil
10	4	-4	$\sqrt{10}\rho^4\sin 4\theta$	Oblique quadrafoil
11	4	-2	$\sqrt{10}(4\rho^4-3\rho^2)\sin 2\theta$	Secondary oblique astigmatism
12	4	0	$\sqrt{5}(6\rho^4-6\rho^2+1)$	Spherical aberration
13	4	2	$\sqrt{10}(4\rho^4-3\rho^2)\cos 2\theta$	Secondary horizontal astigmatism
14	4	4	$\sqrt{10}\rho^4\cos 4\theta$	Horizontal quadrafoil
15	5	-5	$\sqrt{12}\rho^5\sin 5\theta$	Vertical pentafoil
16	5	-3	$\sqrt{12}(5\rho^5-4\rho^3)\sin 3\theta$	Secondary vertical trefoil
17	5	-1	$\sqrt{12}(10\rho^5-12\rho^3+2\rho)\sin\theta$	Secondary vertical coma
18	5	1	$\sqrt{12}(10\rho^5-12\rho^3+2\rho)\cos\theta$	Secondary horizontal coma
19	5	3	$\sqrt{12}(5\rho^5-4\rho^3)\cos 3\theta$	Secondary horizontal trefoil
20	5	5	$\sqrt{12}\rho^5\cos 5\theta$	Horizontal pentafoil
21	6	-6	$\sqrt{14}\rho^6\sin 6\theta$	Oblique hexafoil
22	6	-4	$\sqrt{14}(6\rho^6-5\rho^4)\sin 4\theta$	Secondary oblique quadrafoil
23	6	-2	$\sqrt{14}(15\rho^6-20\rho^4+6\rho^2)\sin 2\theta$	Tertiary oblique astigmatism
24	6	0	$\sqrt{7}(20\rho^6-30\rho^4+6\rho^2-1)$	Secondary spherical aberration
25	6	2	$\sqrt{14}(15\rho^6-20\rho^4+6\rho^2)\cos 2\theta$	Tertiary horizontal astigmatism
26	6	4	$\sqrt{14}(6\rho^6-5\rho^4)\cos 4\theta$	Secondary horizontal quadrafoil
27	6	6	$\sqrt{14}\rho^6\cos 6\theta$	Horizontal hexafoil

There are several useful features of the Zernike polynomial representation. First, each term in the polynomial is independent of the other terms. Any truncation or expansion of the polynomials does not alter the values of the remaining coefficients. Therefore, the polynomials can be expanded into infinite terms or up to any order of interest.

Second, each term/order of the polynomials gives a specific pattern (Webb, 1992). For example, Z_2^0 represents spherical defocus, Z_2^{-2} and Z_2^2 represent astigmatism. The effects of second-order aberrations can be corrected in clinical practice using spherocylindrical lenses. Third order aberrations include comatic aberrations, whereas fourth order terms include spherical aberration.

Third, Zernike terms at the upper and middle parts of the pyramid are usually dominant in magnitude (Howland and Howland, 1977; Walsh et al., 1984; Porter et al., 2001). First and second order aberrations, the lower order aberrations, account for 90% of overall aberrations and the remaining 10% are HOAs (Porter et al., 2001; Castejon-Mochon et al., 2002). Comas (Z_3^{-1} and Z_3^1) and spherical aberration (Z_4^0) are relatively more important, because of their higher magnitudes among other HOA terms (Wang and Koch, 2003).

Another feature is the summation property of the terms in the polynomials. Mathematically, each coefficient in the polynomial represents a standard deviation. The sum of the squared coefficients gives the variance and it is commonly presented as root-mean-square (RMS) value (Thibos et al., 2002b). It provides an overall metric for aberration terms of similar nature. For example, the effect of HOAs up to the order of interest can be grouped and simplified as HO RMS (RMS values of total HOAs). Similarly, spherical and comatic aberrations RMS can be used to represent the influence of RMS values of spherical-like and comatic-like aberration terms, up to the order of interest.

However, one drawback is the loss of the direction (sign) of the aberrations. Only the magnitude of the term is described and the compensatory effect of some terms is masked. For orthogonal aberrations, the RMS of whole or certain terms in the Zernike polynomials is calculated as

$$RMS = \sqrt{\sum (Z_n^m)^2} \qquad (2.3)$$

where RMS represents the wavefront error(s), Z is the Zernike coefficient of specific term, and m and n are the angular and radial orders, respectively.

In addition, for the ease of clinical understanding for practitioners, instead of wavefront presentation, Thibos (2001) also attempted to convert aberration measures (μm) into equivalent spherical defocus (D) using the equation

$$Equivalent\ defocus = \frac{-4\sqrt{3}Z_2^0}{r^2} \qquad (2.4)$$

where r is the radius of the pupil analysed and Z_2^0 is the Zernike coefficient of defocus, respectively.

2.2.3 Measurements

While there are many methods to measure aberrations of the eye (Carvalho et al., 2002; Atchison, 2005; Charman, 2005), the Shack-Hartmann wavefront aberrometer or equivalent remains the main one used to perform wavefront measurements, because of its robust, precise, and repeatable objective measurement properties (Liang et al., 1994; Cheng et al., 2003b; Salmon and van de Pol, 2005). It is able to measure the optical aberrations of the entire eye.

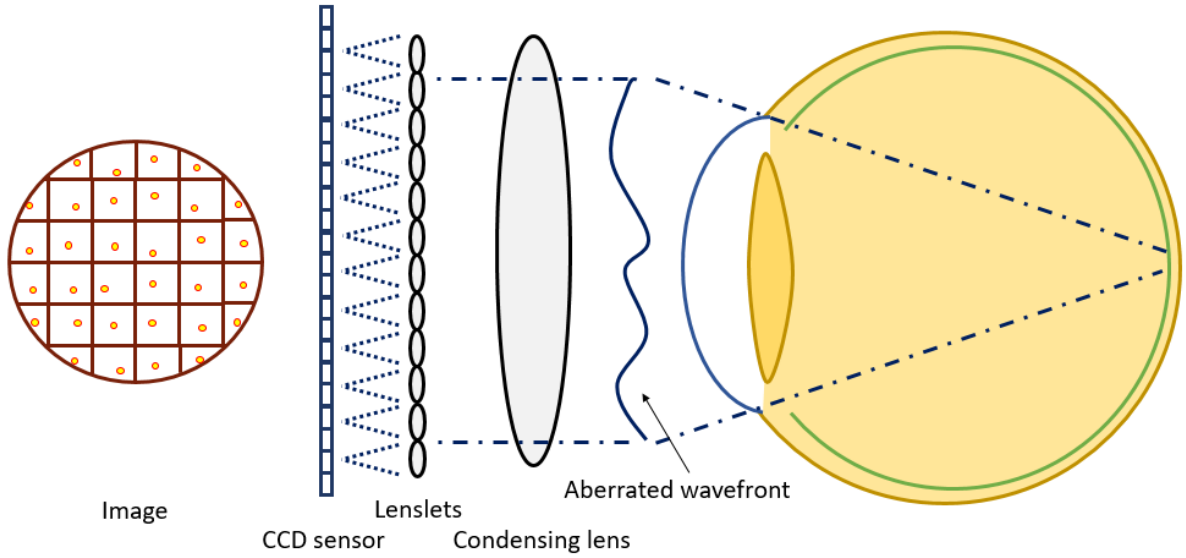


Figure 2.3 Basic design of a Shack-Hartmann aberrometer. Aberrated wavefront exits the eye and passes through a condensing lens and lenslets is captured. The displacement of each point on CCD sensors is calculated for the determination of wavefront aberration. The figure is adapted from Thibos (2000).

Figure 2.3 shows the basic design of the instrument, which projects a narrow, low energy infra-red light beam onto the retina. By the property of light reflection, the light bounces back and experiences local phase shifts along the pathway. With a microlens array placed on the pupil conjugate plane, the light coming from each small part of the pupil can be separated. Any misalignment of each point compared with a perfect wavefront can be captured using a CCD sensor in the focal plane of the microlenses. The relative displacement of each focused spot is linearly proportional to the slope of the wavefront error. After computational analysis for all the deviations, a Zernike polynomial can be generated to represent the optics of the eye.

2.3 Characteristics of ocular higher order aberrations

2.3.1 Compensation

Ocular aberrations in human eyes, based on the origins of the aberrations, can be further described as corneal (from the anterior cornea) or internal (mainly from the crystalline lens (Dubbelman et al., 2007)) aberrations (Equation 2.5). These aberrations have compensating properties, as they are usually opposite in signs (corneal: positive; internal: negative) (Artal and Guirao, 1998; He et al., 2003).

$$Ocular\ aberrations = Corneal\ aberrations + Internal\ aberrations \quad (2.5)$$

Artal et al. (2001) investigated aberrations measured from the cornea, the internal ocular optics, and the complete eye. They found that the corneal HO RMS was greater than that for the whole eye, which meant that the internal optics partially compensated for the anterior corneal optics, resulting in an improved retinal image. This compensatory effect is particularly pronounced for vertical coma (Z_3^{-1}), horizontal coma (Z_3^1), and spherical aberration (Z_4^0) (He et al., 2003; Kelly et al., 2004; Wang et al., 2005; Wei et al., 2006; Tabernero et al., 2007; Atchison and Markwell, 2008; Atchison et al., 2016). However, the internal compensatory effect is disturbed in older subjects, in whom the internal HOAs increased threefold, while corneal HOAs remain stable from age 20 to 70 years (Artal et al., 2002), potentially due to growth and age-related changes within the crystalline lens (Wang et al., 2005; Lyall et al., 2013; Namba et al., 2015).

2.3.2 Mirror symmetry

It is well documented that defocus and astigmatism are strongly correlated between the two eyes of an individual (Touzeau et al., 2003; Guggenheim et al., 2008; Li and Bao, 2014). Similarly, some HOA terms are highly, negatively correlated between the two eyes, known as mirror symmetry or optical enantiomorphism (Liang and Williams, 1997; Porter et al., 2001; Castejon-Mochon et al., 2002; Smolek et al., 2002; Thibos et al., 2002b; Wang et al., 2003b; Wang and Koch, 2003; Kelly et al., 2004; Gatinel et al., 2005; Wang et al., 2005; Lombardo et al., 2006; Plainis and Pallikaris, 2008; Bao et al., 2009; Hartwig and Atchison, 2012; Lyall et al., 2013; Oberholzer et al., 2014; Papamastorakis et al., 2015). Mirror symmetry along the vertical axis is suggested to be due to both anatomical and genetic factors (Porter et al., 2001). Mathematically, the signs of Zernike terms with positive odd (Z_3^1, Z_3^3, Z_5^1, Z_5^3, and Z_5^5; Table 2.1) and negative even m indices (Z_4^{-4}, Z_4^{-2}, Z_6^{-6}, Z_6^{-4}, and Z_6^{-2}; Table 2.1) for the left eye can be reversed and "flipped" over the y-axis for between-eye comparison (Porter et al., 2001; Atchison, 2004).

2.4 Factors affecting ocular higher order aberrations

Ocular HOAs vary from individual to individual and the sign of individual Zernike terms may vary between subjects (Porter et al., 2001; Castejon-Mochon et al., 2002; Wang and Koch, 2003; Amano et al., 2004; Wei et al., 2006). A number of ocular HOAs, especially for spherical and comatic aberrations, deviate significantly from zero (Porter et al., 2001; Thibos et al., 2002b; Atchison and

Markwell, 2008; Papamastorakis et al., 2015; Atchison et al., 2016). For example, Porter et al. (2001) examined 109 subjects (age range: 21 – 65 years) across a 5.7-mm pupil and found that the mean values of most HOA terms were close to zero, but spherical aberration (Z_4^0) was positive, in line with the findings of Carkeet et al. (2002) and Bao et al. (2009). Salmon and van de Pol (2006) analysed HOA measurements from 1433 subjects (mean age: 33.8 ± 7.8 years) over a 6-mm pupil and, in additional to spherical aberration (Z_4^0), all the third order aberrations (Z_3^{-3}, Z_3^{-1}, Z_3^1, and Z_3^3) were also found to be significantly different from zero. However, Hashemi et al. (2015) determined the distribution of Zernike coefficients in 577 subjects (mean age: 49.5 ± 5.7 years) over a 5-mm pupil and reported no significant difference from zero for spherical aberration (Z_4^0). A number of factors, including age and pupil size, may affect ocular on-axis HOAs, which are discussed in the following sections.

2.4.1 Ageing

A number of observational studies have demonstrated a linear relationship of total ocular HOAs increase with age (Guirao et al., 2000; McLellan et al., 2001; Artal et al., 2002; Kuroda et al., 2002b; Wang and Koch, 2003; Amano et al., 2004; Fujikado et al., 2004; Wei et al., 2006; Applegate et al., 2007; Atchison and Markwell, 2008; Berrio et al., 2010; Lyall et al., 2013; Wan et al., 2014; Namba et al., 2015; Zhang et al., 2018). Similar trends have also been observed for spherical (Smith et al., 2001) and comatic (Plainis and Pallikaris, 2008; Hashemi et al., 2015) aberration RMS.

Although some studies failed to show significant changes in corneal HOAs throughout adulthood (Artal et al., 2002; Amano et al., 2004; Fujikado et al., 2004), others reported a small increase with age in corneal HOAs (Oshika et al., 1999; Guirao et al., 2000; Wang et al., 2003b), particularly for comatic aberration RMS. Other studies have reported that internal HOAs, especially spherical aberration RMS, increase with age (Artal et al., 2002; Wang et al., 2005).

The increase in ocular HOAs with age is, therefore, primarily attributed to the loss of a compensatory effect between corneal and internal HOAs arising from age-related changes in the eyes, including, but not limited to, changes in anterior corneal asphericity (Brunette et al., 2003), lens refractive index gradient (Radhakrishnan and Charman, 2007), lens dimension (Glasser and Campbell, 1998), lens geometry (Berrio et al., 2010), and cataract formation (Kuroda et al., 2002a; Sachdev et al., 2004; Rocha et al., 2007).

Regarding the contribution of various HOAs over time, the majority of the above mentioned studies investigated changes in RMS error values. Salmon and van de Pol (2006) and Radhakrishnan and Charman (2007) examined individual Zernike terms and showed that spherical aberration (Z_4^0) gradually increased with age, whereas Atchison and Markwell (2008) noted that only horizontal coma (Z_3^1) decreased significantly with age.

Brunette et al. (2003) determined ocular HOAs in 114 subjects over a wide age range from 5.7 to 82.3 years and suggested a quadratic relationship between ocular HOAs and age: ocular HOAs decreased slightly in childhood, reaching a minimal level in middle adulthood, and then increased progressively in the elderly. This also applied to the changes in spherical and comatic aberrations RMS. In addition, these researchers measured the anterior corneal curvature and its asphericity and found that the corneal shape also varied with age, slightly flattening from childhood to adulthood before steepening in old age. Namba et al. (2017) confirmed this second-order relationship by adjusting for other possible confounding factors in their modelling analyses of 227 subjects (age range: 37 – 86 years), in line with the regression fit used by Salmon and van de Pol (2006) (n = 1433, mean age: 33.8 ± 7.8 years). Their findings were in agreement with the observation of a decreasing trend of ocular HOAs in children, compared with adults (He et al., 2002), and stable HOA levels in adults (Levy et al., 2005; Radhakrishnan and Charman, 2007).

There are inconsistencies between studies when analysing the changes in ocular or corneal HOAs over time (Levy et al., 2005), which may be explained by the incorporation of linear or quadratic modelling and limited sample size over a narrow age range.

2.4.2 Pupil size

The effect of pupil size on ocular HOAs has been well documented (Wang et al., 2003c; Salmon and van de Pol, 2006; Applegate et al., 2007). Since aberrations represent the wavefront error over a fixed pupil size, aberrations increase with a larger pupil size following a quasi-linear function. Therefore, when analysing wavefront error, it is important to consider the same pupil size for controlled comparisons between studies.

Many researchers have considered rescaling the Zernike coefficients from a larger pupil to smaller sizes for the ease of comparison between studies (Schwiegerling, 2002; Campbell, 2003; Dai, 2006). However, it should be noted that, on the contrary, scaling HOAs up to a larger pupil size may result in considerable variations, which are significantly different from the clinically measured values and this should be avoided (Ommani et al., 2014).

2.4.3 Refractive error

Numerous studies have investigated the association between HOAs and refractive error (Carkeet et al., 2002; Little et al., 2014; Hashemi et al., 2015). However, there is still no clear conclusion and their relationship remains equivocal. The inconsistencies reported between studies may be attributed to variations, in age, sample size, instruments used, ethnicity, control for accommodation, and pupil size.

2.4.3.1 Adults

In adults, some studies have demonstrated that hyperopic eyes display more HO RMS than myopic eyes (Llorente et al., 2004; Philip et al., 2012; Philip et al., 2018). Llorente et al. (2004) investigated a group of hyperopic and myopic young adults (n = 46, mean age: 30.4 ± 4.5 years) and showed higher levels of HO RMS, spherical and comatic aberrations RMS, and spherical aberration (Z_4^0) in hyperopes, compared with age-matched myopes. Additionally, Philip et al. (2012;

2018), in their analyses of over 600 adolescents (age range: 11.1 –19.0 years), reported that hyperopes had a higher level of spherical aberration (Z_4^0) than emmetropes and myopes, the latter two groups having aberrations of a similar magnitude, similar to the findings of Hashemi et al. (2015).

In contrast, some studies demonstrated an opposite trend in the relationship between HOAs and refractive status (Paquin et al., 2002; Yazar et al., 2014). Paquin et al. (2002) reported that myopes exhibited more HOAs, spherical, and comatic aberrations RMS in young adults (n = 35, age range: 18 – 32 years), compared with emmetropes. Yazar et al. (2014) examined 1034 subjects aged 18.3 to 22.1 years and found comparable associations of refractive error with HO RMS and comatic aberration RMS as Paquin et al. (2002).

However, most studies have demonstrated no association between HOAs and refractive errors (Collins et al., 1995; Porter et al., 2001; Cheng et al., 2003a; Zadok et al., 2005; Wei et al., 2006; Bao et al., 2009; Kwan et al., 2009; Karimian et al., 2010; Little et al., 2014; Wan et al., 2014). Nevertheless, the association between refractive error and spherical aberration (Z_4^0) cannot be precluded, because some studies have indicated that spherical aberration (Z_4^0) decreases with increasing myopia (Kwan et al., 2009; Hartwig and Atchison, 2012; Yazar et al., 2014; Papamastorakis et al., 2015).

2.4.3.2 Children

The association between refractive error and HOAs remains controversial in children. Some studies have reported that the magnitude of HOAs is higher in hyperopes compared with emmetropes (Martinez et al., 2009; Thapa et al., 2011). Thapa et al. (2011) noted a small, but significant correlation between HO RMS and refractive error (r = 0.23) in 423 emmetropic and hyperopic pre-school children. Martinez et al. (2009) also indicated that eyes with more hyperopia exhibited a higher level of spherical aberration (Z_4^0) (mean differences ranged between 0.02 ± 0.01 and 0.09 ± 0.02 μm for low, moderate, and high hyperopes, compared with emmetropes) in a large cohort of 634 children between six and 12 years old.

In contrast, other studies reported a higher level of ocular HOAs in myopes than hyperopes (He et al., 2002; Kirwan et al., 2006). He et al. (2002) determined a higher mean HO RMS in moderate myopes compared to age-matched emmetropes in their study (n = 170). A similar trend was also observed in the young adults in the same study (n = 146). These findings were supported by the work of Kirwan et al. (2006), who examined 82 children (age range: 4 – 14 years) and showed a higher level of vertical coma (Z_3^{-1}) in myopes, compared with hyperopes (mean difference: 0.08 ± 0.03 μm).

Other studies observed no significant difference in HOAs across different refractive groups (McLellan et al., 2001; Carkeet et al., 2002; Brabander et al., 2004; Li et al., 2012; Little et al., 2014; Zhang et al., 2018). Overall, therefore, it remains impossible to draw a consensus. Little et al. (2014) demonstrated negative associations between axial length and HO RMS and spherical aberration RMS (n = 313, mean age: 10.1 ± 0.4 years), and highlighted the importance of axial length when analysing HOAs. Zhang et al. (2018) investigated ocular HOAs in 1634 subjects aged from three to 17 years with refraction ranging from -10.00 to +8.25 D and did not observe any differences in Zernike coefficients or RMS error values among different refractive groups.

2.4.3.3 Anisometropia

Given that ocular HOAs vary with numerous factors making inter-subject variations substantial confounders, studying subjects with anisometropia (with significant refractive difference between their eyes in the absence of ocular pathology) may help towards the understanding of the relationship between refraction and HOAs.

However, similar to the findings for different ametropias, ocular HOAs in anisometropes remain ambiguous (Kwan et al., 2009; Tian et al., 2011; Vincent et al., 2011; Hartwig and Atchison, 2012; Hartwig et al., 2013). In early studies, Tian et al. (2011) compared the ocular HOAs in 15 young anisometropic myopes and showed that more myopic eyes exhibited more positive spherical aberration, but Kwan et al. (2009) demonstrated that eyes with less myopia were more aberrated in terms of HO RMS, third order aberration RMS, and spherical aberration (Z_4^0). Vincent et al. (2011) studied 34 myopic anisometropic young adults (mean age: 24 ± 4 years) with at least 1.00 D spherical equivalent difference between their eyes. They found no significant relationships between the interocular difference in corneal and ocular HOAs and the magnitude of anisometropia, which was confirmed by the findings of Hartwig et al. (2013) in 20 anisometropes (mean age: 43 ± 17 years).

2.4.4 Accommodation

HOAs change with accommodation, because of the geometric changes in shape and position of the crystalline lens (Brown, 1973; Koretz et al., 2002). Many studies have shown a consistent and significant increase of HO RMS during accommodation (Atchison et al., 1995; Collins et al., 1995; He et al., 2000; Ninomiya et al., 2002; Cheng et al., 2004). In order to investigate the origin of HOA changes, Li et al. (2011) evaluated the changes in RMS error values during accommodation in 42 subjects (n = 82 eyes) and found that internal spherical aberration RMS, but not corneal HOAs, increased significantly during accommodation. To examine the changes in HO RMS under different accommodative stimuli (0 to 6 D), He et al. (2000) measured the HOA responses during accommodation. They found that HO RMS decreased when the accommodative stimulus changed from 0 to approximately 3.00 D and then increased progressively with further stimuli, which was confirmed by later studies (Cheng et al., 2004; Buehren and Collins, 2006; Zhou et al., 2015). They noted that the changes were predominantly from Zernike coefficients of lower than or equal to the fourth order.

With respect to individual Zernike coefficients, during accommodation, there is a progressive shift in spherical aberration (Z_4^0) in the negative direction (less positive or more negative) (Atchison et al., 1995; He et al., 2000; Ninomiya et al., 2002; Cheng et al., 2004; Plainis et al., 2005; Collins et al., 2006b; Radhakrishnan and Charman, 2007; Lopez-Gil et al., 2008; Lopez-Gil and Fernandez-Sanchez, 2010; Ghosh et al., 2011; Li et al., 2011; Zhou et al., 2015), in agreement with the classic trend proposed by Koomen et al. (1949) and also the accommodation-dependent eye model suggested by Navarro et al. (1985). However, the trend was not always followed, as in the Atchison et al. (1995) study where only half of the subjects' measurements followed the trend. When considering the decrease in spherical aberration (Z_4^0) across different refractive error groups, Collins et al. (1995) compared 37 young subjects (21 myopes, 16 emmetropes; mean age: 21 ± 3 years) and showed that myopes presented a lower mean value of spherical aberration (Z_4^0). Their results were confirmed by Buehren et al. (2005) and Tarrant et al. (2010). However, the magnitude of the decrease over different accommodative stimuli was similar among myopes and emmetropes (Collins et al., 1995; Tarrant et al., 2010).

Other Zernike coefficients may also change during accommodation. For example, secondary spherical aberration (Z_6^0) changes slightly with accommodation (Ninomiya et al., 2002; Lopez-Gil and Fernandez-Sanchez, 2010; Ghosh et al., 2011; Li et al., 2011). In contrast, the effect of accommodation on coma remains inconclusive, with some studies reporting no change (He et al., 2000), whilst Plainis et al. (2005) showed a positive correlation between both vertical (Z_3^{-1}) and horizontal (Z_3^1) coma and accommodative response. Buehren et al. (2005) analysed near work induced HOA changes in myopia over a 4-mm pupil. They found that both vertical coma (Z_3^{-1}) and trefoil along 30° significantly changed after two hours of reading, with the eyes in downgaze position. Another study, examining the influence of downgaze on ocular HOAs over a shorter time (10 minutes), reported a shift to the negative direction for horizontal coma (Z_3^1) (Ghosh et al., 2011). Changes in HOAs during accommodation between primary and downward gaze suggest that the changes in coma are likely to be due to the changes in corneal optics resulting from the pressure of the eyelid in the downgaze position (Buehren et al., 2003; Collins et al., 2006a; Shaw et al., 2008).

The changes in HOAs during accommodation may vary with age. Lopez-Gil et al. (2008) investigated the relationship between HOAs and accommodation in 60 subjects covering a wide age range (mean age: 41.3 ± 13.1 years). They reported a higher rate of decrease (or negative shift) in spherical aberration (Z_4^0) in the older subjects. However, for natural pupil sizes, there were no significant differences between different age groups for the changes of HO RMS. They also reported an increase in a 4-mm pupil, which was similar to those reported in previous studies (Atchison et al., 1995; Collins et al., 1995; He et al., 2000; Ninomiya et al., 2002; Cheng et al., 2004). Their results suggested that the accommodative miosis is a potential adaptive mechanism of the eye to maintain retinal image quality during accommodation. Buehren and Collins (2006) also emphasised the important interaction between pupil size and HOAs affecting retinal image quality. Collins et al. (2006b) examined retinal image quality, taking the accommodation lag into account for analysis. They reported higher accommodation lags in myopes compared to emmetropes and highlighted the potential interaction between lower order and HOAs in reducing retinal image quality. Further, accommodation lead (over-accommodation at a low demand) and lag (under-accommodation at a high demand) (Morgan, 1952) were suggested by Lopez-Gil and Fernandez-Sanchez (2010) to be another compensating mechanism of the visual system to counteract the change of spherical aberration during the accommodation process in selecting the best image plane.

2.5 Influence of ocular aberrations on visual development

Emmetropisation refers to the regulatory mechanism for controlling eye growth and its refractive state towards emmetropia, which is the ideal, precise condition that results in the image of a distant object being focused on the retina without accommodation.

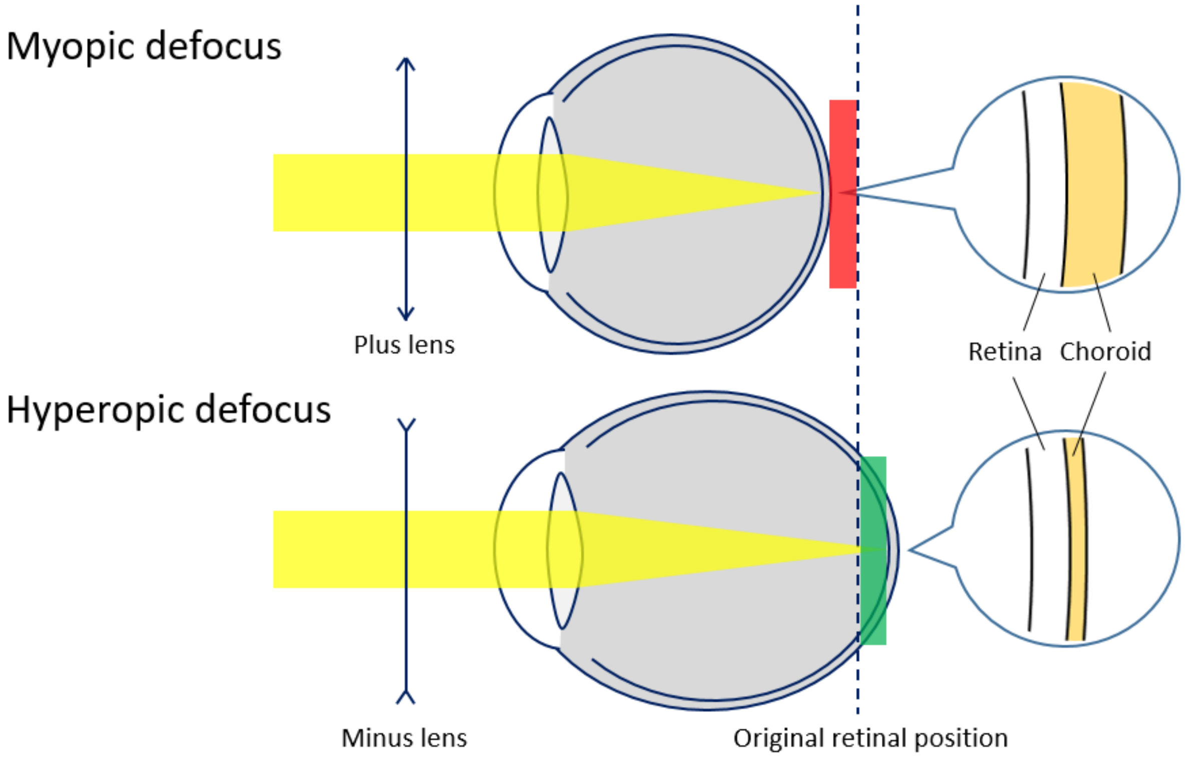


Figure 2.4 Illustrations showing axial and choroidal responses to defocus. Under myopic defocus (induced by plus lens), the choroid is thickened and axial shortening (red box) is observed, where under hyperopic defocus (induced by minus lens), the choroid is thinned and axial elongation (green box) is observed.

2.5.1 Effect of lower order aberrations

Evidence from a number of animal models, utilising chicks (Schaeffel et al., 1988), tree shrews (Norton et al., 2006), marmosets (Troilo et al., 2009), and rhesus monkeys (Smith and Hung, 1999), and other species (Wallman and Winawer, 2004), suggest that bidirectional changes in eye growth result from imposed defocus. Exposure to myopic defocus leads to axial shortening, while axial elongation occurs in response to hyperopic defocus (Figure 2.4). These studies demonstrated that emmetropisation is an active rather than passive process (Wallman and Winawer, 2004). The feedback mechanism from visual experience seems to provide some plausible clues to visual development as well as axial elongation, however, definite afferent and efferent pathways remain unclear (Troilo, 1992).

In human studies, transient and bidirectional changes in axial length (Read et al., 2010; Chakraborty et al., 2012, 2013; Delshad et al., 2020) and choroidal thickness (Chiang et al., 2015; Wang et al., 2016; Chiang et al., 2018), which are in reverse directions, responding to the imposed defocus have also been reported (Figure 2.4). In brief, Read et al. (2010) examined the changes in axial length and choroidal thickness in young adults (n = 28) with imposed monocular defocus (± 3.00 D) and the fellow eye with best refractive correction as control for 60 minutes. Small, but significant, changes of approximately 10 μm in axial length were observed. The choroidal thickness showed slightly smaller changes, but in opposite direction to that of axial length. Eyes under myopic defocus also exhibited more changes compared with those exposed to hyperopic defocus. Similar findings were reported in other studies on adults with different levels of defocus (within ±3.00 D) (Chakraborty et al., 2012, 2013; Chiang et al., 2015; Chiang et al., 2018; Delshad et al., 2020). Diurnal variations of axial length and choroidal thickness are also disrupted by imposed defocus (Chakraborty et al., 2012, 2013). Wang et al. (2016) also examined short-term choroidal thickness changes in 51 children (mean age: 12.2 ± 0.5 years) and showed consistent findings to those in adults. However, it would be of interest to investigate if there is a dose dependent relationship between the degree of defocus and choroidal response.

The regional changes in choroidal thickness in response to defocus were examined by Hoseini-Yazdi et al. (2019). When imposing myopic defocus (+3 D) in either the superior or inferior hemifield, the choroid exposed to the defocus thickened, more so than in the opposite hemifield. This implied the choroid was able to provide localised response to regional defocus consistent with animal models (Smith et al., 2010, 2013).

Researchers have attempted to study the influence of myopic defocus on slowing myopia progression and axial elongation. Li et al. (2015b) observed the effect of under-correction in 253 Chinese children (mean age: 12.7 ± 0.4 years) for one year. While, a smaller change in spherical equivalent refraction (SER) was weakly associated with the magnitude of under-correction ($r = 0.14$, $p = 0.02$), no association was observed for axial elongation ($r = 0.06$, $p = 0.38$). In addition, no significant differences in myopia progression or axial elongation were observed between children who were under-corrected, or those with full myopic correction. Another study followed 121 myopic children (mean age: 12.7 ± 0.5 years) with either full or no correction for two years (Sun et al., 2017b). They found that imposing myopic defocus, without refractive correction slowed myopia progression. However, the subjects were not randomised and the results could be affected by the variation in the time spent engaged in near work and outdoor activities. A retrospective analysis, on the contrary, showed a positive correlation between under-correction and myopia progression (Vasudevan et al., 2014). Some randomised clinical trials further attempted to arrest myopia progression by imposing myopic retinal defocus via incorporating under-correction of 0.50 – 0.75 D over one to two years (Chung et al., 2002; Adler and Millodot, 2006; Koomson et al., 2016). However, the results indicated that this accelerates or shows no effect on myopia progression in young myopes.

Phillips et al. (2005) evaluated the feasibility of arresting myopia progression by under-correcting the non-dominant eye of up to +2.00 D, while keeping the dominant eye fully corrected, in 13 children. After monitoring the subjects for up to 30 months, the inter-eye difference in myopia progression and vitreous chamber depth were 0.36 D/year and 0.13 mm/year, respectively. However, the study contained limited sample size, uncontrolled amount of myopic defocus, in terms of under-correction, and non-uniform follow-up schedule, and further randomised clinical trials are required to warrant the effect of monovision on slowing myopia progression.

Logan and Wolffsohn (2020) recently conducted a meta-analysis of nine studies and demonstrated no evidence of clinical benefits from using no correction, monovision, under- or over-correction. More frequent follow-ups and updates on refractive correction should be implemented in further studies to reduce the influence of potential under-correction presented between visits.

2.5.2 Effect of higher order aberrations

Despite no or low refractive error, Zadnik et al. (2004) found that in their 194 emmetropic subjects, aged between 6 and 14 years, axial elongation and changes in other ocular parameters, such as anterior chamber depth and vitreous chamber depth, were associated with age (in a logarithmic relationship). Zadnik et al. (2003) examined the refractive errors and ocular components (anterior chamber depth, lens thickness, vitreous chamber depth, and axial length) of 2583 schoolchildren and found that these parameters were also associated with sex. They also showed a trend of becoming less hyperopic or more myopic over time.

In their review on myopia control interventions, Saw et al. (2002) observed that in all the young myopic subjects optimally corrected with single-vision spectacles or contact lenses in the control groups, myopia progression still occurred (mean annual progression ranged from 0.30 to 0.93 D per year).

Since emmetropisation is a visually dependent process, one possible cue to myopia development is the visual signal in the form of a poor retinal image quality produced by the ocular HOAs (Collins et al., 1995; Liang and Williams, 1997; Campbell et al., 2002; He et al., 2002; Collins et al., 2006b). Wilson et al. (2002) demonstrated the ability of discriminating the point spread function, composed of different magnitudes of HOAs, in individuals. Buehren et al. (2007)

computed various simulations of different levels of spherical aberration (Z_4^0), vertical coma (Z_3^{-1}), and trefoil along 30°, and found that spherical aberration (Z_4^0) of 0.2 – 0.3 µm or more (over a 5-mm pupil size) is sufficient to result in a clinically significant correction (0.25 D) for optimisation of retinal image quality. Thibos et al. (2013a) also stressed the importance of the interaction between defocus and spherical aberration during accommodation had the potential role in guiding emmetropisation. They proposed that positive spherical aberration together with hyperopic defocus would result in a better contrast of retinal image. An alteration of this interaction to retinal image quality was also noted in another study investigating the predictive values of different optical quality metrics during accommodation (Tarrant et al., 2010). This combination may therefore provide a protective effect against myopia progression in young children.

A retrospective study (Zhang et al., 2013) examined the correlation between ocular HOAs and myopia progression in 148 Chinese children aged 6-16 years old, over a 6-mm pupil. The subjects were classified into fast and slow progressors, based on a split of annual progression 0.50 D/y. Fast progressors demonstrated higher levels of ocular HO RMS, third order aberration RMS, and more negative vertical coma (Z_3^{-1}). However, this study contains some methodological flaws. For instance, aberration data from both eyes was considered without proper statistical adjustment and follow-up visits were at arbitrary intervals between subjects. In addition, the aberrometer used may not provide highly repeatable measurements for HOAs (Dobos et al., 2009).

A few longitudinal studies have also investigated the association between HOAs and axial elongation or refractive development. Philip et al. (2014) monitored a total of 166 emmetropic adolescents (mean age: 17.1 ± 0.7 years) of mixed ethnicity for five years. They analysed ocular HOAs across a 5-mm pupil and showed that subjects with a myopic shift had lower levels of baseline third order and comatic aberrations RMS. Myopia progression was also associated with lower levels of spherical aberration (Z_4^0), fourth order aberration RMS, and a higher level of comatic aberration RMS. However, since the baseline HOAs were not statistically significant in the modelling analysis (p = 0.053), after adjustment for age, ethnicity, and follow-up time, they concluded that there was no significant association between HOAs and retinal image quality and myopia development and progression.

Hiraoka et al. (2017) investigated the relationship between HOAs and myopia progression in a younger myopic cohort of children (n = 64, mean age: 9.2 ± 1.6 years). They showed that faster myopia progression was associated with lower levels of corneal HO RMS, vertical coma (Z_3^{-1}), higher levels of horizontal coma (Z_3^1), and corneal spherical aberration (Z_4^0), when controlling for age in a multiple regression analysis. In the analysis using axial length, more positive ocular spherical aberration (Z_4^0) was also associated with less axial elongation, consistent with the suggestion by Little et al. (2014) on the importance of axial length when analysing spherical aberration.

However, it should be noted that eyes with a higher level of HO RMS tend to have poor retinal image contrast (Williams et al., 2000; Oshika et al., 2006; Zhao et al., 2017) and visual acuity (Applegate et al., 2003; Marcos et al., 2008).

The same RMS error value does not necessarily result in the same extent of reduction in visual quality, and the variation of acuity depends how the HOAs are mixed and combined (Applegate et al., 2003). Neural processing of the visual system, together with optical information, may also affect overall visual performance (Applegate et al., 2003; Thibos et al., 2004; Watson and Ahumada, 2008).

In conclusion, ocular HOAs vary with different factors and these may potentially be associated with refractive development in young children. By understanding the relationship between HOAs and axial eye growth and refractive development, specific modifications to optical interventions such as ortho-k to customise the HOA profile may be a future treatment option to enhance myopia control.

Chapter 3

Orthokeratology and higher order aberrations

3.1 The need for myopia control

Uncorrected refractive error is the leading cause of moderate-to-severe vision impairment and the second most common cause of blindness worldwide (Flaxman et al., 2017). The prevalence of myopia (SER ≤ -0.50 D) has also been reported to be alarming high in the population, especially in East Asian countries (Grzybowski et al., 2020). Yam et al. (2020) recently reported that at least one tenth of Hong Kong children aged six in their study were myopic, which was confirmed by Choy et al. (2020). Rudnicka et al. (2016) estimated that more than 80% of Hong Kong citizens would be myopic by the age of 18. It is also projected that almost half of the world population will become myopic by 2050 if no interventions are applied (Holden et al., 2016), of whom, one tenth will be highly myopic (SER ≤ -5.00 D). The risk of ocular complications, such as glaucoma, cataract, macular and other chorioretinal abnormalities, increases with the severity of myopia, which is associated with longer axial length (Zadnik, 1997; Gaurisankar et al., 2019; Leveziel et al., 2020). Bullimore and Brennan (2019) recently analysed 21000 patients from five population-based studies and showed that slowing myopia by 1.00 D reduces the risk of developing myopic maculopathy by 40%. The potential economic burden arising from myopia should not be underestimated (Naidoo et al., 2019). Therefore, a multifaceted system to slow myopia progression in early childhood is imperative (Ang et al., 2020).

A meta-analysis of the rate of myopia progression in 2194 spectacle-wearing children from 14 myopia intervention studies and six longitudinal clinical trials has shown that the estimated annual progression in Asians decreases from 1.32 D/y at the age of six to 0.50 D/y at the age of 12 (Donovan et al., 2012). However, the data was extracted mainly from the control subjects in previous studies and may not be representative, as children with higher progression rate may selectively opted to drop out to seek myopia control treatment. In addition, the progression rate may vary with different timings of the clinical studies. These discrepancies may explain the differences in myopia progression reported when compared with other studies (French et al., 2013; Chua et al., 2016; Zhou et al., 2016; Hsu et al., 2017; Kim et al., 2017; Wu et al., 2018).

Population growth curves based on cross-sectional data have also been used to predict the risk and progression of myopia. Chen et al. (2016a) constructed a population centile curve with 4572 Chinese children and showed that the progression rate was approximately -0.58 D/y on average over 5 – 15 years old. Sanz Diez et al. (2019) recently conducted a clinical growth curve for the axial length in 12554 Chinese children. The axial elongation (50th percentile) was about 1.22 mm for children aged between six and nine years and 0.67 mm for those between nine and 12 years. On the contrary, Tideman et al. (2018)

examined 12386 European children and demonstrated an axial elongation of 0.72 mm aged between six and nine years and 0.35 mm between nine and 12 years. Variation in ethnicity remains an important issue in affecting the predictive value of these tools.

In short, the major contributing factor to myopia progression is the age of onset (Jensen, 1995; Iribarren et al., 2009; Price et al., 2013; Sankaridurg and Holden, 2014; Chua et al., 2016). The earlier a child becomes myopic, the faster the rate of progression.

Whilst the nature and nurture debate continues, various genetic and environmental risk factors of myopia progression have been identified. Sanfilippo et al. (2010) conducted a meta-analysis and estimated the heritability (proportion of variation transmitted from the parents to the offspring) of both refractive error and axial length at 0.71. However, genome-wide association studies identifying more than 140 loci for refractive error only explain a small variance in refractive error (Verhoeven et al., 2013). A simple and direct way to access the risk of developing myopia or progression with respect to genetics is parental myopia. The odds ratio (OR) of having a myopic child if both parents are myopic can be up to 2.96 (95% CI: 1.53 – 2.39) (Zhang et al., 2015). The rate of axial elongation is also associated with the number of myopic parents (Lam et al., 2008). A pedigree analysis also demonstrated the importance of the degree of myopia of the parents in predicting myopia development and progression in their children (Wenbo et al., 2017). However, the interaction of genetics and environmental factors cannot be completely isolated (Fan et al., 2016).

In some genetics studies, the importance of a light-dependent signalling cascade as a driver to refractive development is highlighted (Tedja et al., 2018). An epidemiology study, investigating the prevalence of myopia in Caucasian and Asian children showed comparable results, suggested that not only genetics but environmental factors may also have some impact on myopia development and progression (French et al., 2013; Coviltir et al., 2019), in line with the suggestion arising from the analysis conducted by Wenbo et al. (2017). The two major potential environmental components are the time spent on outdoor activities and near work (Ramamurthy et al., 2015). Xiong et al. (2017) conducted a systemic review and demonstrated the dose-dependent protective effect of outdoor time on the onset of myopia. However, paradoxically, it did not slow the myopia progression. The mixed results may be affected by the seasonal variation in myopia progression (Gwiazda et al., 2014). Following positive findings in a randomised clinical trial, longer time spent on outdoor activities ($\geq$ 200 minutes per week) with relatively lower light intensity ($\geq$ 1000 lux) is recommended to reduce the myopic change (Wu et al., 2018), and this may reduce the number of children with reduced uncorrected visual acuity (Wu et al., 2020).

Near work is also associated with myopia (Huang et al., 2015). More near work is associated with a higher risk of myopia development (OR: 1.85, 95% CI: 1.31 – 1.62). Every dioptre-hour of near work per week is associated with 2% higher chance of having myopia. Some more studies also confirmed the association between near work and myopia development and progression (Pärssinen et al., 1989; Hepsen et al., 2001; Zhang et al., 2010; Lee et al., 2015; Li et al., 2015a; Wu et al., 2015; You et al., 2016; Hsu et al., 2017; Sun et al., 2018), yet a few studies yield no association (Saw et al., 2000; Low et al., 2010). Living conditions are also considered to be associated with myopia progression. In the review by Rudnicka et al. (2016), children living in urban areas demonstrated a higher risk of developing myopia (OR: 2.61, 95% CI: 1.79 – 3.86). This was later confirmed by other studies investigating the risk factors of myopia in terms of population density, housing environment, and home size (Wu et al., 2016; Choi et al., 2017).

Binocular vision may also be important in the onset and progression of myopia. Accommodation lag is believed to impose a hyperopic blur to the retina and stimulate the emmetropisation process, resulting in axial elongation and myopia progression (Gwiazda et al., 2004). Higher accommodation lag is found in myopes compared to emmetropes (Gwiazda et al., 1993; Mutti et al., 2006). However, this difference is only observed at the time of onset and cannot predict the rate of myopia progression (Mutti et al., 2006; Weizhong et al., 2008). Other studies did not show any association between accommodation lag and myopia progression (Berntsen et al., 2011; Berntsen et al., 2012). In addition, simply measuring accommodation error may not completely represent the retinal image quality due to the interaction between defocus and spherical aberration, as well as pupil size, involved during the process, which may increase the depth of focus (Buehren and Collins, 2006; Tarrant et al., 2010; Thibos et al., 2013b).

The accommodative convergence-to-accommodation ratio may also have some effects on myopia development because it tends to be higher before the onset of myopia (Gwiazda et al., 2005; Mutti et al., 2017), in spite of its clinically insignificant association with myopia progression (Correction of Myopia

Evaluation Trial 2 Study Group for the Pediatric Eye Disease Investigator, 2011).

Both genetic and environmental factors contribute to myopia development. Low et al. (2010) suggested that the development of early-onset myopia may be primarily driven by genetics and later associated more with environmental factors, while Morgan and Rose (2019) believed that environmental exposure, with observed variations among different societies, appears to be more relevant to myopia development. However, the relative influence of genetic and environmental factors in myopia development remains unknown. Practitioners should, therefore, comprehensively scrutinise the risk factors to rapid myopia progression and discuss with the parents what measures should be taken in order to best suit the situation of their children (McCrann et al., 2018).

3.2 Peripheral refraction and myopia

Relative peripheral refraction is defined as the refractive error difference between the central and peripheral retina (Hoogerheide et al., 1971; Rempt et al., 1971). In some animal studies, monkeys treated with foveal ablation showed central emmetropisation in response to induced defocus or form-deprivation (Smith et al., 2005; Smith et al., 2007; Smith et al., 2009). This indicates that central vision alone is not necessary for accurate refractive development. Peripheral refraction also influences the regulation of axial elongation in various animal models (Smith et al., 2009; Smith, 2011). In comparisons between human subjects of different refractive status, myopic eyes show relative peripheral hyperopia, whereas hyperopic eyes show relative peripheral myopia (Millodot, 1981; Mutti et al., 2000; Seidemann et al., 2002; Atchison et al., 2005; Chen et al., 2010b; Lee and Cho, 2013b). The variation in peripheral refraction in myopia is predominantly along the horizontal meridian rather than the vertical visual field (Atchison et al., 2006).

In order to study the influence of peripheral refraction on myopia development, Mutti et al. (2007) monitored almost a thousand children aged six to 14 years for 11 years. They found that emmetropes who became myopic showed more relative peripheral hyperopia at least two years before the onset of myopia. However, their follow-up study did not show any relationship between the relative peripheral hyperopia and myopia progression (Mutti et al., 2011). Some longitudinal studies further suggest that relative peripheral hyperopia is the result, rather than the cause, of myopia (Sng et al., 2011; Lee and Cho, 2013b; Atchison et al., 2015).

Rosén et al. (2012b) raised a concern about the misinterpretation of the findings of Hoogerheide et al. (1971), in which refraction data did not appear to be taken before myopia onset and the results did not indicate any pattern of myopia development. Atchison et al. (2015) further reviewed the five longitudinal studies mentioned above and suggested that relative peripheral hyperopia does not help to predict myopia development or progression in children. However, children involved in the analysis were cyclopleged and the effect of near work was not considered. The interaction between accommodation, changes in optics, and peripheral refraction may still be an important factor in myopia development to be established (Brennan and Cheng, 2019), particularly given the reported association between near work activities and the prevalence of myopia. Relative peripheral hyperopia may exert a mild protective effect against myopia development and progression (Atchison and Rosen, 2016), but the interaction with other confounding factors remains unclear.

The sensitivity to defocus, particular peripheral refraction, also remains questionable (Neil Charman and Radhakrishnan, 2010). Papadogiannis et al. (2020) recently examined the peripheral sensitivity to defocus with and without chromatic and HOAs in nine subjects. They found that, with HOA correction, the peripheral sensitivity was improved. However, it should also be noted that, despite less sensitivity to peripheral hyperopic defocus in myopes (Rosén et al., 2012a), low-contrast resolution acuity is better under hyperopic defocus (Radhakrishnan et al., 2004). The less reduction in spatial visual performance under hyperopic defocus observed in myopes (Radhakrishnan et al., 2004) could be explained by the incorporation of HOAs similarly observed under central defocus (Guo et al., 2008).

3.3 Introduction of orthokeratology

Orthokeratology (Ortho-k) was first introduced by Jessen (1962) as orthofocus treatment, where a flat fitting conventional polymethylmethacrylate contact lens was used for refractive correction. However, poor centration, instability, and unpredictability resulted in its unpopularity. In the late 1980s to early 1990s, the lens manufacturing process was ameliorated and the orthofocus lens was revolutionised into a three-zone, reverse geometry lens, including a flat central base curve, a steep intermediate curve, and a peripheral curve (Wlodyga and Harris, 1993). In recent decades, four or five curves lens designs significantly improved the fitting performance and outcomes. The introduction of high oxygen permeability lens materials has also significantly reduced the risk of hypoxic complications during overnight wear (O'Neal et al., 1984; Harvitt and Bonanno, 1999; Lin et al., 2002).

Due to the increasing prevalence of myopia globally, researchers have investigated different pharmacological and optical interventions to slow myopia progression (Saw et al., 2002; Maduka Okafor et al., 2009; Walline, 2015; Huang et al., 2016; Leo et al., 2017; Kang, 2018; Sankaridurg et al., 2018). Retrospective and prospective cohort studies (Cho et al., 2005; Walline et al., 2009; Kakita et al., 2011; Hiraoka et al., 2012; Santodomingo-Rubido et al., 2012; Chen et al., 2013; Downie and Lowe, 2013; Zhu et al., 2014b; Paune et al., 2015; He et al., 2016; Santodomingo-Rubido et al., 2017), randomised clinical trials (Cho and Cheung, 2012; Charm and Cho, 2013), and meta-analyses (Si et al., 2015; Sun et al., 2015; Wen et al., 2015; Huang et al., 2016; Li et al., 2016b; Li et al., 2017b; Prousali et al., 2019; Guan et al., 2020) have shown the effectiveness of ortho-k for myopia control to be approximately 50% (VanderVeen et al., 2019), compared with single-vision spectacles or soft contact lenses, over a two-year period. On average, axial elongation is slowed by 0.27 mm over a two-year period with ortho-k treatment (95% confidence interval [CI]: 0.23-0.32 mm) (Li et al., 2016b). Cho and Cheung (2017b) also reported a similar result based on two of their ortho-k clinical trials. Their analysis revealed that 50% of young children (aged 6 – 8) treated with ortho-k would be prevented from developing rapid axial elongation (> 0.36 mm/year). In addition, other ortho-k studies using twins (Chan et al., 2014), monocular correction (Na and Yoo, 2018; Tsai et al., 2019; Fu et al., 2020), and contralateral cross-over study design (Swarbrick et al., 2015) also confirmed the effectiveness of ortho-k for myopia control. Cho and Cheung (2017a) investigated the effect of discontinuation of ortho-k on myopia progression. Despite a potential rebound effect that was observed in subjects who stopped lens wear, compared with the control group or subjects continuing lens wear, resumption of lens wear slowed the axial elongation again.

Despite the variation in effectiveness (in terms of percentage) for myopia control, it should be noted that it is more important to consider the actual magnitude of reduction in axial elongation. For instance, in young children, who are faster progressors, a smaller reduction in effectiveness (%) but a larger reduction in axial elongation (mm) could still have a great impact (Cheung et al., 2019). Brennan and Cheng (2019) added that, in general, treatment effectiveness diminishes over time, and they suggested that both absolute (in mm) and relative (as percentage) treatment effectiveness should be presented. Conceiving an effective treatment simply based on percentage reduction may overestimate the actual progression and anticipated prevalence of high myopia.

Spectacle-free convenience and good unaided vision during the daytime provided by ortho-k treatment make it the most preferred option among parents (Cheung et al., 2014) and practitioners (Wolffsohn et al., 2016; Wolffsohn et al., 2020) in Asian countries. Patients can also benefit from good unaided visual outcomes (Cheung and Cho, 2004; Hiraoka et al., 2009b; Santolaria et al., 2013) and quality of life (Santodomingo-Rubido et al., 2013b). Daytime visual correction independence in subjects undergoing ortho-k is comparable with those treated with refractive surgery (Queirós et al., 2012). In addition, it does not come with dose-dependent adverse effects, such as photophobia and decreased near vision, associated with atropine eye drops (Gong et al., 2017; Yam et al., 2018). Although cases of keratitis are occasionally reported, the risk of infectious keratitis is similar to overnight soft contact lenses (about 14 per 10000) (Van Meter et al., 2008; Bullimore et al., 2013). The incidence of adverse events in ortho-k are also comparable with children using soft contact lenses for myopia control over a ten-year treatment period (Hiraoka et al., 2018).

3.4 Refractive correction and compression factor

The Food and Drug Administration (FDA) of the United States first approved the use of reverse geometry designed contact lenses from Contex Inc. (Sherman Oask, CA) for refractive correction. However, they were only approved for daily wear, and overnight use was not approved until 2002, for CRT™ lenses (Paragon Vision Sciences, Mesa, AZ). CRT rigid gas permeable contact lenses can reduce myopia and astigmatism up to 6.00 and 1.75 D, respectively, in young adults aged more than 18 years (Van Meter et al., 2008). In 2004, Euclid Systems Corp. (Herndon, VA) also received FDA approval for vision shaping treatment, with refractive correction up to 5.00 D myopia and 1.50 D astigmatism, with no age restriction (Van Meter et al., 2008). However, to date, no ortho-k lenses have been approved for myopia control and its current application for such purpose is off label.

Currently, ortho-k is generally accepted for temporary refractive correction for low to moderate myopia, although some studies have shown its capability of reducing myopia up to 6.00 D (Cho and Tan, 2019) or slightly more (Yu et al., 2020), astigmatism up to 3.50 D using toric lens designs (Paune et al., 2012; Chen et al., 2013; Luo et al., 2014), a certain amount of hyperopia (Gifford and Swarbrick, 2008; Gifford et al., 2009), or presbyopia using monovision (Gifford and Swarbrick, 2013). Most myopic correction occurs during the first week and becomes stabilised in the first month of lens wear (Swarbrick et al., 1998; Nichols et al., 2000; Alharbi and Swarbrick, 2003; Soni et al., 2003; Tahhan et al., 2003; Owens et al., 2004; Sorbara et al., 2005; Mika et al., 2007). In general, refractive error returns to approximately baseline levels around two weeks after cessation of lens wear (Soni et al., 2004; Kang et al., 2007; Wu et al., 2009).

For myopic ortho-k fitting, it is suggested that the base curve of the lens should be determined by the amount of targeted myopia reduction (Jessen, 1962). For example, in order to correct 3.00 D myopia, would require a lens 3.00 D flatter than the flattest corneal curvature. However, daily regression of the corneal flattening throughout the day should also be considered for clear daytime vision. Mountford (1998) first investigated the daytime regression in ortho-k treated subjects. He noted that the effect of refractive correction was temporary and there was a daily regression in the apical corneal power of 0.37 to 0.75 D. Other studies (Nichols et al., 2000; Soni et al., 2003; Barr et al., 2004; Johnson et al., 2007) also showed a similar refractive regression during the day. However, in a study investigating the performance of fenestrated and non-fenestrated ortho-k lenses (Cho et al., 2012), the authors did not find any significant changes in residual refraction throughout the day (< 0.25 D) using either lens design. Chen et al. (2010a) also found no significant changes in SER (mean changes: -0.06 ± 0.11 D) in 28 young adults (mean age: 23.1 ± 3.0 years) eight hours after lens removal.

The regression appeared to be larger in individuals with higher myopia (Barr et al., 2004), but was rather consistent regardless of the length of lens wear (Nichols et al., 2000). As a result, most manufacturers add an extra compression factor to the base curve of the lens so as to counteract the corneal rebound and corresponding refractive correction (Equation 3.1)

$$BOZR = K_f - T - CF, \qquad (3.1)$$

where $BOZR$ is the back optic zone radius of the lens, K_f is the flattest corneal curvature, T is the desired myopia reduction, and CF is the compression factor (all in dioptres).

Despite the use of a conventional compression factor of 0.50 to 0.75 D, researchers have shown a discrepancy between the attempted and achieved correction, and subjects tended to be under-corrected (Rah et al., 2002; Sorbara et al., 2005). Rah et al. (2002) found almost 10% of the subjects were under-corrected (SER < -1.00 D) after one month of lens wear, similar to the findings by Sorbara et al. (2005). Tahhan et al. (2003) investigated the corrective performance among four ortho-k brands and showed an under-correction of around 0.50 D (with no significant differences between brands) after one-month lens wear. Chan et al. (2008b) conducted a retrospective analysis of 63 ortho-k patients and investigated the validity of the compression factor. They showed that, based on a regression modelling analysis, the conventional amount is insufficient to obtain the desired end-of-day refraction and suggested increasing the compression factor to approximately 1.50 D. However, no other studies have verified this suggestion or the corresponding structural and optical changes to the eye associated with the increased compression factor.

3.5 Major ocular changes from orthokeratology

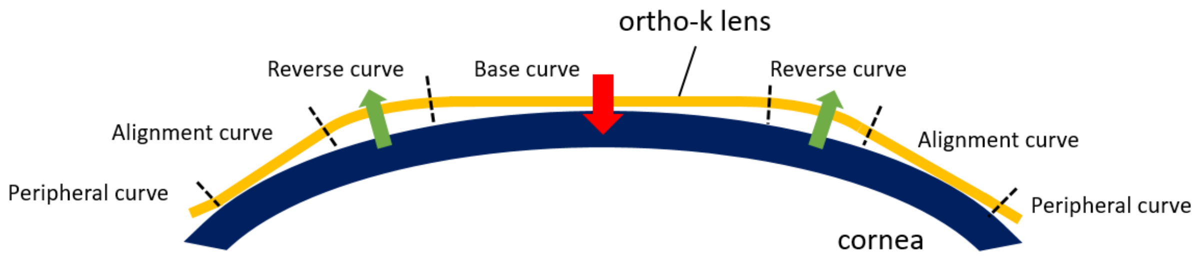


Figure 3.1 Structure of an orthokeratology lens on the cornea. Different curves of a lens and the directions of forces, from differences in hydraulic pressures, on the cornea are shown (green arrows: negative; red arrow: positive).

The base curve, reverse curve, alignment curve, and peripheral curve together form the basic geometry of an ortho-k lens (Figure 3.1). The base curve is flatter than the cornea and is determined by the targeted myopic correction and compression factor. The reverse curve assists corneal moulding and the alignment curve is designed for fitting and lens centration. The peripheral curve is associated with edge lift which allows tear change during open eye condition and facilitates lens removal. Due to the presence of different curves and uneven tear lens thickness amongst different regions underneath the lens, the difference in hydraulic pressure results in a positive compression force at the central cornea and a negative suction force against the mid-peripheral region. The central corneal tissue is pushed inwards, whereas the tissue near the mid-peripheral cornea is pulled outwards (Figure 3.1). Therefore, the corneal shape and structure is temporarily altered, and these changes are summarised below.

3.5.1 Corneal thickness

During ortho-k lens wear, the epithelial cells are first compressed at the central cornea and later redistributed to the mid-peripheral region (Abbott et al., 1998; Swarbrick et al., 1998; Alharbi and Swarbrick, 2003; Wang et al., 2003a; Choo et al., 2004; Haque et al., 2004, 2007; Reinstein et al., 2009; Nieto-Bona et al., 2011a, b; Lian et al., 2013; Lian et al., 2014; Kim et al., 2018; Swarbrick et al., 2020; Zhang et al., 2020), although Sridharan and Swarbrick (2003) found no significant thickening of the epithelium at the mid-periphery. The differences may be due to variations in study designs and measurement methods. Li et al. (2016a) conducted a meta-analysis involving 239 patients wearing ortho-k lenses and found a significant mean reduction in central corneal thickness of approximately 6 μm after one month of lens wear which persisted for one month. Most reduction was observed during the first week of lens wear. The amount of central corneal thinning is also proportional to the degree of myopia reduction (Swarbrick et al., 1998; Alharbi and Swarbrick, 2003; Kim et al., 2018). Interestingly, Lian et al. (2013) found mid-peripheral epithelial thickening at the temporal and nasal cornea while the superior mid-peripheral corneal epithelium thinned. Individualised investigation on the location of the cornea examined may be required since ortho-k lenses tend to decentre to the inferior and temporal cornea (mean decentration: 0.85 ± 0.51 mm) (Hiraoka et al., 2005; Hiraoka et al., 2009a).

In contrast, using optical coherence tomography (OCT), Kim et al. (2018) found almost 1% stromal thickening at the mid-peripheral cornea, which was consistent with other studies (Sridharan and Swarbrick, 2003; Alharbi et al., 2005). The absence of stromal thickening in the central cornea is probably due to the clamping effect between the lens-induced pressure and intraocular pressure (Alharbi et al., 2005). The normally observed lens-induced hypoxic corneal oedema may have therefore been prevented, or directed towards the mid-peripheral stroma.

3.5.2 Corneal curvature

Flattening of the central area and steepening of the mid-peripheral region of the anterior cornea are reported during ortho-k treatment (Swarbrick et al., 1998; Nichols et al., 2000; Sridharan and Swarbrick, 2003; Chan et al., 2008a; Tsukiyama et al., 2008; Villa-Collar et al., 2009; Zhong et al., 2009; Chen et al., 2010a; Queirós et al., 2010; Maseedupally et al., 2013). The cornea gradually changes from a prolate (steeper at the centre and flatter at the periphery) to an oblate shape (flatter at the centre and steeper at the periphery). The rate of corneal change is proportional to the amount of myopic correction (Villa-Collar et al., 2009; Kim et al., 2018). A greater flattening in the temporal central cornea, compared with the nasal region (Maseedupally et al., 2013; Zhong et al., 2014; Santodomingo-Rubido et al., 2018) is probably due to a tendency of ortho-k lenses to decentre (Hiraoka et al., 2005; Hiraoka et al., 2009a) on an asymmetric cornea (Dingeldein and Klyce, 1989; Modis et al., 2004; Li et al., 2017a; Gu et al., 2019).

The changes in corneal curvature are likely due to the redistribution of corneal epithelial cells. Corneal bending, however, does not seem to be the main factor causing refractive correction in ortho-k treatment. Most studies did not find significant changes in corneal sagittal height (Swarbrick et al., 1998), flattening in posterior corneal curvature (Tsukiyama et al., 2008; Chen et al., 2010a; Yoon and Swarbrick, 2013), or shortening in anterior chamber depth (Tsukiyama et al., 2008; Walline et al., 2009; Cheung and Cho, 2013, 2016), although a few studies found positive results regarding posterior corneal changes (Owens et al., 2004) and anterior chamber depth reduction (Gonzalez-Mesa et al., 2013). However, Owen et al. (2004) did not use cycloplegia, therefore failure to control for accommodation during the measurement may have resulted in shortening of the anterior chamber depth (Gonzalez-Mesa et al., 2013).

In addition, changes in refractive correction, corneal curvature, and corneal thickness fully recover after two weeks of lens discontinuation in subjects with short-term ortho-k (Soni et al., 2004; Kang et al., 2007; Villa-Collar et al., 2009; Wu et al., 2009), although some changes may be retained after long-term lens wear (Wu et al., 2009; Lee and Cho, 2013a; Santodomingo-Rubido et al., 2014), which further regress over time (Kobayashi et al., 2008; Lee and Cho, 2010). The time required for the cornea to return to its original shape is therefore likely to be dependent on the duration of the treatment.

3.5.3 Higher order aberrations

Since ortho-k treatment significantly changes the shape (geometry) of the anterior cornea, both corneal and ocular HOAs are also altered. Joslin et al. (2003) first studied the changes in ocular HOAs in 18 eyes of nine subjects (mean age: 34.4 ± 10.5 years) using 3- and 6-mm pupil sizes. After one-month ortho-k lens wear, HO RMS increased significantly (around 2.5 times) and was more prominent across the larger pupil. Further studies with larger sample sizes showed that the increase in HO RMS ranged between 0.03 and 1.04 μm (1.5 to 3.6 times) for 3- to 6.5-mm pupil sizes (Berntsen et al., 2005; El Hage et al., 2007; Hiraoka et al., 2007; Stillitano et al., 2007b; Hiraoka et al., 2008a; Hiraoka et al., 2008b; Stillitano et al., 2008; Anera et al., 2009; Gifford et al., 2013; Kang et al., 2013; Hiraoka et al., 2015; Chen et al., 2017; Santodomingo-Rubido et al., 2017; Sun et al., 2017a; Kim et al., 2019). The changes in corneal and ocular HOAs are similar in early lens wear, but there is a trend of dissociation over time (corneal > ocular), indicating a potential compensation mechanism from the internal optics (Gifford et al., 2013; Lian et al., 2014), which is discussed in the next section.

The most affected Zernike coefficient, spherical aberration (Z_4^0), increased (shifted positively) by two to seven times (Joslin et al., 2003; Berntsen et al., 2005; El Hage et al., 2007; Stillitano et al., 2007b; Stillitano et al., 2008; Gifford et al., 2013; Kang et al., 2013; Faria-Ribeiro et al., 2016a; Chen et al., 2017;

Santodomingo-Rubido et al., 2017; Kim et al., 2019). The amount increases as larger myopic correction is attempted, due to more corneal flattening and reduction in corneal asphericity (Joslin et al., 2003; Hiraoka et al., 2007; Gifford et al., 2013; Chen et al., 2017). Significant changes in horizontal coma (Lian et al., 2014; Faria-Ribeiro et al., 2016a; Chen et al., 2017; Kim et al., 2019) and vertical coma (Hiraoka et al., 2005; Faria-Ribeiro et al., 2016a; Chen et al., 2017; Santodomingo-Rubido et al., 2017; Kim et al., 2019) are likely due to lens decentration (Joslin et al., 2003; Hiraoka et al., 2005; Hiraoka et al., 2009a; Lian et al., 2014; Chen et al., 2018).

The increase in ocular HOAs, being positively correlated with the amount of myopic correction (Hiraoka et al., 2005; Hiraoka et al., 2007; Hiraoka et al., 2009a), probably results from the increase in corneal thickness at the mid-peripheral cornea (Lian et al., 2014). Therefore, changes in HOAs should be stabilised after one month of lens wear when most myopic correction has already taken place (Hiraoka et al., 2008a), and the majority of changes occurs in the first week of lens wear (Stillitano et al., 2007b; Stillitano et al., 2008). There is also a small variation in HOAs throughout the day, except for spherical aberration (Z_4^0) which decreases over time (Berntsen et al., 2005; Stillitano et al., 2007a).

On the other hand, the increase in HOAs does not significantly affect high-contrast visual acuity, but compromises low-contrast vision (Berntsen et al., 2005; Cheung et al., 2007; Hiraoka et al., 2007; Hiraoka et al., 2008a; Hiraoka et al., 2008b; Stillitano et al., 2008; Hiraoka et al., 2009a; Santolaria Sanz et al., 2015; Santolaria-Sanz et al., 2016; Chang and Cheng, 2019). The quality of vision also decreases with increasing lens decentration (Hiraoka et al., 2009a). Reversible recovery of contrast sensitivity is also observed after cessation of lens wear (Hiraoka et al., 2009c; Santolaria-Sanz et al., 2016). It should also be noted that the same extent of HO RMS does not necessarily generate an equivalent deterioration in visual acuity as interactions (or compensation) may be present between the various aberration terms (Applegate et al., 2002).

3.5.4 Accommodation

One potential reason for the larger corneal than ocular spherical aberration during the treatment, is the change in ocular accommodation, as the posterior cornea showed minimal changes in ortho-k (Tsukiyama et al., 2008; Chen et al., 2010a; Yoon and Swarbrick, 2013; Batres et al., 2020).

It is known that spherical aberration decreases (shifts negatively) with accommodation (Atchison et al., 1995; He et al., 2000; Ninomiya et al., 2002; Cheng et al., 2004; Plainis et al., 2005; Collins et al., 2006b; Radhakrishnan and Charman, 2007; Lopez-Gil et al., 2008; Lopez-Gil and Fernandez-Sanchez, 2010; Ghosh et al., 2011; Li et al., 2011; Zhou et al., 2015). Ortho-k wearers may slightly accommodate to compensate for the small degree of over-correction (hyperopia), which counteracts daytime regression, and results in less ocular compared to corneal spherical aberration. Tarrant et al. (2009) found increased accommodative responses and decreased accommodative lags in 28 myopic subjects after wearing ortho-k lenses for one month. Some small improvements in various measures of accommodation were also found in other studies (Ren et al., 2016; Gifford et al., 2017; Kang et al., 2018; Yang et al., 2018; Gifford et al., 2019).

A randomised clinical trial of 240 children attempted to investigate the changes in the accommodative response in children wearing single-vision spectacles, specially-designed spectacles, and ortho-k treatment (Han et al., 2018). The accommodation lag was significantly reduced and the accommodative facility was improved in children undergoing ortho-k for one year. A Chinese study (Zhu et al., 2014a) showed improved myopia control in children treated with ortho-k with a lower initial amplitude of accommodation, suggesting a relationship between accommodation and ortho-k, although this was disputed by others (Felipe-Marquez et al., 2015). Further investigations are warranted to better understand the effect of ortho-k on accommodation and binocular visual function.

3.5.5 Choroidal thickness

Axial shortening has been reported in some subjects undergoing ortho-k treatment. In a randomised clinical trial, Cho and Cheung (2012) found that 14% of older subjects (age range: 9 – 12 years) showed an axial shortening after two years of lens wear and a similar phenomenon was also reported in adolescents (mean age: 13.4 ± 1.9 years) wearing ortho-k lenses for six months (Swarbrick et al., 2015). The axial shortening may possibly be due to central corneal thinning and choroidal thickening (Swarbrick et al., 2015; Cho and Cheung, 2017b). However, changes in choroidal thickness after the treatment remain disputed.

Gardner et al. (2015) first analysed the choroidal changes in nine children (mean age: 13.6 ± 1.3 years) after nine months of ortho-k lens wear with an optical low-coherence reflectometry. However, the instrument appeared to come with high frequency of missing data, especially in children with a relatively thicker choroid. They also applied OCT in detecting the potential choroidal thickening but the changes were smaller than the 95% limits of agreement of around ±45 μm.

Chen et al. (2016b) investigated the changes in choroidal thickness in 77 (control: n = 38; ortho-k: n = 39) children (mean age; 10.3 ± 2.6 years) and showed an increase in choroidal thickness of approximately 20 μm after three weeks of lens wear, along with a weak association between choroidal thickening and axial shortening (correlation coefficient: -0.35). Another study (Jin et al., 2018) found a thickening of about 8 – 14 μm across the horizontal meridian in 30 children (mean age: 11.3 ± 1.7 years; correlation coefficients with axial length changes: -0.4 – -0.3) wearing ortho-k lenses for three months. Similarly, Li et al. (2017c) observed a choroidal thickening of about 15 – 20 μm in 30 children (mean age: 12.0 ± 1.7 years) wearing ortho-k lenses after one and six months. They also found stronger correlations between axial elongation and choroidal thickening (correlation coefficients: -0.64 and -0.67 at one- and six-month visits, respectively). In their later study (Li et al., 2018), they showed that the thickening was sustained after one year of ortho-k treatment. The amount of subfoveal choroidal thickening at the one-month visit was associated with the axial elongation at 13-month. However, this potential predictor of using choroidal thickness for myopia control effectiveness of ortho-k treatment requires further confirmation.

3.6 Mechanism of orthokeratology for myopia control

The mechanism by which ortho-k slows myopia progression is still debated. Different hypotheses for refractive development and axial elongation have been proposed.

3.6.1 Peripheral refraction

Peripheral defocus remains the most popular explanation as the mechanism of ortho-k treatment for myopia control. Relative peripheral myopia is induced when central myopic refractive error is corrected due to central corneal flattening and the annulus of mid-peripheral steepening.

Charman et al. (2006) first reported on the changes in horizontal peripheral refraction using an autorefractor in four adults who had worn ortho-k lenses for one to two weeks. Myopic correction decreased at a reduced rate towards the periphery within the central 20^{o}. Queiros et al. (2010) further confirmed this change of peripheral refraction in 16 myopic children. They added that the amount of myopia induced is proportional to the amount of baseline refraction, in line with the findings later reported by Gonzalez-Meijome et al. (2016) and Gifford et al. (2020a). The relative peripheral myopia is also induced in both horizontal and vertical directions (Kang and Swarbrick, 2016) and becomes stable after one month of lens wear (Gifford et al., 2020a).

Kang et al. (2013) endeavoured to change the lens parameters, by reducing the optic zone diameter and steepening the peripheral tangent of the lens, in order to alter the peripheral refraction. Gifford et al. (2020b) reduced the optic zone diameter and altered the back optic zone asphericity and intermediate lens curves, but the modifications did not result in any difference in peripheral refraction or corneal topography, in spite of a reduced treatment zone diameter (Gifford et al., 2020b). It seems to be a difficult task to manipulate the peripheral refraction induced by ortho-k treatment.

The alteration of relative peripheral refraction has also been observed in other studies investigating ortho-k (Kang and Swarbrick, 2011, 2013; Gonzalez-Meijome et al., 2016; Queirós et al., 2018; Gifford et al., 2020a) and soft multifocal contact lenses of +3.00 D add (Queiros et al., 2016). Interestingly, Ticak and Walline (2013) showed an increase in relative peripheral myopia in subjects undergoing ortho-k, but not in subjects wearing soft bifocal lenses of +2.00 D addition power.

Gifford et al. (2020a) examined the association of relative peripheral refraction and myopia progression in ortho-k treated children. They monitored 12 children (mean age: 13.2 ± 2.1 years) and eight adults (mean age: 23.4 ± 3.5 years) with low-to-moderate myopia for one year. However, they did not observe any relationship between changes in relative peripheral refraction and axial elongation. This negative result may be due to stable axial length throughout the study period, after commencement of ortho-k lens wear. Lee (2015) also found no association between peripheral refraction (at the post-treatment stabilised visit), retinal contour and central refractive changes nor any relationship with axial elongation in both spectacle-wearing and ortho-k treated children.

While open-field auto-refraction is a commonly used method for measuring peripheral refraction (Fedtke et al., 2009), its low repeatability (coefficient of repeatability at 30° temporal: ± 0.71 D in untreated eyes, ± 3.00 D in ortho-k treated eyes (Lee and Cho, 2012)) does not provide a reliable method to assess the association between peripheral refraction and axial elongation in ortho-k treatment, given the changes in peripheral refraction found at 30° are below 3.00 D (Queiros et al., 2010; Kang and Swarbrick, 2011; Kang et al., 2013; Gonzalez-Meijome et al., 2016; Queirós et al., 2018; Gifford et al., 2020a).

Kang and Swarbrick (2013) utilised a corneal topographer and measured peripheral corneal refractive power to indirectly investigate the effect of induced peripheral refraction on axial elongation. Both peripheral refraction and corneal refractive profile displayed a similar trend of changes.

Zhong et al. (2014) analysed the refractive power across the cornea in 27 children (mean age: 10.4 ± 1.2 years), and examined its association with the two-year axial elongation. A negative correlation between axial elongation and corneal relative peripheral power changes was identified. Their later study, of 64 ortho-k fitted myopic children (mean age: 9.6 ± 1.7 years), also demonstrated a similar relationship, after adjusting for age (Zhong et al., 2015). Lee et al. (2018) also found that the post-treatment relative peripheral corneal power was significantly correlated with slower axial elongation. They suggested peripheral refraction changes may be a possible mechanism of slowing myopia progression in ortho-k. Wang et al. (2018) developed a novel method to examine the effect of relative corneal refractive power in 55 children wearing ortho-k lenses. The modulation, determined by refractive power and corneal profile in terms of asymmetry and astigmatism, was found to be associated with better myopia control. Hu et al. (2019) also attempted to evaluate the total corneal power shift over the central 4-mm area. They showed that larger corneal power changes after one month of lens wear were associated with slower axial elongation at the one-year visit.

In contrast, Santodomingo-Rubido et al. (2018) did not demonstrate any association between relative changes in corneal power and axial elongation in 31 subjects (mean age: 9.6 ± 1.6 years). They attributed the discrepancies between studies to possible variations in pupil size, as the pupil controls and limits the amount of incoming light from the central and peripheral cornea. A larger pupil may also affect the changes in corneal and ocular HOAs. In other studies or modelling, subjects or eyes with larger pupil diameters tended to have better myopic control with ortho-k (Chen et al., 2012; Santodomingo-Rubido et al., 2013a; Faria-Ribeiro et al., 2016b), although this relationship was not found elsewhere (Wang et al., 2017; Kim et al., 2019). Further careful evaluation of the impact of pupil size may be warranted.

3.6.2 Higher order aberrations

A few longitudinal studies have investigated the effect of ocular HOAs on axial elongation in children undergoing ortho-k treatment. Santodomingo-Rubido et al. (2017) followed 29 children (mean age: 9.6 ± 1.6 years) who wore ortho-k lenses for two years. They measured corneal HOAs over a 5-mm entrance pupil, but did not find any association of the changes in the optical metrics with axial elongation. However, since the internal optics partially compensates for the increase in HOAs from the anterior cornea (Gifford et al., 2013; Lian et al., 2014), using corneal HOAs only may not reflect the actual retinal image quality which likely influences axial elongation.

Conversely, Hiraoka et al. (2015) determined the ocular HOAs across a 4-mm pupil in 55 children (mean age: 10.3 ± 1.4 years) treated with ortho-k for one year. They found that more changes in comatic aberration RMS were significantly correlated with slower axial elongation. They proposed that asymmetric corneal changes (coma), instead of a concentric and radial corneal profile (spherical aberration), was the most relevant factor in slowing axial elongation. Likewise, Kim et al. (2019) attempted to investigate the predictive factors associated with axial elongation in ortho-k wearers (mean age: 8.6 ± 0.8 years). They found that apart from baseline axial length and baseline refraction, asymmetric optical changes (presented as comatic aberration RMS) was also significantly associated with slower myopia progression. However, it should be noted that the ocular HOA data analysed in these two studies did not consider the interaction of HOAs and accommodation, which may be especially important in Asian countries where children commonly undertake extensive near work (Huang et al., 2015).

In short, there is no consensus on the mechanism underlying the myopia control effect of ortho-k treatment. Different proposed strategies may contribute together in various proportions, or interact with other factors in slowing down axial elongation. Among all the potential factors, studying the changes in ocular HOAs may be beneficial, because it may help understanding how optical changes induced by ortho-k affect the retinal image quality, and therefore axial elongation. The interaction of peripheral refraction and its interaction with accommodation lag and pupil size can be indirectly evaluated. However, a balance between visual quality and myopia control effect should be maintained, or there may be a trade-off between the pros and cons when using ortho-k lenses.

Chapter 4

Objectives and hypotheses

Despite their small magnitude relative to lower order aberrations, ocular HOAs can affect retinal image quality, although their influence on altering axial elongation in young children remains inconclusive (Section 2.5.2). Also, the mechanism underlying the myopia control effect of ortho-k remains unclear and there is no single persuasive explanation as yet (Section 3.6). Therefore, this thesis serves to investigate the relationship between ocular HOAs in axial elongation during childhood in primarily myopic spectacle-wearing and ortho-k treated children. If a positive association exists, after accounting for known confounding variables, modifications to lens designs, for example, increasing the compression factor of ortho-k lens, may be used to alter the induced ocular HOAs, and thereby improve the effectiveness of ortho-k for myopia control. The objectives and hypotheses of the corresponding experiments are outlined below.

Experiment 1 (Chapter 5):

Objective: To investigate the association between ocular HOAs and axial elongation and their predictive values of HOAs for axial elongation in a cohort of young children (irrespective of refractive error) monitored for two years.

Hypothesis: Higher levels of ocular HOAs will be associated with slower axial elongation in young children, after adjusting for other confounders such as age, sex, and SER.

Experiment 2 (Chapter 6):

Objective: To investigate the association between ocular HOAs and axial elongation in a cohort of young myopic children after receiving two-year ortho-k treatment.

Hypothesis: Ortho-k will significantly increase ocular HOAs and these changes will be significantly associated with axial elongation, after adjusting for other confounders such as age, sex, and baseline HOAs.

Experiment 3 (Chapter 7):

Objective: To investigate the short-term effect of modifying the compression factor of an ortho-k lens on ocular HOAs and choroidal thickness changes after one month of lens wear.

Hypothesis: Increasing the compression factor of ortho-k lenses by 1.00 D will increase the magnitude of myopia correction and increase ocular HOAs. A greater increase in choroidal thickness will also be observed with an increased compression factor.

Experiment 4 (Chapter 7):

Objective: To investigate the long-term effect of wearing ortho-k lenses with modified compression factor on myopia control, and the predictive values of HOAs at one month for axial elongation.

Hypothesis: Increasing the compression factor of ortho-k lenses by 1.00 D will alter the amount of myopia correction and ocular HOAs and result in greater slowing of axial elongation in ortho-k over two years. Changes in HOAs after one month of lens wear will be associated with axial elongation after two years of treatment.

Chapter 5

Ocular higher order aberrations and axial elongation in young children

5.1 Introduction

Ocular HOAs can potentially affect axial elongation by altering retinal image quality.

To date, only three studies have investigated the influence of ocular HOAs on axial elongation/myopia progression in children. However, they showed contradictory results. Philip et al. (2014) did not show any predictive value of baseline HOAs in estimating the development of myopia from emmetropia over a five-year period. Zhang et al. (2013) found a weak correlation between HO RMS, comatic aberration RMS, and myopia progression in a cohort of children monitored for one to three years. In contrast, Hiraoka et al. (2017) followed a group of schoolchildren for two years and found that higher level of HO RMS, spherical aberration RMS, and comatic aberration RMS were associated with slower axial elongation. Importantly, none of these previous studies accounted for multiple potential confounding variables in their analyses.

In this study, the association between ocular HOAs and axial elongation and the predictive values of HOAs for axial elongation in a cohort of children (irrespective of refractive error) monitored for two years were determined.

5.2 Methods

5.2.1 Study design

This is a retrospective anaylsis of the ocular HOAs and axial length measured annually over a two-year period. Subjects previously enrolled as the control group (irrespective of refractive error) in four two-year longitudinal clinical trials (Cho and Cheung (2012): 41; Chen et al. (2013): 23; Charm and Cho (2013): 16; Lee and Cho (2013b): 58) were included for analysis.

All studies were conducted according to the tenets of the declaration of Helsinki and were approved by the Departmental Research Committee, the School of Optometry of the Hong Kong Polytechnic University. Written informed consents were also obtained from both the parents and children. The studies were registered at ClinicalTrials.gov (Cho and Cheung (2012): NCT00962208; Chen et al. (2013): NCT00978692; Charm and Cho (2013): NCT00977236; Lee and Cho (2013b): NCT00978679).

5.2.2 Subjects and procedures

Subjects with myopia (≥ 0.50 D) were fully corrected with single-vision spectacles and emmetropes or mild hyperopes were left uncorrected.

All subjects underwent annual cycloplegic data collection – measurements were performed at least 30 minutes after instillation of 0.5% proparacaine, 1% tropicamide, and 1% cyclopentolate, one drop each separated by five minutes.

Axial length was measured using the IOL Master (model 500; Carl Zeiss Meditec AG, Jena, Germany). The average of five measurements, with an inter-reading difference of less than 0.02 mm and a signal-to-noise ratio of more than 3.5, was used for analysis (Cho and Cheung, 2012).

Monochromatic ocular HOAs for a wavelength of 555 µm were captured by a Shack-Hartmann aberrometer (Complete Ophthalmic Analysis System [COAS]; Wavefront Sciences Ltd., New Mexico, USA). The HOA data obtained from the COAS were fitted with a sixth order Zernike polynomial and rescaled to a fixed 6-mm pupil diameter. At least five measurements at each time point were averaged for each subject. HO RMS was computed as the total RMS values from the third to the sixth order terms. Spherical aberration RMS included terms Z_4^0 and Z_6^0, whereas comatic aberration RMS included the terms Z_3^{-1}, Z_3^1, Z_5^{-1}, and Z_5^1.

5.2.3 Statistical analyses

Data analysis was performed using right eyes only (SPSS version 23; IBM Corp., Armonk, NY. USA). Since the four different studies, which the subjects participated in, covered a relatively wide range of ages, a logarithmic transformation of age was performed for a better fit for modelling purposes (Zadnik et al., 2004). The association between ocular HOAs and axial length and axial elongation were assessed using a linear mixed model, which accounted for sporadic missing data. In the modelling, sex and SER were also included as confounders. Individual subject's slope and intercept were included as random factors to control for inter-subject variations. A backward stepwise approach was applied with the least significant factor(s) removed from the model. The Akaike information criterion was used as a metric to determine the relative fitness and quality of each model considered. The model was repeated using other RMS metrics and individual Zernike coefficients, respectively, to investigate the potential effect of specific terms or metrics. Since myopes and hyperopes may exhibit different HOAs and patterns of eye growth, the above stated linear mixed models were also repeated excluding hyperopes and emmetropes (myopia < 0.50 D).

In order to better evaluate the cause-and-effect relationship and predictive value of ocular HOAs in axial elongation, baseline demographics and data (age, sex, and SER) and baseline HOAs were included as fixed factors in further linear mixed models. The models were repeated for (Model 1) HO RMS, (Model 2) spherical and comatic aberrations RMS, and (Model 3) individual Zernike coefficients. The above modelling was performed in all subjects and in myopes only. A p value of less than 0.05 indicated statistical significance.

5.3 Results

Data of all subjects with axial length, ocular HOAs, and cycloplegic refraction over two years were retrieved. One subject was excluded due to poor COAS image quality, resulting in data from a total number of 137 subjects for analysis. Table 5.1 summarises the baseline demographics and data of the subjects from the retrospective analysis of longitudinal clinical trials. The subjects included in this analysis covered a relatively wide range of refractive errors, including low to high myopia, high astigmatism, and low hyperopia. Table 5.2 shows the baseline demographics, data, and HOA terms of the pooled subjects, respectively.

Table 5.1 Baseline demographics and data (mean ± SD) of control subjects (irrespective of refractive error) from four completed myopia control studies.

Studies	**Cho and Cheung (2012)**	**Chen et al. (2013)**	**Charm and Cho (2013)**	**Lee and Cho (2013b)**
Description	Low to moderate myopia	High astigmatism	High myopia	Low hyperopia and myopia
Sample size	40	23	16	58
Age, y	9.2 ± 1.1	9.4 ± 1.6	10.5 ± 1.1	7.8 ± 0.8
Myopia, D	2.23 ± 0.85	1.97 ± 1.26	6.34 ± 0.76	0.01 ± 1.41
Astigmatism, D	0.27 ± 0.34	1.76 ± 0.61	0.98 ± 0.35	0.34 ± 0.38
SER, D	-2.36 ± 0.87	-2.85 ± 1.27	-6.84 ± 0.85	-0.18 ± 1.37
Axial length, mm	24.40 ± 0.85	24.19 ± 1.02	25.97 ± 0.53	23.32 ± 1.02

SER: spherical equivalent refraction.

Table 5.2 Pooled baseline demographics, data, and higher order aberration control subjects (irrespective of refractive error) from four completed myopia control studies. Note: only subjects with available data at baseline are presented.

	Mean ± SD	Median	Range
Demographics and data (n = 137)			
Age, y	8.8 ± 1.4	8.6	6.1 – 12.6
SER, D	-2.04 ± 2.38	-2.00	-8.63-+2.50
Axial length (mm)	24.09 ± 1.24	24.10	21.35 – 27.06
Higher order aberrations (n = 128)			
Zernike coefficient, µm			
Z_3^{-3}	0.057 ± 0.120	0.054	-0.229 – 0.372
Z_3^{-1}	0.083 ± 0.175	0.064	-0.380 – 0.580
Z_3^{1}	0.004 ± 0.091	0.008	-0.226 – 0.225
Z_3^{3}	-0.019 ± 0.098	-0.029	-0.324 – 0.261
Z_4^{-4}	0.027 ± 0.033	0.027	-0.099 – 0.117
Z_4^{-2}	-0.023 ± 0.031	-0.021	-0.181 – 0.072
Z_4^{0}	0.076 ± 0.108	0.069	-0.174 – 0.349
Z_4^{2}	0.014 ± 0.061	0.020	-0.148 – 0.338
Z_4^{4}	0.026 ± 0.051	0.021	-0.093 – 0.268
Z_5^{-5}	-0.012 ± 0.021	-0.011	-0.091 – 0.046
Z_5^{-3}	0.001 ± 0.025	0.002	-0.153 – 0.080
Z_5^{-1}	0.015 ± 0.030	0.013	-0.091 – 0.098
Z_5^{1}	0.002 ± 0.016	0.002	-0.047 – 0.049
Z_5^{3}	0.005 ± 0.014	0.005	-0.037 – 0.043
Z_5^{5}	0.008 ± 0.020	0.008	-0.085 – 0.060
Z_6^{-6}	0.000 ± 0.013	0.000	-0.042 – 0.047
Z_6^{-4}	-0.005 ± 0.010	-0.003	-0.060 – 0.017
Z_6^{-2}	0.000 ± 0.008	0.001	-0.021 – 0.028
Z_6^{0}	-0.023 ± 0.018	-0.024	-0.076 – 0.042
Z_6^{2}	0.004 ± 0.014	0.002	-0.046 – 0.088
Z_6^{4}	-0.006 ± 0.014	-0.006	-0.042 – 0.069
Z_6^{6}	0.002 ± 0.018	0.000	-0.046 – 0.127
RMS, µm			
SA RMS	0.112 ± 0.076	0.091	0.015 – 0.352
Coma RMS	0.185 ± 0.112	0.159	0.023 – 0.583
HO RMS	0.320 ± 0.105	0.292	0.133 – 0.674

SER: spherical equivalent refraction, RMS: root-mean-square value, HO: higher order aberrations, SA: spherical aberration

5.3.1 Association between changes in ocular higher order aberrations and axial length/elongation

Table 5.3 shows the significant fixed effects and parameter estimates on the changes in axial length. The axial elongation (presented as the interaction with time) was also determined. The three models show the associations of axial length and axial elongation with (Model 1) HO RMS, (Model 2) spherical and comatic aberrations RMS, and (Model 3) individual Zernike coefficients.

Among all subjects (n = 137), in general, axial length increased with age ($p < 0.001$). Girls exhibited 0.27 – 0.28 mm shorter axial length, compared with boys ($p < 0.001$). Every dioptre increase (more myopic) in SER was associated with 0.31 – 0.32 mm increase in axial length ($p < 0.001$). Higher levels of HO RMS, vertical trefoil (Z_3^{-3}), and primary spherical aberration (Z_4^0), and a lower level of oblique trefoil (Z_3^3), were associated with a longer axial length (0.20-0.28 mm longer per 0.1 μm increase in these HOAs, all $p < 0.05$).

Regarding the association of HOAs with axial elongation, higher levels of HO RMS, spherical aberration RMS, vertical trefoil (Z_3^{-3}), and primary spherical aberration (Z_4^0), and a lower level of oblique trefoil (Z_3^3), were associated with slower axial elongation (all $p < 0.05$). Axial elongation was slowed by 0.10 – 0.13 mm/y per 0.1 μm increase in these HOAs.

Table 5.3 Significant fixed effects and parameter estimates of higher order aberrations on axial length and its elongation (interaction with time) in control subjects (irrespective of refractive error).

Parameters	All subjects (n = 137)		Myopes only (n = 113)	
	ß	p value	ß	p value
Model 1 – HO RMS				
Intercept	20.23	**< 0.001**	19.96	**< 0.001**
ln(age)	1.68	**< 0.001**	1.80	**< 0.001**
Sex†	-0.67	**< 0.001**	-0.60	**< 0.001**
SER	-0.32	**< 0.001**	-0.31	**< 0.001**
HO RMS‡	0.20	**0.046**	0.22	0.071
Time by HO RMS‡	-0.10	**0.030**	-0.11	**0.048**
Model 2 – SA and coma RMS				
Intercept	20.51	**< 0.001**	20.21	**< 0.001**
ln(age)	1.55	**< 0.001**	1.68	**< 0.001**
Sex†	-0.67	**< 0.001**	-0.60	**< 0.001**
SER	-0.31	**< 0.001**	-0.31	**< 0.001**
Time by SA RMS‡	-0.13	**0.037**	-0.16	**0.037**
Model 3 – individual Zernike terms				
Intercept	20.29	**< 0.001**	20.09	**< 0.001**
ln(age)	1.64	**< 0.001**	1.75	**< 0.001**
Sex†	-0.68	**< 0.001**	-0.60	**< 0.001**
SER	-0.31	**< 0.001**	-0.30	**< 0.001**
Individual Zernike terms‡				
Z_3^{-3}	0.25	**0.011**	0.22	0.085
Z_3^3	-0.28	**0.041**	-0.23	0.170
Z_4^0	0.26	**0.032**	0.33	**0.031**
Time by individual Zernike terms‡				
Time by Z_3^{-3}	-0.11	**0.012**	-0.10	0.064
Time by Z_3^3	0.13	**0.033**	0.11	0.122
Time by Z_4^0	-0.11	**0.032**	-0.14	**0.042**

SER: spherical equivalent refraction, RMS: root-mean-square value, HO: higher order aberrations, SA: spherical aberration.
Parameter estimates †for girls and ‡per 0.1 µm.

In myopic subjects (n = 113), similar results were obtained (Table 5.3). Axial length increased with age and SER, and was shorter in girls (all p < 0.001). A higher level of primary spherical aberration (Z_4^0) was associated with a longer axial length (0.33 mm longer per 0.1 μm increase, $p = 0.03$). Higher levels of HO RMS, spherical aberration RMS, and primary spherical aberration (Z_4^0) were associated with slower axial elongation by 0.11 – 0.16 mm/y per 0.1 μm increase in these HOA metrics or Zernike terms (all $p < 0.05$).

5.3.2 Predictive values of baseline higher order aberrations for axial elongation

Table 5.4 shows the association between baseline demographics and baseline HOAs with axial elongation. As expected, considering either model using all subjects with baseline HOAs ($n = 128$) or myopes only ($n = 104$), older children with less SER exhibited slower axial elongation (all $p < 0.001$). Girls tended to have 0.27 – 0.33 mm/y slower axial elongation than boys ($p < 0.001$).

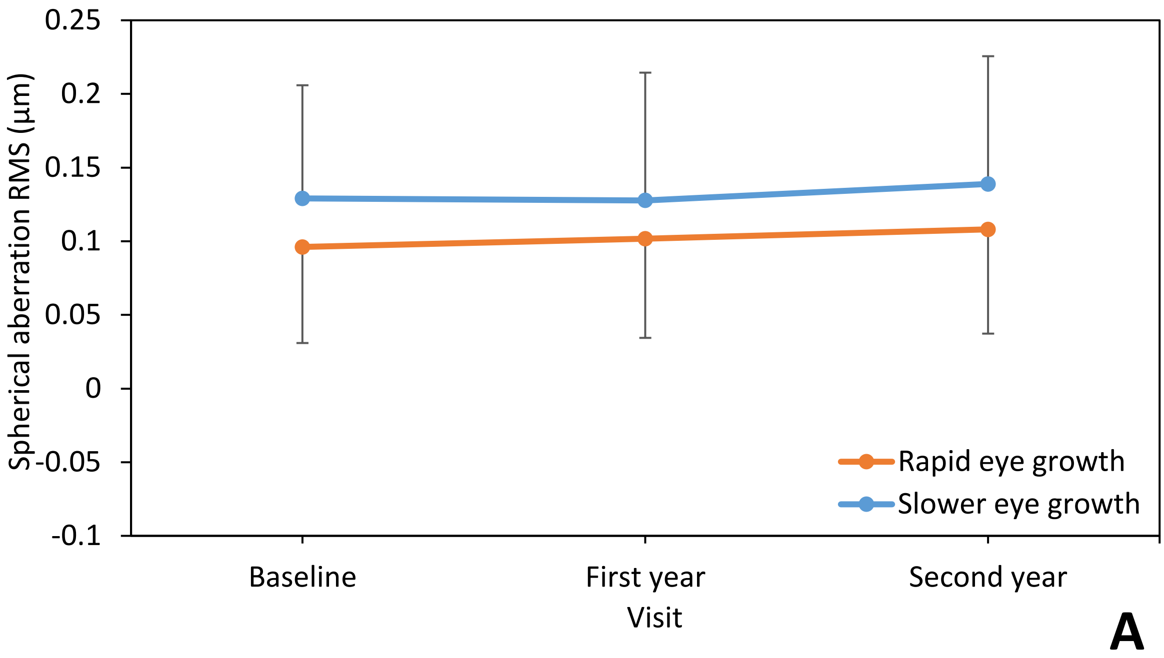
Regarding the influence of HO RMS, no significant association of its baseline level with axial elongation was found (both $p > 0.05$). In both models using spherical aberration RMS and corresponding Zernike terms, higher baseline levels of spherical aberration RMS and spherical aberration (Z_4^0) were associated with slower axial elongation (Figure 5.1, all $p < 0.001$). Every 0.1 μm increase in baseline spherical aberration RMS or baseline spherical aberration (Z_4^0) was associated with 0.14 – 0.15 mm/y slower axial elongation.

In addition, among all subjects, higher baseline levels of vertical trefoil (Z_3^{-3}) and oblique astigmatism (Z_4^2) were associated with 0.03 and 0.15 mm/y slower axial elongation per 0.1 μm increase in these HOAs, respectively (both $p < 0.05$).

Table 5.4 Significant fixed effects and parameter estimates of baseline higher order aberrations on axial length and its elongation (interaction with time) in control subjects (irrespective of refractive error).

Baseline parameters	All subjects (n = 128)		Myopes (n = 104)	
	ß	**p value**	**ß**	**p value**
Model 1 – HO RMS				
Intercept	23.08	**< 0.001**	23.45	**< 0.001**
Baseline ln(age)	-2.75	**< 0.001**	-3.05	**< 0.001**
Time by sex†	-0.30	**< 0.001**	-0.28	**< 0.001**
Time by baseline SER	-0.19	**< 0.001**	-0.16	**< 0.001**
Time by baseline HO RMS‡	-0.03	0.191	-0.03	0.213
Model 2 – SA RMS and coma RMS				
Intercept	21.89	**< 0.001**	22.21	**< 0.001**
Baseline ln(age)	-2.18	**< 0.001**	-2.48	**< 0.001**
Time by sex†	-0.29	**< 0.001**	-0.27	**< 0.001**
Time by baseline SER	-0.18	**< 0.001**	-0.16	**< 0.001**
Time by baseline SA RMS‡	-0.15	**< 0.001**	-0.14	**< 0.001**
Model 3 – individual Zernike terms				
Intercept	21.60	**< 0.001**	21.42	**< 0.001**
Baseline ln(age)	-2.04	**< 0.001**	-2.11	**< 0.001**
Time by sex†	-0.33	**< 0.001**	-0.32	**< 0.001**
Time by baseline SER	-0.19	**< 0.001**	-0.17	**< 0.001**
Individual Zernike terms‡				
Time by baseline Z_3^{-3}	-0.03	**0.031**	-0.04	0.360
Time by baseline Z_4^0	-0.15	**< 0.001**	-0.14	**< 0.001**
Time by baseline Z_4^2	-0.15	**0.006**	-0.12	0.093

SER: spherical equivalent refraction, RMS: root-mean-square value, HO: higher order aberrations, SA: spherical aberration.
Parameter estimates †for girls and ‡per 0.1 μm.



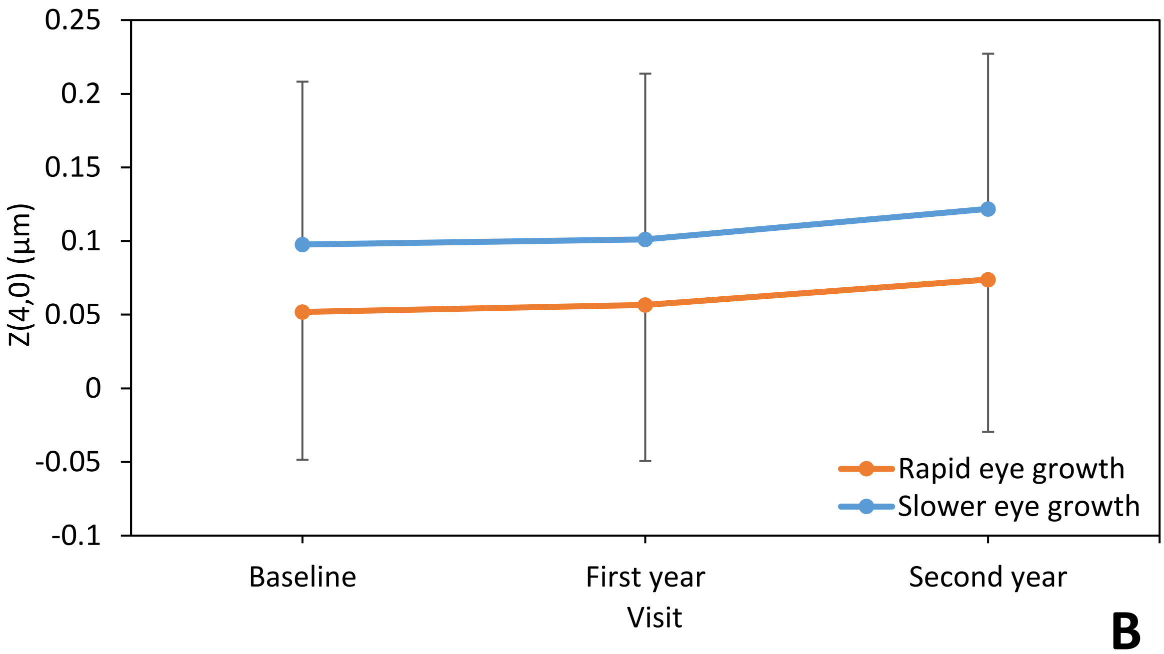


Figure 5.1 Changes in (A) spherical aberration RMS and (B) primary spherical aberration (Z_4^0) in subjects exhibited relatively faster (n = 64, mean: 0.45 ± 0.12 mm/y) and slower (n = 64, mean: 0.20 ± 0.07 mm/y) axial elongation, based on a median split of the axial elongation over the two-year period. Each error bar represents one standard deviation. RMS: root-mean-square value.

Figure 5.1 shows that unadjusted changes in spherical aberration RMS and primary spherical aberration (Z_4^0) in subjects with relatively faster (n = 64, mean: 0.45 ± 0.12 mm/y) and slower (n = 64, mean: 0.20 ± 0.07 mm/y) axial elongation. The subjects were separated into two groups based on the median rate of axial elongation. Subjects with relatively slower axial elongation exhibited significant greater levels of spherical aberration RMS and primary spherical aberration (Z_4^0) at baseline and throughout the study period (all $p < 0.05$).

5.4 Discussion

The current retrospective analysis of control subjects (irrespective of refractive error) of previous longitudinal clinical trials shows the association between ocular HOAs and axial elongation in Hong Kong children, after adjusting for other known potential confounding factors. Higher levels of HO RMS, spherical aberration RMS, and primary spherical aberration (Z_4^0) were associated with slower axial elongation.

The mean baseline HO RMS for a 6-mm pupil was 0.320 ± 0.105 μm, consistent with other studies (Kirwan et al., 2006; Zhang et al., 2018). The current study supported the hypothesis that HOAs could provide a directional cue to the visually driven mechanism for axial elongation (Wilson et al., 2002; Buehren et al., 2007). Compared to three previous studies on associations between ocular HOAs and axial elongation, the current study is only in agreement with the findings of Hiraoka et al. (2017). A higher level of HO RMS was associated with slower axial elongation. Hiraoka et al. (2017) showed that corneal HO RMS was the only significant factor associated with myopia progression and axial elongation, after adjusting for age. However, the HOA data they analysed was the average of five visits over two years and therefore the true temporal relationship between HOAs and axial elongation may not be reflected in their analysis. Conversely, Zhang et al. (2013) demonstrated a weak correlation between HO RMS and axial elongation in 148 eyes of 74 schoolchildren ($r = 0.19$). The ocular HOAs of the subjects with fast myopia progression (myopia progression ≥ 0.50 D/y) were 0.05 μm greater than those with slower progression. However, the ocular HOAs measured in Zhang et al.'s study were obtained using an aberrometer with a low level of repeatability (Dobos et al., 2009). In addition, they measured ocular HOAs only at the last study visit and used the data for the analysis which does not provide information on the causal nature of the relationship. Including data from both eyes may also inflate statistical associations (Armstrong, 2013) and may lead to any potential errors due to mirror symmetry between the eyes (Porter et al., 2001), if the sign of the individual Zernike coefficients is unaccounted for. Philip et al. (2014) monitored 166 emmetropic children over a five-year period and found no significant relationship between baseline HOAs and myopia development ($p = 0.053$). However, the axial elongation of those subjects was small (0.05 mm/y), compared with that of the subjects in the current study (0.33 mm/y). The borderline statistical insignificance and limited axial elongation presented in their subjects may mask the association between ocular HOAs and axial elongation.

Our findings showed that axial elongation decreased by approximately 0.1 mm/y per 0.1 µm increase in spherical aberration, in line with the study of Hiraoka et al. (2017), who showed that a higher level of spherical aberration was correlated with slower myopia progression and axial elongation. Our results were also in agreement with Philip et al.'s (2014) observation in a group of young emmetropes that, more positive spherical aberration was associated with less myopic shift. Positive spherical aberration may interact with hyperopic defocus (accommodation lag) which is commonly observed in progressing myopes (Abbott et al., 1998), and provide a protective effect against axial elongation (Thibos et al., 2013a). Although Little et al. (2014) showed that longer eyes exhibited less spherical aberration and HO RMS, Carkeet et al. (2002) demonstrated more positive spherical aberration in myopes, compared with hyperopes. These results were derived from using a cross-sectional study design where inter-subject variations might contribute to substantial variations (Porter et al., 2001).

On the other hand, trefoil terms (Z_3^{-3} and Z_3^{3}) were associated with axial length and its elongation. Carkeet et al. (2002) investigated ocular HOAs in more than 500 children of different refractive groups, and reported that myopes exhibited less vertical trefoil (Z_3^{-3}) than emmetropes and hyperopes, whereas in a study of more than 300 children, Little et al. (2014) observed that myopes displayed more vertical trefoil (Z_3^{-3}) and less oblique trefoil (Z_3^{3}) than hyperopes, which is consistent with the present study. Similarly, Hiraoka et al. (2017) demonstrated that comatic aberration RMS, which was characterised by asymmetrical corneal shape, tended to be the most relevant HOA terms among different significantly correlated aberrations associated with axial elongation.

Philip et al. (2014) also showed that emmetropic subjects without a myopic shift after five years possessed more comatic aberration RMS, although no significant association was observed between coma and axial elongation in the current study.

In view of the predictive values of ocular HOAs for axial elongation, a higher level of baseline spherical aberration (both RMS and individual Zernike coefficient) displayed a negative association with axial elongation (0.15 mm/y slower axial elongation per every 0.1 μm increase in baseline spherical aberration). This further supports the potential role of spherical aberration in providing a directional cue to the retina and hence the emmetropisation process from the visual input. Interestingly, no similar significant association was observed in HO RMS. This could be interpreted that, simply considering the magnitude of the overall HOAs (RMS values) may mask the impact of certain features of HOAs (i.e. the sign of the coefficients). This also highlights the importance of analysing individual Zernike terms in analyses related to axial elongation and myopia progression.

There were some limitations to the current study. The relatively limited sample size prevented further statistical analyses on the relationship between HOAs and axial elongation in different refractive groups. For example, subjects with astigmatism may behave differently as their cornea is intrinsically more toric and potentially the magnitude of comatic aberration (Hu et al., 2004). The current study serves as a general understanding of the influence of ocular HOAs on axial length and its elongation. In addition, the short two-year follow-up period may impede drawing any conclusion on how ocular HOAs are associated with myopia development, or when the critical period of ocular HOAs affecting axial elongation the most/least is. The HOA data used in the study was obtained after cycloplegia. Since the pupil constricts during accommodation and different levels of accommodation lag may be present in normal viewing conditions, further studies examining the association between ocular HOAs and axial elongation, without the use of cycloplegia and under different accommodation stimuli may help to provide a better insight on the vision-dependent mechanisms involved in axial eye growth.

5.5 Conclusion

This study provides insights into the potential visual feedback mechanism of ocular HOAs and axial elongation, when controlling for known confounding factors. Higher levels of HOAs, particularly spherical aberration, was associated with longer axial length and slower axial elongation. The findings support the potential role of HOAs as a vision-dependent mechanism of driving or slowing axial elongation.

Paper published from work reported in this chapter:

Lau JK, Vincent SJ, Collins MJ, Cheung SW, Cho P. (2018). Ocular higher-order aberrations and axial eye growth in young Hong Kong children. Sci Rep 8:6726.

Chapter 6

Higher order aberrations and axial elongation in myopic children treated with orthokeratology

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6.1 Introduction

In the experiment described in the previous section (Chapter 5), ocular HOAs were associated with axial elongation in children wearing single-vision spectacles. Children's eyes with higher levels of HO RMS displayed slower axial elongation. The finding supports the potential role of a vision-dependent mechanism in regulating the emmetropisation process and myopia development (Section 2.5.2 and Chapter 5).

Ortho-k treatment, which uses specially designed overnight wear contact lenses, retards axial elongation by approximately 50%. It is well known that ortho-k alters the corneal profile, that is, the central cornea is flattened while the mid-peripheral cornea is steepened. However, its mechanism for myopia control is not understood (Section 3.6).

Two longitudinal two-year studies have investigated the influence of induced HOAs of ortho-k on axial elongation, however, the results are inconsistent. Santodomingo-Rubido et al. (2017) showed no association between changes in corneal HOAs and axial elongation, whereas Hiraoka et al. (2015) found a significant relationship between changes in ocular HOAs and axial elongation in their regression analyses.

Therefore, this retrospective longitudinal study aimed to investigate the relationship between changes in ocular HOAs and axial elongation in children receiving ortho-k treatment for myopia control.

6.2 Methods

6.2.1 Study design

This is a retrospective analysis of ocular HOAs and axial elongation measured annually over a two-year period. Myopic subjects who previously completed longitudinal clinical trials and had been wearing ortho-k lenses for two years were included for analysis. The data from 112 subjects was retrieved (Cho and Cheung (2012): 37; Chen et al. (2013): 35; Charm and Cho (2013): 12; Lee and Cho (2013b): 28) and were included for analysis.

All studies were conducted according to the tenets of the declaration of Helsinki and were approved by the Departmental Research Committee, the School of Optometry of the Hong Kong Polytechnic University. Written informed consent was obtained from both the parents and children. The studies were also registered at ClinicalTrials.gov (Cho and Cheung (2012): NCT00962208; Chen et al. (2013): NCT00978692; Charm and Cho (2013): NCT00977236; Lee and Cho (2013b): NCT00978679).

6.2.2 Subjects and procedures

All subjects, except for high myopes from Charm and Cho (2013), with different levels of myopia and astigmatism were fully corrected with ortho-k lenses. The subjects from Charm and Cho (2013), were partially corrected by 4.00 D using ortho-k lenses and residual refractive error was corrected with single-vision spectacles. Annual cycloplegic data of axial length and ocular HOAs were collected as described in Section 5.2.2.

In brief, the average of five axial length measurements, with an inter-reading difference of less than 0.02 mm and a signal-to-noise ratio of more than 3.5, measured by IOL Master (model 500; Carl Zeiss Meditec AG, Jena, Germany) were analysed. At least five HOA measurements, measured by the COAS aberrometer (Wavefront Sciences Ltd., New Mexico, USA), were fitted with a Zernike polynomial up to the sixth order and rescaled to a 6-mm pupil. The Zernike coefficients were later averaged. The RMS values for total HOAs (from third to sixth orders, inclusively), spherical aberration (Z_4^0 and Z_6^0 combined), comatic aberration (Z_3^{-1}, Z_3^1, Z_5^{-1}, and Z_5^1), and corresponding Zernike terms were used for analysis.

6.2.3 Statistical analyses

To prevent the potential errors associated with mirror symmetry of HOAs (Porter et al., 2001) and the inflation of p values by using both eyes (Armstrong, 2013), analysis (SPSS version 23; IBM Corp., Armonk, NY. USA) was performed on data from the right eyes only. Repeated measures ANOVAs were used to compare the changes in axial length, SER, and ocular HOAs over time. Post hoc tests with Bonferroni corrections were presented for any identified significant variables.

Since ocular HOAs were shown to be associated with axial elongation in young spectacle-wearing children, linear mixed models were used to examine the effects of age, sex, and axial length (other models using SER separately were repeated to avoid multicollinearity) on baseline ocular HOAs. Individual subject's slope and intercept were included as random factors to control for inter-subject variations.

Similar to the linear mixed models described in Section 5.2.3, the association between ocular HOAs and axial elongation was examined. Baseline SER and baseline HOAs, in addition to sex and age, were added to the model to control for their influence on axial elongation. The above models were repeated for spherical aberration RMS, comatic aberration RMS, and corresponding Zernike coefficients. A p value of less than 0.05 was regarded as statistical significant.

6.3 Results

Data from 103 subjects, excluding those with missing baseline HOA data or poor COAS images, were retrieved. Table 6.1 shows the description and baseline demographics and data of subjects from studies included in the current study.

Table 6.1 Baseline demographics and data (mean ± SD or median [range]) of orthokeratology subjects from four completed myopia control studies.

Studies	**Cho and Cheung (2012)**	**Chen et al. (2013)**	**Charm and Cho (2013)**	**Lee and Cho (2013b)**
Description	Low to moderate myopia	High astigmatism	High myopia	Low hyperopia and myopia
Sample size	34	34	7	28
Age, y	9.3 ± 1.0	9.4 ± 1.4	10.6 ± 0.9	8.2 ± 0.9
Myopia, D	2.05 ± 0.75	2.49 ± 1.34	6.82 ± 0.95	3.11 ± 0.65
Astigmatism, D	0.00 [0.00, 1.00]	1.63 ± 0.60	0.61 ± 0.40	0.38 [0.00, 1.00]
SER, D	-2.17 ± 0.80	-3.30 ± 1.44	-7.13 ± 0.94	-3.33 ± 0.70
Axial length, mm	24.54 ± 0.68	24.35 ± 0.89	25.61 ± 0.71	24.42 ± 0.65

SER: spherical equivalent refraction

In the pooled population, there were 51 girls and 52 boys. The median (range) baseline age and baseline SER were 9.1 (6.3 – 13.0) years and -2.88 (-8.63 – -0.38) D, respectively. The mean baseline axial length was 24.52 ± 0.80 mm. Table 6.2 shows the demographics, data, and HOAs of the subjects with data available at all visits. Most parameters changed significantly in the first year and were stable thereafter. After two years of ortho-k treatment, the SER decreased by 2.63 ± 1.30 D ($F(1.28, 93.39) = 273.84$, $p < 0.001$) and the axial length increased by 0.41 ± 0.32 mm ($F(1.13, 100.52) = 137.02$, $p < 0.001$). The HO RMS, spherical aberration RMS, and comatic aberration RMS increased by 0.74 ± 0.56, 0.78 ± 0.51, and 0.17 ± 0.29 µm, respectively (HO RMS: $F(1.55, 124.17) = 103.32$, $p < 0.001$; spherical aberration RMS: $F(1.56, 124.40) = 140.72$, $p < 0.001$; comatic aberration RMS: $F(1.75, 139.57) = 19.52$, $p < 0.001$).

Table 6.2 Pooled demographics, data, and ocular higher order aberrations (mean ± SD) of orthokeratology subjects from four completed myopia control studies. Note: only subjects with available data at all visits are presented.

	Baseline	**First year**	**Second year**
Demographics and data			
Age, y (n = 91)	9.3 ± 1.3	10.4 ± 1.2	11.4 ± 1.2
SER, D (n = 74)	-3.11 ± 1.78	-0.61 ± 1.03	-0.48 ± 0.87
Axial length, mm (n = 90)	24.52 ± 0.82	24.75 ± 0.80	24.93 ± 0.82
Ocular higher order aberrations, µm (n = 81)			
HO RMS	0.306 ± 0.094	1.054 ± 0.637	1.045 ± 0.559
Spherical aberration RMS	0.093 ± 0.066	0.851 ± 0.554	0.876 ± 0.526
Z_4^0	0.061 ± 0.090	0.836 ± 0.544	0.862 ± 0.519
Z_6^0	-0.019 ± 0.016	0.082 ± 0.161	0.067 ± 0.161
Comatic aberration RMS	0.188 ± 0.114	0.414 ± 0.385	0.356 ± 0.264
Z_3^{-1}	0.111 ± 0.167	-0.044 ± 0.346	-0.077 ± 0.255
Z_3^1	-0.017 ± 0.080	0.156 ± 0.374	0.094 ± 0.291
Z_5^{-1}	0.021 ± 0.030	0.037 ± 0.106	0.050 ± 0.123
Z_5^1	0.003 ± 0.015	0.011 ± 0.150	-0.017 ± 0.126

SER: spherical equivalent refraction, RMS: root-mean-square value, HO: higher order aberration.

6.3.1 Influence of demographics and data on ocular higher order aberrations at baseline

In view of the influence of subject demographics and data on ocular HOAs at the baseline visit, using SER in the modelling, girls displayed a higher level of primary vertical coma (Z_3^{-1}: ß = 0.07 µm, p = 0.04), and more SER (more myopic) was associated with less horizontal coma (Z_3^1: ß = 0.01 µm/D, Z_5^1: ß = 0.003 µm/D, both p < 0.05). In both the modelling using baseline axial length and SER, older children showed less secondary vertical coma (Z_5^{-1}: ß = -0.01 µm/y, p = 0.02). No associations were found for other HOAs terms or metrics (all p > 0.05).

6.3.2 Association between changes in higher order aberrations and axial length

Table 6.3 shows the linear mixed model analyses for the association of axial length with (Model 1) HO RMS, (Model 2) spherical and comatic aberrations RMS, and (Model 3) spherical Zernike terms (Z_4^0 and Z_6^0). In general, axial length increased with age (p < 0.001). Girls exhibited 0.45 – 0.49 mm shorter axial length than boys (p < 0.005). Every dioptre increase (more myopic) in baseline SER was associated with 0.22 – 0.24 mm longer axial length (p < 0.001).

Regarding the influence of ocular HOAs during ortho-k treatment, after adjusting for baseline HOAs, HO RMS and spherical aberration were associated with an increase in axial length (HO RMS: ß = 0.96 mm/µm, spherical aberration

RMS: ß = 0.91 mm/μm, Z_4^0: ß = 0.99 mm/μm, all $p < 0.01$). Higher levels of HO RMS and spherical aberration were also significantly associated with slower axial elongation. Axial elongation was slowed down by 0.43, 0.39, and 0.46 mm/y per every micron increase in HO RMS, spherical aberration RMS, and Z_4^0, respectively (all $p < 0.01$). No association of axial length or its elongation were found with comatic aberration (neither RMS values nor individual Zernike coefficients).

Table 6.3 Significant fixed effects and parameter estimates of higher order aberrations on axial length and its elongation (interaction with time) in orthokeratology subjects (n = 103).

Parameters	ß	p value
Model 1 – HO RMS		
Intercept	19.00	**< 0.001**
Sex†	-0.46	**< 0.001**
ln(age)	2.33	**< 0.001**
Baseline SER	-0.24	**< 0.001**
HO RMS	0.96	**< 0.001**
Time by HO RMS	-0.43	**< 0.001**
Model 2 – spherical and comatic aberrations RMS		
Intercept	19.23	**< 0.001**
Sex†	-0.45	**0.002**
ln(age)	2.23	**< 0.001**
Baseline SER	-0.24	**< 0.001**
Spherical aberration RMS	0.91	**0.008**
Time by spherical aberration RMS	-0.39	**0.007**
Model 3 – spherical Zernike terms (Z_4^0 and Z_6^0)		
Intercept	19.30	**< 0.001**
Sex†	-0.46	**< 0.001**
ln(age)	2.28	**< 0.001**
Baseline SER	-0.22	**< 0.001**
Baseline Z_4^0	-1.42	**0.012**
Baseline Z_6^0	9.28	**0.012**
Z_4^0	0.99	**0.007**
Time by Z_4^0	-0.46	**0.004**

SER: spherical equivalent refraction, RMS: root-mean-square value, HO: higher order aberration.
†Parameter estimate for girls.

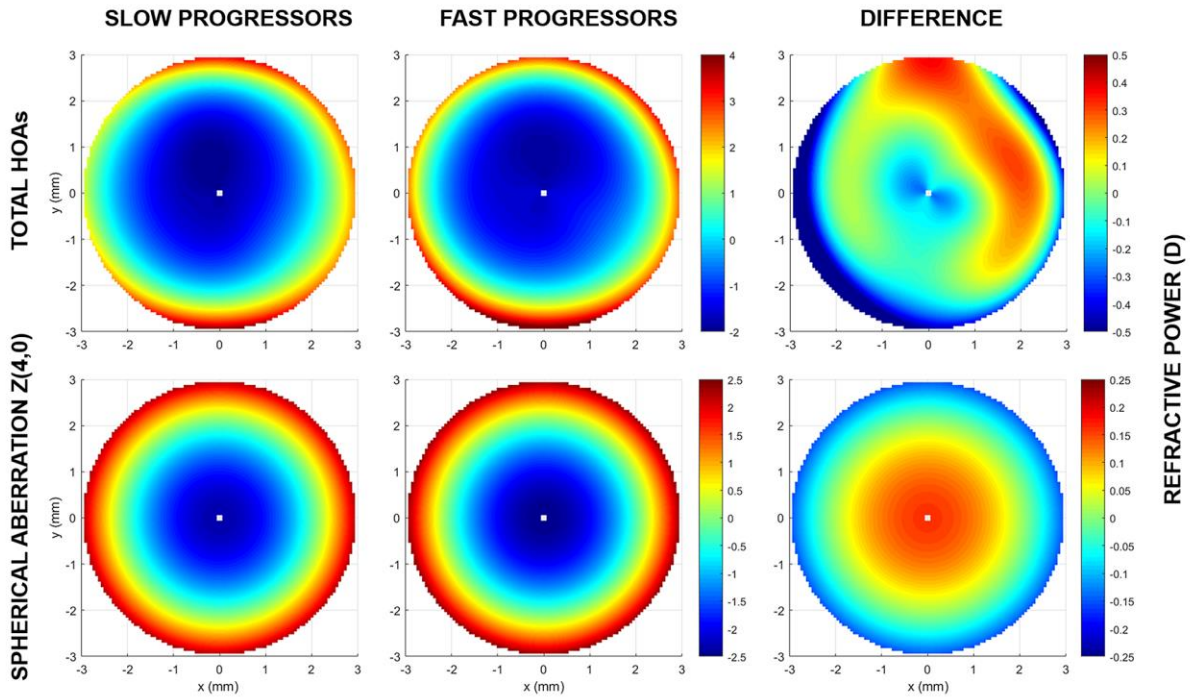


Figure 6.1 Refractive power difference maps (two-year visit minus baseline visit, left and middle columns) generated from the ocular higher-order aberration (HOAs) for subjects (with complete axial length and HOA data at the baseline and two-year visit) who exhibited relatively slower (n = 43, mean axial elongation: 0.19 ± 0.16 mm) and faster (n = 40, mean axial elongation: 0.67 ± 0.28 mm) axial elongation, based on a median split of the axial elongation. The difference maps (right column, slow minus fast progressors) highlight differences in the change in the HOA profile between the two groups. Note: the scales are adjusted for the HOA metric and term.

Figure 6.1 shows the refractive power difference maps (two-year visit minus baseline visit) generated from the HOA data (Iskander et al., 2007), for subjects with axial length and HOA data at the baseline and two-year visit who exhibited relatively slow (n = 43, mean elongation: 0.19 ± 0.16 mm) and fast (n = 40, mean elongation: 0.67 ± 0.28 mm) axial elongation over the two-year study period, based on a median split. This figure highlights that subjects who exhibited slower elongation exhibited a significantly greater increase in spherical aberration (Z_4^0) (consistent with Model 3 of Table 6.3, spherical aberration (Z_4^0) by time interaction). However, it should be noted that the data in this figure does not control for variations in age, sex, baseline SER, and baseline HOAs (or RMS) between the two cohorts (which was accounted for in the modelling).

6.4 Discussion

This retrospective analysis demonstrates the association between ocular HOA changes and axial elongation in children wearing ortho-k lenses. The current study supports that axial elongation may respond to subtle changes in visual input such as HOAs, which are known to affect retinal image quality and visual function (Yang et al., 2019). Subjects with greater changes in HOAs, particularly spherical aberration (Z_4^0), were associated with slower axial elongation.

The increase in HOAs after ortho-k treatment is well documented (Joslin et al., 2003; Berntsen et al., 2005; Stillitano et al., 2008; Gifford et al., 2013; Lian et al., 2014; Hiraoka et al., 2015). In the current study, HO RMS, spherical aberration RMS, and comatic aberration RMS increased by three, nine, and two times, respectively, after ortho-k treatment, whereas Gifford et al. (2013) observed a double in these RMS values (over a 4-mm pupil size) in 18 subjects (mean age: 21.1 ± 1.8 years) wearing ortho-k lenses for one week, and Hiraoka et al. (2015) reported a triple increase in the above mentioned RMS values (over a 6-mm pupil) in 59 subjects (mean age: 10.3 ± 1.4 years) wearing the lenses for a year. The increases may vary between studies because of various pupil sizes

(Carkeet et al., 2003; Applegate et al., 2007), subject age (Brunette et al., 2003), and follow-up time (Gifford et al., 2013; Lian et al., 2014).

In agreement with previous studies (Joslin et al., 2003; Chen et al., 2017), spherical aberration (Z_4^0) and horizontal coma (Z_3^1) changed the most after ortho-k treatment. The increase in spherical aberration is primarily due to the alteration of corneal asphericity from prolate to oblate shape which is proportional to the myopia correction (Gifford et al., 2013), and the increase in comatic aberration is related to the decentration of the treatment zone (Hiraoka et al., 2009a; Chen et al., 2018).

In the current study, the changes in ocular HOAs due to ortho-k were significantly associated with slower axial elongation. Conversely, Santodomingo-Rubido et al. (2017) did not find a relationship between corneal HOAs and axial elongation in 31 children (mean age: 9.6 ± 1.6 years) undergoing ortho-k treatment for two years, however, they did not adjust for other confounding factors such as age and sex. More importantly, corneal HOAs may not reflect the true retinal image quality, because of the compensatory characteristics of internal HOAs against corneal HOAs (Artal et al., 2001; Kelly et al., 2004). In contrast, Hiraoka et al. (2015) showed that the increase in ocular HO RMS was negatively correlated with axial elongation (r = -0.46), which is similar to our findings that, ocular HO RMS was associated with slower axial elongation, after adjusting for potential confounding factors such as age, sex, baseline SER, and baseline HOAs.

Spherical aberration was significantly associated with axial elongation in the current study. However, in both the studies of Hiraoka et al. (2015) and Kim et al. (2019), a higher level of comatic aberration, rather than spherical aberration, was associated with slower axial elongation. The authors concluded that an asymmetric optical effect induced by the treatment was responsible for its myopia control effect. However, simply selecting significant factors from correlation analyses without consideration of other confounding variables in a multivariate regression model may lead to incorrect conclusions (Armstrong, 2019). Multicollinearity might also present if both defocus (second order aberration) and SER were considered in the same regression model, due to their high correlation. The magnitudes of spherical aberration from these two previous studies were also extracted (using WebPlotDigitizer, https://automeris.io/WebPlotDigitizer/) and rescaled to a 6-mm pupil for comparison (Schwiegerling, 2002). The mean changes in primary spherical aberration (Z_4^0) in the studies of Hiraoka et al. (2015) and Kim et al. (2019) were +0.51 and +0.34 μm, respectively, which are considerably smaller than that of +0.80 μm found in the current study. The difference may be due to different myopia corrections between the studies (current study: 3.11 D, Hiraoka et al. (2015): 1.78 D, Kim et al. (2019): 2.59 D). However, in our study, even after controlling for the baseline SER, more spherical aberration was significantly associated with slower axial elongation, indicating a potential link to the underlying visual mechanism of ortho-k.

According to a computational algorithm using different Zernike coefficients that vary significantly following reading (Buehren et al., 2005), Buehren et al. (2007) showed that the influence imposed by 0.2 – 0.3 μm spherical aberration requires a clinically significant change in defocus to optimise retinal image quality (0.25 D for a 5-mm pupil), equivalent to 0.4 – 0.6 μm over a 6-mm pupil diameter. The interaction between spherical aberration and defocus may also change the retinal image quality (Tarrant et al., 2010). Positive spherical aberration, in combination with hyperopic defocus, which is commonly seen in ortho-k treated children or young myopes with a lag of accommodation during near work (Gwiazda et al., 1993; Gwiazda et al., 1995), would provide a protective effect against axial elongation, whereas those with negative spherical aberration and hyperopic defocus may be a risk factor (Thibos et al., 2013a).

In comparison to the association between ocular HOAs and axial elongation in spectacle-wearing children (Chapter 5) and those undergoing ortho-k treatment, the beta coefficients of ocular HOAs in both modelling were smaller than the coefficients for age, sex, and SER. However, it should be noted that, after receiving ortho-k treatment, ocular HOAs increased substantially by a factor of three to nine (even 14 times for primary spherical aberration). This would therefore increase the impact of ocular HOAs on slowing axial elongation, comparing with those wearing single-vision spectacles.

Other researchers have endeavoured to slow axial elongation by manipulating the HOA profile. Allen et al. (2013) examined the myopia control effect using a contact lens which changes the spherical aberration of subject to -0.1 μm, because of its previously reported improvement in reducing accommodation lag (Allen et al., 2009; Gambra et al., 2009; Theagarayan et al., 2009). However, the authors were unable to confirm the role of negative spherical aberration or reduced accommodation lag in retarding axial elongation. A possible reason for such negative findings could be that the interaction between the induced negative spherical aberration and the reduced accommodation lag produces an unfavourable retinal image or directional cue of slowing down the progression. Sankaridurg et al. (2019) recently examined the myopia control effect of an extended depth-of-focus contact lens (+1.25 and +1.75 D) with specific HOA profiles (details not provided) in over 500 children (mean age: 10.4 ± 1.3 years). They showed a modest effect (25 – 28%) of 0.15 – 0.17 mm slower axial elongation, compared with children using single-vision contact lenses, over a two-year period. On the other hand, Cheng et al. (2016) examined the use of a contact lens with positive spherical aberration of about 0.175 µm (for a 5-mm pupil) for myopia control in 127 children (mean age: 9.2 ± 1.1 years). A moderate effect (39%) of 0.14 mm shorter axial elongation, compared with the single-vision contact lens group, was observed at the one-year visit. Summarising the findings of previous research and the current study, positive spherical aberration is associated with slower axial elongation. It should be noted that the amount of spherical aberration induced by ortho-k treatment is much larger (+0.39 µm over a 5-mm pupil in the current study, compared with approximately +0.20 µm or less in previous studies). The effect of using spherical aberration for myopia control may be dose dependent as observed for atropine eye drops (Yam et al., 2018). The dose-and-effect relationship and the "minimum effective dose" for myopia control are yet to be investigated and further studies in this aspect are warranted.

Since baseline HOAs are associated with axial elongation (Chapter 5), the relationship between ocular HOAs and other demographics at baseline was evaluated. Most HOA metrics and Zernike terms (except for horizontal coma [Z_3^1 and Z_5^1]) were not associated with axial elongation in this cohort of subjects. These parameters were controlled in the linear mixed models of the current study to avoid any potential confounding effects. However, one limitation of the current study was the relatively small sample size. This study serves as a general understanding to the ocular HOAs on axial elongation in myopic subjects undergoing ortho-k treatment.

6.5 Conclusion

This study examined the relationship between ocular HOAs and axial elongation in subjects undergoing ortho-k treatment. Subjects with greater changes in ocular HOAs, especially a positive shift in primary spherical aberration, were associated with slower axial elongation, after adjusting for known confounding factors and baseline HOAs. Optical alteration of specific ocular HOAs may be a possible mechanism of ortho-k treatment for myopia control.

Paper published from work reported in this chapter:

Lau JK, Vincent SJ, Cheung SW, Cho P. (2020). Higher-order aberrations and axial elongation in myopic children treated with orthokeratology. Invest Ophthalmol Vis Sci 61:22.

Chapter 7

The short-term influence of orthokeratology lenses with different compression factors

7.1 Introduction

Given the association between ocular HOAs and axial elongation in spectacle-wearing (Chapter 5) and ortho-k treated (Chapter 6) children, modifications to ortho-k lenses to alter the magnitude of ocular HOAs may result in a greater myopia control effect.

As previously mentioned (Section 3.4), the commonly used compression factor of 0.50 – 0.75 D may not be sufficient to ensure full correction at the end of the day, and ortho-k subjects are usually under corrected. Chan et al. (2008b) therefore suggested adding an extra compression factor of approximately 1.00 D to the lens to counteract the daytime refractive regression. However, no studies have investigated its feasibility and the influence of an increased compression factor on ocular HOAs.

Axial length is the gold standard for monitoring myopia progression in clinical myopia control trials (Wolffsohn et al., 2019). However, its changes usually require months to demonstrate any difference. The choroid, as a thin, vascular tissue located posterior to the retina, which has been shown to be a short-term biomarker which responds to imposed defocus (Read et al., 2010; Chakraborty et al., 2012, 2013; Chiang et al., 2015; Wang et al., 2016; Chiang et al., 2018), and negatively associated with the changes in axial length (Read et al., 2015), may provide a quantitative method to predict the potential changes, prior to longer-term changes in axial length. However, the repeatability of OCT measurements need to be determined to confirm any significant changes in choroidal thickness.

This study therefore aimed to investigate the weekly changes in ocular HOAs and corresponding changes in choroidal thickness in eyes wearing ortho-k lenses of different compression factors for one month.

7.2 Methods

7.2.1 Study design

This was a prospective, double-blinded, randomised, self-controlled (contralateral comparison) clinical trial investigating the influence of ortho-k lenses with different compression factors on ocular HOAs in young myopic children. The fellow eyes of the subjects were randomly fitted with ortho-k lenses of different compression factors (one eye with 0.75 D and the other eye with 1.75 D) and were monitored weekly for one month. All the study protocols followed the tenets of the Declaration of Helsinki and the study was approved by the Departmental Research Committee of the School of Optometry of The Hong Kong Polytechnic University. The nature and possible consequences of the treatment were explained, and written informed consent was obtained from the parents before the commencement of the study. The study was also registered at ClinicalTrial.gov (NCT02643875).

7.2.2 Subjects

Subjects were recruited via an advertisement in a local newspaper posted from February to June 2016. Telephone interviews and screening examinations were performed to examine if the subject fulfilled the inclusion or exclusion criteria. Chinese children aged between six and less than 11 years, with low myopia (0.50 – 4.00 D, inclusive), low astigmatism (≤ 1.25 D), low anisometropia (≤ 1.00 D), and low corneal toricity (< 2.00 D), were recruited. Subjects with any prior history of myopia control treatment, ocular or systemic conditions that affect refractive development, contact lens wear, or non-compliance to ortho-k lens wear and follow-up schedules were excluded. Both the parents and the children received training on lens handling and cleaning procedures. Randomisation of the lenses assigned on each eye were performed only when both the parents and the children were competent in demonstrating proper handling procedures.

7.2.3 Lens parameters and solutions

Eligible subjects were fitted with four-zone ortho-k lenses, of either spherical or toric lens design (Menicon Z Night lenses; NKL Contactlenzen B.V., Emmen, The Netherlands), on both eyes. The lenses were made of hyper-oxygen permeability (Menicon Z, Dk 163 [ISO unit]), and the parameters were determined, with the aid of a computerised software (Easyfit, version 2013; NKL Contactlenzen B.V., Emmen, The Netherlands) based on the subjective refraction, horizontal visible iris diameter, and corneal topography, to minimise any subjective bias in lens selection or adjustment. Full correction was ordered for the eye with conventional compression factor (0.75 D), and an additional 1.00 D correction was ordered for the fellow eye assigned to the increased compression factor (1.75 D). The subjects wore the lenses on a daily overnight basis and a lens wear diary was given for recording the time and duration of lens wear.

The subjects were required to clean and rub the lenses every day and perform weekly protein removal procedures (cleaner: Menicon Spray and Clean; disinfecting solution: MeniCare Plus; protein removal solution: Menicon Progent A & B; Menicon Co., Ltd., Nagoya, Japan). Saline (Ophtecs cleadew; Ophtecs Corp., Tokyo, Japan) and artificial tears (Precilens Aquadrop+; Precilens, Creteil, France) were provided for lens rinsing and cushioning the lenses before insertion to avoid any formation of air bubbles.

7.2.4 Visits and examination procedures

Ortho-k lenses were dispensed at the baseline visit and weekly data collection visits were conducted for one month. The subjects also had to attend any other unscheduled aftercares necessary to have their vision and ocular health monitored. Except for the first overnight visit which was scheduled within two hours after waking, the data collection visits were performed at a similar time to the baseline (within 2 hours) to minimise the potential influence of diurnal variation.

At each data collection visit, unaided and best-corrected visual acuities (ETDRS charts, 90% contrast; Precision Vision, Woodstock, IL, USA), non-cycloplegic subjective refraction, and external ocular health condition were assessed by an unmasked examiner. Maximum plus for maximum visual acuity approach was used for the determination of refractive errors, and ocular health was evaluated using the Efron grading scale (Efron, 1998).

Corneal topography was measured by a masked examiner. The average apical corneal power from four good images (score ≥ 98) was obtained from a corneal topographer (E300 videokeratoscope; Medmont Pty. Ltd., Vermont, Victoria, Australia).

Ocular HOAs were collected by the same masked examiner at each visit. One hundred and twenty-five images of ocular HOAs through natural pupils were captured using the COAS aberrometer (Wavefront Sciences Ltd., New Mexico, USA). A Badal optometer, aligned via a beam splitter but external to the measurement beam of the instrument, with a Maltese cross as the target was set at the SER of the subject to control for accommodation, and the fellow eye was occluded to maintain good central fixation during the measurement. Each captured HOA image was then fitted with a sixth order Zernike polynomial over a 5-mm pupil size, and each Zernike coefficient was later averaged. The signs of some Zernike coefficients (Z_3^1, Z_3^3,Z_4^{-4}, Z_4^{-2}, Z_5^1, Z_5^3, Z_5^5, Z_6^{-6}, Z_6^{-4}, and Z_6^{-2}) for the left eyes were reversed to account for mirror symmetry between the eyes (Porter et al., 2001; Gatinel et al., 2005) to ensure all eyes were analysed as right eyes. The HO RMS (from third to sixth orders, inclusively), spherical aberration RMS (Z_4^0 and Z_6^0 combined), comatic aberration RMS (Z_3^{-1}, Z_3^1, Z_5^{-1}, and Z_5^1 combined), and individual Zernike coefficients were also used for analysis.

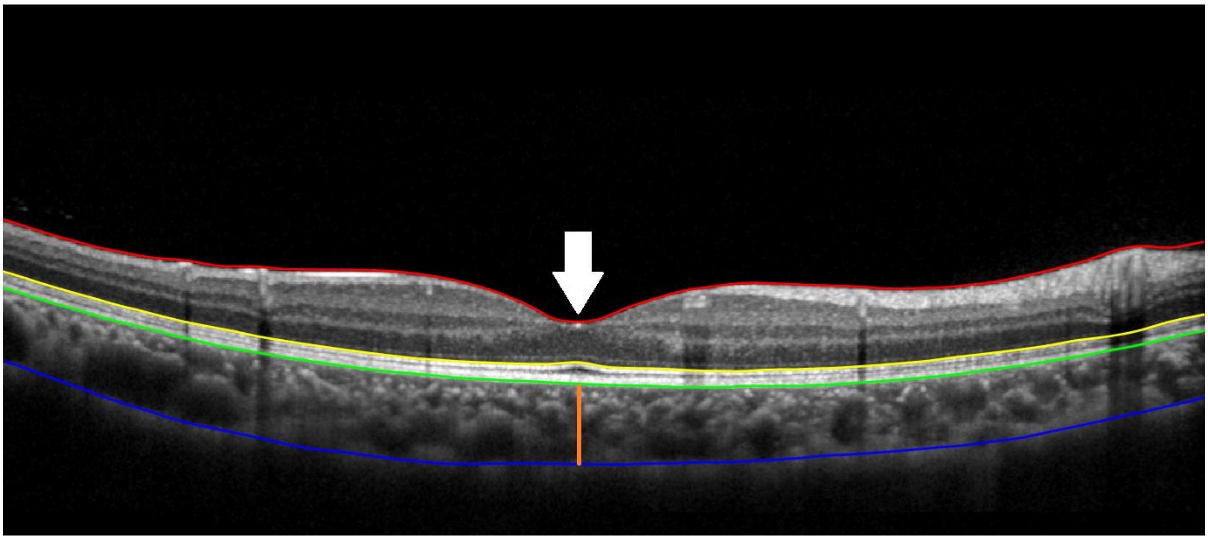


Figure 7.1 Segmented retinal and choroidal layers from the optical coherent tomography image, indicating the inner limiting membrane (red), the inner segment/outer segment junction (yellow), the outer retinal pigment epithelium/Bruch's membrane complex (green), and the inner chorioscleral interface (blue). The centre of the foveal pit at the thinnest retina is manually marked (white arrow). Subfoveal thickness was determined as the thickness between the outer retinal pigment epithelium/Bruch's membrane complex and the inner chorioscleral interface (orange).

The Spectralis SD-OCT (Heidelberg Engineering Inc., Heidelberg, Germany), which provides cross-sectional chorioretinal images with axial resolution of 3.9 µm, was used to determine the subfoveal choroidal thickness. At each visit, six radial line scans (30^{o} long, each consisted of 30 frames and separated by 30^{o}) centred at the fovea were acquired with the enhanced depth imaging mode using the high-speed scanning protocol. Automatic real-time tracking was used throughout the scanning procedure. The baseline scan was set as the reference image for subsequent scans at other visits. The images were then exported to a customised software for segmentation (Alonso-Caneiro et al., 2013). Only the horizontal scans were used for analysis. Figure 7.1 shows the segmented retinal and choroidal layers. The centre of the foveal pit was manually marked and segmentation correction was conducted when necessary. Subfoveal choroidal thickness was determined as the thickness between the outer retinal pigment epithelium/Bruch's membrane complex and the inner chorioscleral interface (Figure 7.1).

Repeatability of choroidal thickness measurements was also assessed using two images obtained at the baseline and week 4 visits. Choroidal thickness measurements of either eye (randomly selected) were analysed (McAlinden et al., 2011).

7.2.5 Sample size calculation

The required sample size for this study was calculated based on the changes in apical corneal power induced by ortho-k lenses of different compression factors. A minimum between-eye difference of 0.50 D, using a within-group SD of 0.70 D (Li et al., 2018), was expected. In order to achieve 80% power at a significance level of 0.05, allowing for a 20% dropout rate (poor lens fitting, missing follow-up, etc.), at least 23 subjects were required.

7.2.6 Statistical analyses

All statistical analyses were performed using SPSS software (version 23; IBM Corp., Armonk, NY. USA). The normality of the data was assessed using Shapiro-Wilk tests. Paired t-tests or Wilcoxon tests, where appropriate, were used to compare the demographics and data, at the baseline and one-month visit between fellow eyes. Linear mixed models were used to assess the influence of different compression factors on ocular HOAs over time, with restricted maximum likelihood estimation and a first-order autoregressive covariance model. The compression factor was added as a within-subject factor to avoid inflation to the degrees of freedom. Each subject's slope and intercept were included as random factors under unstructured covariance. Pairwise comparisons of the estimated marginal means, with Bonferroni correction, were used to compare the between-eye changes. For any significant difference, the estimated marginal means are presented; otherwise, the paired-eye data are presented with adjustment.

Further to the analysis of changes in ocular HOAs, linear mixed models were used to examine the changes in choroidal thickness (and apical corneal power) between the eyes and its association with changes in ocular HOAs (which found significant in the previous modelling).

The repeatability of choroidal thickness measurements was calculated using the measurements obtained from two images at the same visit. The relationship between the mean and the difference of the two measurements was assessed with Pearson's correlation test. The mean differences and 95% limits of agreement (mean ± 1.96 SD) against the differences were determined using Bland and Altman plots (Bland and Altman, 1986). The coefficient of repeatability was calculated as 1.96 times the SD of the differences between measurements. For all analyses, a p value of less than 0.05 indicates a statistical significance.

7.3 Results

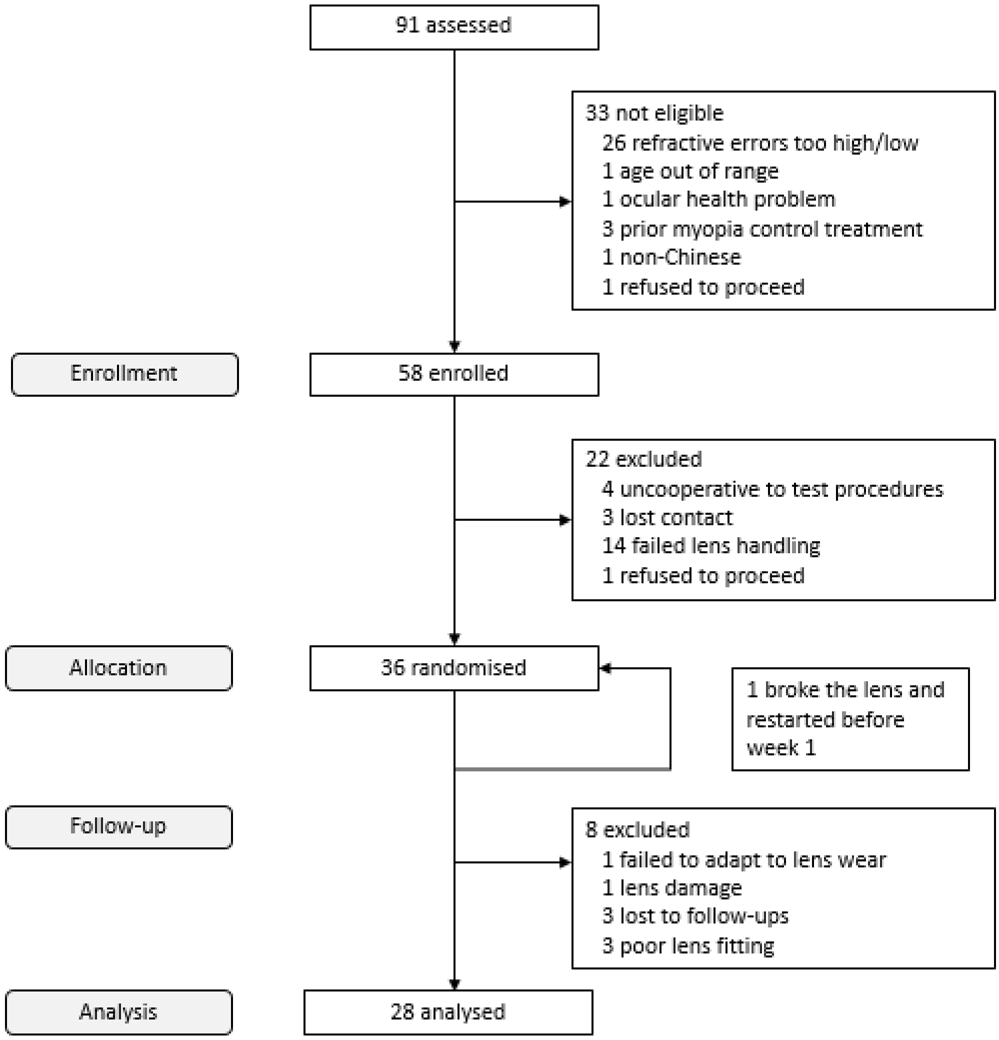


Figure 7.2 Flowchart of the one-month study.

A total of 91 subjects were screened and assessed. Of the 58 eligible subjects, 22 subjects were excluded during lens training for various reasons (Figure 7.2). Therefore, a total of 36 subjects were randomised and commenced the study. However, five subjects dropped out: one subject failed to adapt to lens wear, one refused to continue after breaking the lens during cleaning, and three subjects were lost to follow-up. Three more subjects were excluded from data analysis because of poor lens fitting (significant decentration with induced astigmatism). As a result, the data of 28 subjects who completed one-month ortho-k treatment were analysed. There were 12 boys and 16 girls, with a median (range) age of 9.3 (7.8 – 11.0) years. Eighteen and ten subjects wore spherical and toric lenses, respectively, in both eyes.

Tables 7.1 and 7.2 show the baseline demographics, data, and ocular HOAs. There were no significant differences in most baseline parameters (all $p > 0.05$), except for Z_6^{-6} and Z_6^{-4} (both $p < 0.05$).

Table 7.1 Baseline demographics and data (mean ± SD or median [range]) of the eyes assigned to orthokeratology lenses of different compression factors (n = 28 eyes in each group).

	Compression factor		**p value**
	1.75 D	**0.75 D**	
Visual acuities, logMAR			
Unaided	0.63 ± 0.29	0.65 ± 0.31	0.387
Best-corrected	0.00 ± 0.04	0.00 ± 0.05	0.678
Refraction, D			
Myopia	2.09 ± 0.97	2.12 ± 0.94	0.714
Astigmatism	0.50 [0.00, 1.25]	0.00 [0.00, 1.25]	0.080†
SER	-2.30 ± 1.03	-2.27 ± 0.99	0.646
Ocular parameters			
Apical corneal power, D	43.83 ± 1.21	43.81 ± 1.16	0.801
Subfoveal choroidal thickness, μm	240 [153, 551]	250 [193, 504]	0.339†

SER: spherical equivalent refraction.
p value: probability values of paired t-tests, except for †Wilcoxon tests, for differences between the two eyes.

Table 7.2 Baseline ocular higher order aberrations (mean ± SD or median [range]) of the eyes assigned to orthokeratology lenses of different compression factors (n = 28 eyes in each group).

	Compression factor		**p value**
	1.75 D	**0.75 D**	
Individual Zernike terms, µm			
Z_3^{-3}	0.025 ± 0.080	0.012 ± 0.071	0.327†
Z_3^{-1}	-0.019 ± 0.114	0.000 ± 0.113	0.185†
Z_3^{1}	0.002 [-0.094, 0.110]	-0.013 [-0.104, 0.083]	0.425
Z_3^{3}	-0.008 ± 0.066	-0.009 ± 0.059	0.938†
Z_4^{-4}	0.022 ± 0.022	0.020 ± 0.025	0.604†
Z_4^{-2}	-0.014 [-0.030, 0.026]	-0.006 [-0.039, 0.027]	0.053
Z_4^{0}	0.057 [-0.019, 0.212]	0.067 [-0.020, 0.376]	0.633
Z_4^{2}	-0.003 ± 0.028	-0.006 ± 0.031	0.468†
Z_4^{4}	0.007 ± 0.022	0.013 ± 0.024	0.146†
Z_5^{-5}	0.002 [-0.017, 0.038]	0.001 [-0.020, 0.031]	0.964
Z_5^{-3}	-0.003 [-0.043, 0.020]	-0.004 [-0.070, 0.012]	0.585
Z_5^{-1}	0.009 [-0.015, 0.069]	0.007 [-0.018, 0.035]	0.076
Z_5^{1}	0.001 [-0.014, 0.013]	0.001 [-0.046, 0.011]	0.633
Z_5^{3}	0.001 ± 0.005	0.002 ± 0.005	0.449†
Z_5^{5}	0.002 [-0.015, 0.031]	0.004 [-0.013, 0.047]	0.982
Z_6^{-6}	0.002 [-0.005, 0.009]	-0.001 [-0.012, 0.020]	**0.031**
Z_6^{-4}	-0.003 ± 0.002	-0.001 ± 0.003	**< 0.001†**
Z_6^{-2}	0.000 [-0.008, 0.007]	0.000 [-0.006, 0.018]	0.274
Z_6^{0}	-0.005 [-0.016, 0.026]	-0.005 [-0.016, 0.100]	0.633
Z_6^{2}	-0.001 [-0.026, 0.0100]	0.000 [-0.021, 0.024]	0.274
Z_6^{4}	0.001 [-0.006, 0.015]	-0.001 [-0.067, 0.023]	0.106
Z_6^{6}	-0.002 ± 0.004	-0.001 ± 0.006	0.330†
RMS, µm			
SA RMS	0.057 [0.004, 0.213]	0.068 [0.006, 0.389]	0.187
Coma RMS	0.116 ± 0.064	0.107 ± 0.059	0.411†
HO RMS	0.194 [0.102, 0.316]	0.175 [0.098, 0.536]	0.439

RMS: root-mean-square value, HO: higher order aberration, SA: spherical aberration, p value: probability values of Wilcoxon tests, except for †paired t-tests, for differences between the two eyes

Over the one-month period, there was no significant difference in refractive changes between eyes fitted with the increased and conventional compression factors ($p = 0.07$). During the study period, eyes with increased compression factor showed slightly less myopia by 0.41 ± 0.64, 0.36 ± 0.67, and 0.27 ± 0.64 D at weeks 1, 2, and 3, respectively (all $p \leq 0.05$). However, there was no significant difference at the end of the study (mean difference: 0.19 ± 0.64 D, $p = 0.12$). There were neither clinically (unaided visual acuity: increased compression factor: 0.02 [-0.08 to 0.34] logMAR, conventional compression factor: -0.01 [-0.10 to 0.32] logMAR, $p = 0.04$) nor statistically (best-corrected visual acuity: increased compression factor: -0.04 [-0.14 to 0.18] logMAR, conventional compression factor: -0.02 [-0.14 to 0.08] logMAR, $p = 0.87$) significant differences between the visual acuities of the eyes at the one-month visit.

7.3.1 Changes in ocular higher order aberrations

Figure 7.3 illustrates the changes in HOA terms or metrics of significant differences between the eyes. Among all the HOA terms and metrics, only HO RMS, spherical aberration RMS, and primary spherical aberration (Z_4^0), demonstrated significant differences in changes between the eyes (all $p < 0.05$). After one week of lens wear, the increased compression factor group had greater increases in these terms, compared with the conventional compression factor group (mean difference: HO RMS: 0.147 ± 0.176 µm, spherical aberration RMS: 0.094 ± 0.120 µm, Z_4^0: 0.089 ± 0.139 µm, all $p < 0.01$). These increases stablised thereafter. At the one-month visit, eyes fitted with the increased compression factor showed greater increases in these HOAs than the fellow eyes by 0.096 ± 0.141, 0.083 ± 0.124, and 0.076 ± 0.142 μm, respectively (all $p < 0.01$).

Despite no significant differences in changes between the eyes, some other HOAs significantly changed after short-term ortho-k treatment. Using data from both eyes, after one week of lens wear, primary horizontal coma (Z_3^1) and secondary spherical aberration (Z_6^0) increased by 0.117 ± 0.116 and 0.024 ± 0.032 μm, respectively (both $p < 0.001$). These HOAs did not show further significant changes for the rest of the study. At the end of the study, tertiary horizontal astigmatism (Z_6^2) decreased minimally (mean change: -0.012 ± 0.016 μm, $p = 0.006$).

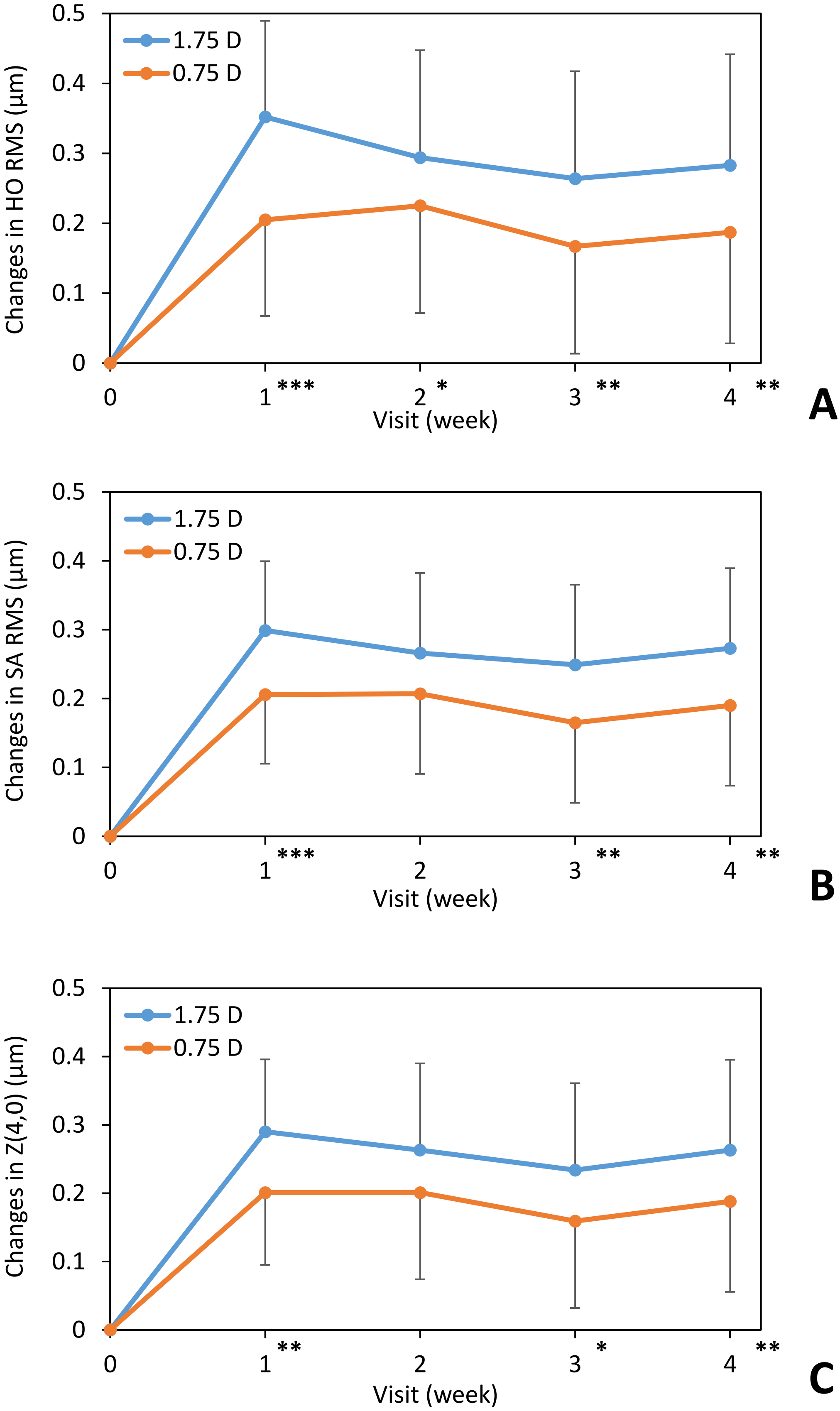
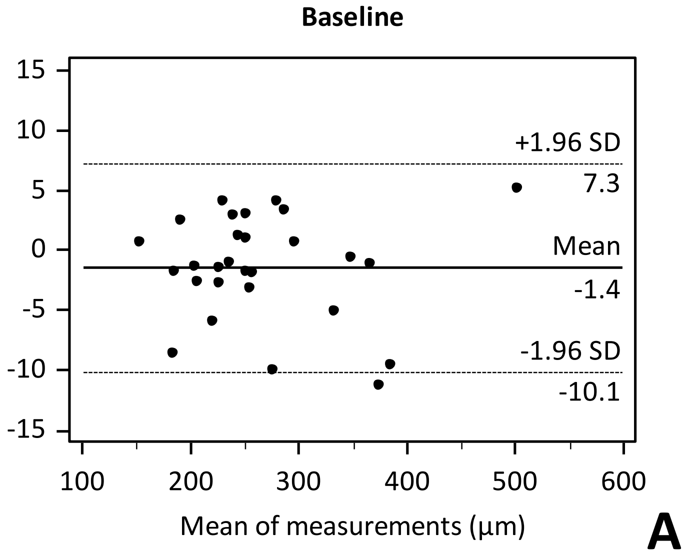


Figure 7.3 Change in (A) HO RMS, (B) SA RMS, and (C) primary SA (Z_4^0) in eyes fitted with orthokeratology lenses of different compression factors (1.75 and 0.75 D, n= 28 eyes in each group) over one month. Each error bar represents one standard deviation and the asterisks represent significant differences between the eyes (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$). RMS: root-mean-square value, HO: higher order aberrations, SA: spherical aberration.

7.3.1 Repeatability of choroidal thickness measurements



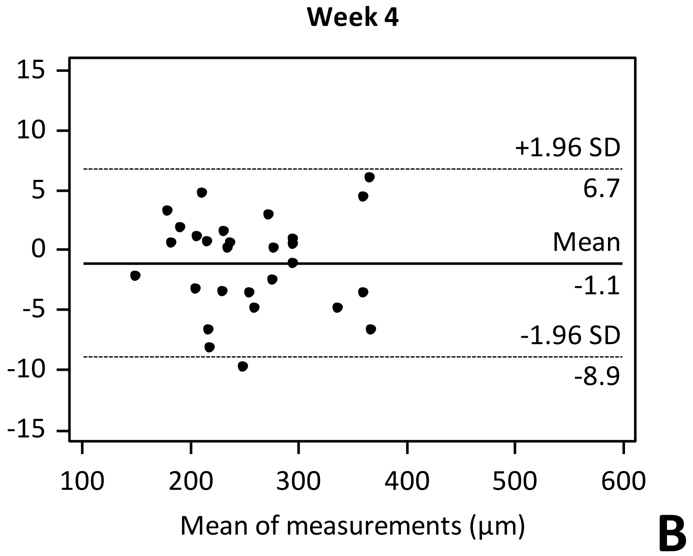


Figure 7.4 Bland and Altman plots illustrating the repeatability of choroidal thickness measurements collected from two images (randomly selected eye from each subject, n = 28 eyes) at (A) baseline and (B) week 4. The solid line represents the mean difference of choroidal measurements and the dashed lines represent the lower and upper 95% limits of agreement (mean difference ± 1.96 x SD of the differences).

Table 7.4 shows the repeatability of choroidal thickness measurements before (baseline) and after (week 4) receiving ortho-k treatment. The mean differences were -1.4 ± 4.4 and -1.1 ± 4.0 μm, respectively. There were no significant correlations between the means and the differences of the measurements (both $p > 0.05$). The limits of agreements were -10.1 to +7.3 and -8.9 to +6.7 μm, and the coefficients of repeatability were 9.0 and 8.0 μm, respectively.

7.3.2 Changes in ocular parameters

No significant between-eye differences in apical corneal power and choroidal thickness were observed (both $p > 0.05$, Table 7.2). Therefore, the paired-eye changes of these parameters are presented (Table 7.3).

At week 1, the apical corneal power was reduced significantly by 1.95 ± 0.52 D ($p < 0.001$). It was stabilised and no further significant changes were found (all $p > 0.05$). At the one-month period, the apical corneal power was reduced by 2.02 ± 0.54 D, compared with the baseline ($p < 0.001$).

The subfoveal choroidal thickness displayed a quadratic change over time ($p < 0.001$): it first decreased by 9.1 ± 12.6 μm after one week of lens wear ($p = 0.002$), and then gradually increased by 4.5 ± 22.8 μm, compared with the baseline, at week 4, but it was not significantly different from the baseline thickness ($p = 1.00$).

Table 7.3 Changes in the apical corneal power and choroidal thickness from baseline (mean ± SD) in eyes fitted with orthokeratology lenses of different compression factors (n = 28 eyes in each group).

	Week 1		**Week 2**		**Week 3**		**Week 4**	
	1.75	**0.75**	**1.75**	**0.75**	**1.75**	**0.75**	**1.75**	**0.75**
Apical corneal power, D	-2.10 ±0.73	-1.80 ± 0.73	-2.28 ± 0.80	-1.91 ± 0.80	-1.95 ± 0.81	-1.73 ± 0.81	-2.12 ± 0.80	-1.93 ± 0.80
Choroidal thickness, µm	7.0 ± 18.0	11.2 ± 17.8	4.0 ± 25.2	4.2 ± 25.1	3.2 ± 29.8	2.4 ± 30.1	-6.9 ± 33.8	-2.0 ± 34.1

Table 7.4 Changes in the apical corneal power and choroidal thickness from baseline (mean ± SD) using paired-eye data (n = 28 subjects).

	Week 1	**Week 2**	**Week 3**	**Week 4**
Apical corneal power, D	-1.95 ± 0.52***	-2.09 ± 0.57***	-1.84 ± 0.57***	-2.02 ± 0.54***
Choroidal thickness, µm	9.1 ± 12.6**	4.1 ± 17.4	2.8 ± 20.4	-4.5 ± 22.8

Asterisks show the significance levels (**p < 0.01, ***p < 0.001).

7.3.3 Associations between choroidal thickening and higher order aberrations

Since a significant choroidal thickening was only observed after one week of lens wear, the associations between changes in choroidal thickness and HOAs were investigated. However, after adjusted for using paired-eye data, no significant associations of choroidal thickening with HO RMS, spherical aberration RMS, nor primary spherical aberration (Z_4^0) were found (all $p > 0.05$).

7.4 Discussion

This is the first prospective study investigating the influence of ortho-k lenses with different compression factors on weekly changes in ocular HOAs, and corresponding changes in choroidal thickness over a one-month period.

Referring to the retrospective analysis by Chan et al. (2008b), in order to produce a slight over-correction of 0.75 D and to counteract refractive regression during the day, an additional compression factor of 1.00 D may be indicated. The current study used a contralateral, randomised, self-controlled study design to control for the intrinsic corneal properties, such as corneal biomechanics (Lam et al., 2018), in affecting the results. However, according to the findings of the current study, no significant between-eye changes in subjective (SER) nor objective (apical corneal power) refractive reduction were observed at the one-month visit. Comparing with the study of Chan et al. (2008b), the eyes fitted with the increased compression factors showed a relatively less myopia (more hyperopia) after wearing the lenses for two weeks. The findings of this study suggest that increasing the compression factor by 1.00 D initially reduces the time taken to achieve the desired refractive correction, but a similar level of SER correction was achieved at the end of one-month lens wear. Other biological limitations, such as corneal epithelial thickness (Kim et al., 2018), may be associated with the capability of maximum refractive changes.

Regarding the changes in ocular HOAs, in the current study, the eyes wearing ortho-k lenses of increased compression factor showed more changes in HO RMS, spherical aberration RMS, and primary spherical aberration (Z_4^0). Given that SER (or apical corneal power) mainly reflects the subjectively perceived images through the central vision (likely the foveal region), while changes in ocular HOAs represent the optics over a fixed pupil diameter, the optical influence of an increased compression factor may be related to changes induced in the mid-peripheral cornea. This is most likely the reason for the discrepancy between the non-significant changes in SER and significant changes in ocular aberrations found.

Since a number of observational (Hiraoka et al., 2017) and interventional (Cheng et al., 2016; Sankaridurg et al., 2019) studies have shown that more positive spherical aberration is associated with slower axial elongation, Kang et al. (2013) tried to modify the induced spherical aberration and peripheral refraction by reducing the optical zone diameter and steepening the alignment curve of the lens. However, neither modifications resulted in significant changes in spherical aberration when compared with the control lenses. The current study, on the other hand, shows that increasing the compression factor of ortho-k lenses by 1.00 D significantly increases the positive shift in spherical aberration by approximately 40%. This may improve the effectiveness of ortho-k in slowing myopia progression and axial elongation. However, a longitudinal study is required to confirm the influence of increased compression factor on myopia control effectiveness.

The choroid has been used as a short-term biomarker responding to defocus in some human studies (Read et al., 2010; Chakraborty et al., 2012, 2013; Chiang et al., 2015; Wang et al., 2016). However, the changes in choroidal thickness during ortho-k treatment remain equivocal. Gardner et al. (2015) reported no significant changes during nine months of lens wear, while an approximately 20 μm of choroidal thickening was found in subjects wearing ortho-k lenses for three weeks (Chen et al., 2016b), and up to one year (Li et al., 2018). However, some of the studies did not control for the potential confounding effects of diurnal variation and the use of cycloplegia, which may affect choroidal thickness and its response to defocus (Chakraborty et al., 2011; Tan et al., 2012; Osmanbasoglu et al., 2013; Sander et al., 2014; Sander et al., 2018).

In the current study, despite the statistically significant choroidal thickening found after one week of lens wear (mean change: 9.1 ± 12.6 μm), this magnitude of change approached the intra-session repeatability of choroidal thickness measurement (coefficient of repeatability: 8 – 9 μm). It is uncertain whether the increase was genuine or related to measurement variability (Vaz et al., 2013). In comparison with manual segmentation of repeatability of approximately 35 μm (Rahman et al., 2011; Hanumunthadu et al., 2017) and automated software with limits of agreement of 14 μm (Twa et al., 2016), the semi-automated software applied in the study has improved the repeatability of choroidal thickness measurement, which was also comparable with the inter-observer repeatability of Li et al. (2018). However, the changes in choroidal thickness in this study were subtle and could not be differentiated from measurement noise. Therefore, the predictive value of using the changes in choroidal thickness in comparing the potential effectiveness for myopia control remains unclear. A longitudinal study investigating the influence of different compression factors may confirm its feasibility of improving myopia control using ortho-k lenses.

One limitation of the current study was that, the study design enhanced its power to control for inter-subject variations, but cannot avoid any potential inter-ocular interactions in response to the intervention (cross-over effect). The actual effectiveness of altering the compression factor of ortho-k lenses for myopia control is yet to be confirmed with further randomised controlled longitudinal clinical trial.

7.5 Conclusion

Increasing the compression factor of ortho-k lenses by 1.00 D amplified the induced HOAs, particularly spherical aberration, after one week of lens wear. However, the short-term changes observed in choroidal thickness may not be real changes as they were similar to the measurement repeatability of the instrument. If more positive spherical aberration is associated with slower axial elongation, altering ortho-k lens designs to increase the magnitude of induced positive spherical aberration may result in an improved better myopia control effect.

Papers published from work reported in this chapter:

Lau JK, Vincent SJ, Cheung SW, Cho P. (2020). The influence of orthokeratology compression factor on ocular higher-order aberrations. Clin Exp Optom 103:123-8.

Lau JK, Wan K, Cheung S-W, Vincent SJ, Cho P. (2019). Weekly changes in axial length and choroidal thickness in children during and following orthokeratology treatment with different compression factors. Transl Vis Sci Technol 8:9.

Lau JK, Cheung SW, Collins MJ, Cho P. (2019). Repeatability of choroidal thickness measurements with Spectralis OCT images. BMJ Open Ophthalmol 4:e000237.

Chapter 8

Long-term effects of orthokeratology lenses of different compression factors

8.1 Introduction

Higher levels of HO RMS and spherical aberration have been shown to be associated with slower axial elongation in spectacle-wearing (Chapter 5) and ortho-k treated (Chapter 6) children. Increasing the compression factor of ortho-k lenses by 1.00 D showed significant increases in the induced HOAs by approximately 40%, without altering the subjective refractive correction of the children (Chapter 7).

Therefore, this longitudinal study primarily aimed at investigating the myopia control effectiveness of ortho-k lenses with different compression factors (0.75 and 1.75 D) on axial elongation in children, and examining the possible predictive values of induced ocular HOAs after one month of treatment in relation to longer-term (two year) axial elongation in ortho-k treatment.

8.2 Methods

8.2.1 Study design

This was a prospective, double-blinded, randomised, controlled clinical trial investigating the influence of ortho-k lenses with different compression factors on axial elongation in young myopic children over a two-year period. The subjects chose to wear either single-vision spectacles or ortho-k lenses (with the compression factor of either 0.75 or 1.75 D randomised for subjects who chose ortho-k treatment). The study protocol followed the tenets of the Declaration of Helsinki and ethics clearance was approved by the Departmental Research Committee of the School of Optometry of The Hong Kong Polytechnic University. The nature and possible consequences of the treatment were explained, and written informed consent was obtained from the parents before the commencement of the study. The study was also registered at ClinicalTrial.gov (NCT02643342).

8.2.2 Subjects

Subjects were recruited via advertisements on posters and mass mails posted on the campus from June 2016 to November 2017. Telephone interviews and screening examinations were performed to examine if the subject fulfilled the inclusion and exclusion criteria (Table 8.1). Chinese children aged between six and less than 12 years, with low myopia (0.50 – 4.00 D, inclusive), low astigmatism (≤ 1.25 D), low anisometropia (≤ 1.00 D), and low corneal toricity (< 2.00 D), were recruited. Subjects with any prior history of myopia control treatment (for more than one month of treatment), ocular or systemic conditions that affect refractive development or contact lens wear, or non-compliance to spectacle or ortho-k lens wear or follow-up schedules, were excluded. For subjects who participated in the ortho-k group, both the parents and the children received training on lens handling and cleaning procedures. Randomisation of the compression factor of the lenses assigned to the subjects were performed only when both the parents and the children were competent in demonstrating proper handling procedures. Subjects who had previously completed the one-month ortho-k study (Chapter 7) were also invited to participate in the current study, after an appropriate washout period (for approximately three weeks), when refraction and apical corneal power were not more than 0.25 D different from their baseline measurements, taken before the previous study.

Table 8.1 Inclusion and exclusion criteria.

Inclusion	Exclusion
• Age: 6 – <12 y • Myopia: 0.50 – 4.00 D, inclusive • Astigmatism: with-the-rule (180 ± 30°): ≤ 1.25 D other axes: ≤ 0.50 D • Anisometropia: ≤ 1.00 D • Corneal toricity: < 2.00 D • Agree to randomisation to different compression factors	• Strabismus • Amblyopia • Ocular or systemic conditions that affect refractive development or contact lens wear • Prior myopia control treatment (for > one month treatment)

8.2.3 Interventions

The study was originally planned to randomise all subjects into three different groups receiving different treatments (spectacles and ortho-k lenses of different compression factors [0.75 and 1.75 D]). However, with a number of pharmacological and optical interventions available in Hong Kong at the time of the study, most subjects were seeking a myopia control intervention and were not willing to be randomised into the spectacle-wearing control group. As a result, the subjects were allowed to choose to wear either spectacles or ortho-k lenses.

8.2.3.1 Spectacles

Subjects in the control group were prescribed single-vision spectacles (1.60 plastic; Hoya Lens Corp., Japan) and instructed to wear the spectacles during the daytime. The prescription was updated when the SER change was at least 0.50 D, or monocular aided visual acuity was worse than 0.18 logMAR.

8.2.3.2 Orthokeratology lenses

The ortho-k subjects were fitted with four-zone ortho-k lenses, of either spherical or toric lens design (Menicon Z Night lenses; NKL Contactlenzen B.V., Emmen, The Netherlands) in both eyes, using the manufacturer's software (Easyfit, version 2013; NKL Contactlenzen B.V., Emmen, The Netherlands). The lenses were made of material of hyper-oxygen permeability (Menicon Z, Dk 163

[ISO unit]). Full correction was ordered for the subjects in the conventional compression factor (0.75 D) group, and an additional 1.00 D correction was ordered for the subjects in the increased compression factor (1.75 D) group. The subjects were required to wear the lenses every night for at least eight hours, and to regularly record the lens wearing schedule on their diary for monitoring their compliance.

The subjects were required to clean and rub the lenses every day and perform weekly protein removal procedures (cleaner: Menicon Spray and Clean; disinfecting solution: MeniCare Plus; protein removal solution: Menicon Progent A & B; Menicon Co., Ltd., Nagoya, Japan). Saline and artificial tears (Ophtecs cleadew and TearW; Ophtecs Corp., Tokyo, Japan) were provided for lens rinsing and cushioning of lens before insertion to avoid any formation of air bubbles, respectively.

Any eyes with poor lens fitting, characterised by significant lens decentration with induced astigmatism, were re-fitted by adjusting the fitting (alignment) curve without altering the targeted correction, i.e. base curve.

Since the study aimed to investigate the influence of ortho-k lenses with different compression factors, which was correlated to the desired myopia correction, the lenses would not be adjusted for any under-correction. For any under-correction or myopia progression with residual SER of 0.50 D or more, or unaided visual acuity worse than 0.18 logMAR, a pair of spectacles was prescribed for daytime use to correct the residual refractive error.

8.2.4 Visits and examination procedures

Regular eye examination and data collection visits were conducted every six months over two years. The spectacles or ortho-k lenses were dispensed at the baseline visit. Ortho-k subjects had to return to the clinic for aftercare consultations after the first overnight, one, two, four weeks, and every three months of lens wear. Except for the first overnight visit which was scheduled within two hours after wakening, other data collection visits were performed at a similar time to the baseline (within 2 hours) to minimise any potential influence of diurnal variation. Subjects were also reminded to report any adverse effects and additional follow-up visits would be scheduled as necessary.

At each data collection visit, unaided and best-corrected visual acuities (ETDRS charts, 90% contrast; Precision Vision, Woodstock, IL, USA), non-cycloplegic subjective refraction, and external ocular health were assessed by an unmasked examiner. Maximum plus for maximum visual acuity approach was used for the determination of refractive errors, and ocular health was evaluated using the Efron grading scale (Efron, 1998). Corneal topography was measured by the same examiner using a corneal topographer (E300 videokeratoscope; Medmont Pty. Ltd., Vermont, Victoria, Australia) to assess the lens centration (for ortho-k subjects only) and the changes in corneal profile.

Non-cycloplegic ocular HOAs of the subjects were also collected using COAS aberrometer (Wavefront Sciences Ltd., New Mexico, USA). A Badal optometer, with a Maltese cross as the target, was used, to ensure relaxed accommodation. The fellow eye was occluded to maintain good central fixation during the measurement. In total, 125 repeated measures of ocular HOAs through natural pupils were captured.

Each captured HOA measurement was then fitted with a sixth order Zernike polynomial and rescaled to a 5-mm pupil, and each Zernike coefficient was later averaged for analysis. The HO RMS (from third to sixth orders, inclusively), spherical aberration RMS (Z_4^0 and Z_6^0 combined), comatic aberration RMS (Z_3^{-1}, Z_3^1, Z_5^{-1}, and Z_5^1 combined), and corresponding Zernike coefficients were also used for analysis. In addition to the regular data collection visits, data was also obtained at the one-month aftercare visit to examine the predictive value of induced HOAs for axial elongation after two years of lens wear.

Axial length (IOL Master, model 500; Carl Zeiss Meditec AG, Jena, Germany) was obtained by a masked examiner after cycloplegia, with two drops of 1% cyclopentolate, administered five minutes apart. Five measurements, with a minimum signal-to-noise ratio of 5.0 and a maximum inter-reading difference of 0.02 mm, were obtained and the axial length reported by the instrument software was used for data analysis. Cycloplegic subjective refraction and best-corrected visual acuities were also measured by the same masked examiner.

8.2.5 Sample size calculation

The sample size of this study was determined based on the reported two-year axial elongation in previous studies (Cho and Cheung, 2012; Charm and Cho, 2013). A minimum difference of 0.27 mm and a SD of 0.06 mm between the ortho-k and the control groups were expected at the end of the study. In order to achieve a 80% power at a significance level of 0.05, allowing for a 30% dropout rate (poor lens fitting, missing follow-up, etc.), at least 20 subjects in each group were required.

8.2.6 Statistical analyses

All statistical analyses were performed using SPSS software (version 23; IBM Corp., Armonk, NY. USA). To avoid the possible inflation of statistical results when including data from fellow eyes, only data from the right eyes were used. The normality of the data was assessed using Shapiro-Wilk tests. One-way ANOVA (or unpaired t-tests) or Kruskal-Wallis tests (or Mann-Whitney U tests), where appropriate, were used to compare the baseline demographics and data between all groups (or between the two ortho-k groups only). Only subjects who completed the two-year study were analysed.

Linear mixed models were used to assess the influence of different compression factors on axial elongation over time, with restricted maximum likelihood estimation and a first-order autoregressive covariance model. Inter-subject slopes and intercepts were included as random effects under an unstructured covariance matrix. The between-group differences were compared using estimated marginal means with Bonferroni correction. The models were repeated to compare the changes in SER, visual acuities, and ocular HOAs (HO RMS, spherical aberration RMS, comatic aberration RMS, and corresponding Zernike coefficients from the one month, one year, and two year study visits only, because HOAs basically were stable from the one month visit onwards) over time relative to baseline measurements.

The association between ocular HOAs and axial elongation was examined using similar linear mixed models in ortho-k subjects. Since a difference in residual SER was noted between the ortho-k groups, which may potentially influence the axial elongation of the subjects, it was included in the analyses as a confounding factor, in addition to sex, baseline age, and baseline HOAs. The modelling was repeated using (Model 1) HO RMS, (Model 2) spherical aberration RMS and comatic aberration RMS, and (Model 3) Zernike coefficients of primary and secondary spherical and comatic aberrations.

To examine the predictive values of induced HOAs for axial elongation at each visit across the two-year period among the two groups of ortho-k subjects, the changes in ocular HOAs at the one-month visit were incorporated into linear mixed model analyses, adjusting for other confounding factors, such as sex, residual SER, and baseline age. A p value of less than 0.05 was regarded as statistically significant for all analyses.

8.3 Results

Figure 8.1 shows the number of subjects at different stages of the study. A total of 132 children were screened and 81 eligible subjects were enrolled. Fifteen subjects withdrew from the study because of failure to insert and remove lenses safely even after the training, lost to contact, or uncooperative during test procedures. The remaining 66 subjects proceeded with the study, with 30 and 36 subjects allocated to the control and ortho-k groups, respectively. In addition, 33 subjects who completed the one-month study (Chapter 7) also participated in this study after a washout period of about three weeks. Subjects in the ortho-k group were further randomly assigned to ortho-k lenses with compression factor of 0.75 (n = 34) and 1.75 D (n = 35), respectively. During the study, 19 control subjects dropped out and the majority of them (n = 12) decided to seek myopia control interventions elsewhere due to myopia progression, and seven of them were lost to follow-up. Five ortho-k subjects from the conventional compression factor group also dropped out: one subject experienced seasonal allergic conjunctivitis, two were not compliant with lens wear (no lens wear for more than one month) because of low refractive error, one sought ortho-k treatment elsewhere, and one was lost to follow-up, and were therefore excluded from analysis. Two subjects (one from each ortho-k group) needed to wear spectacles to correct the residual refractive error.

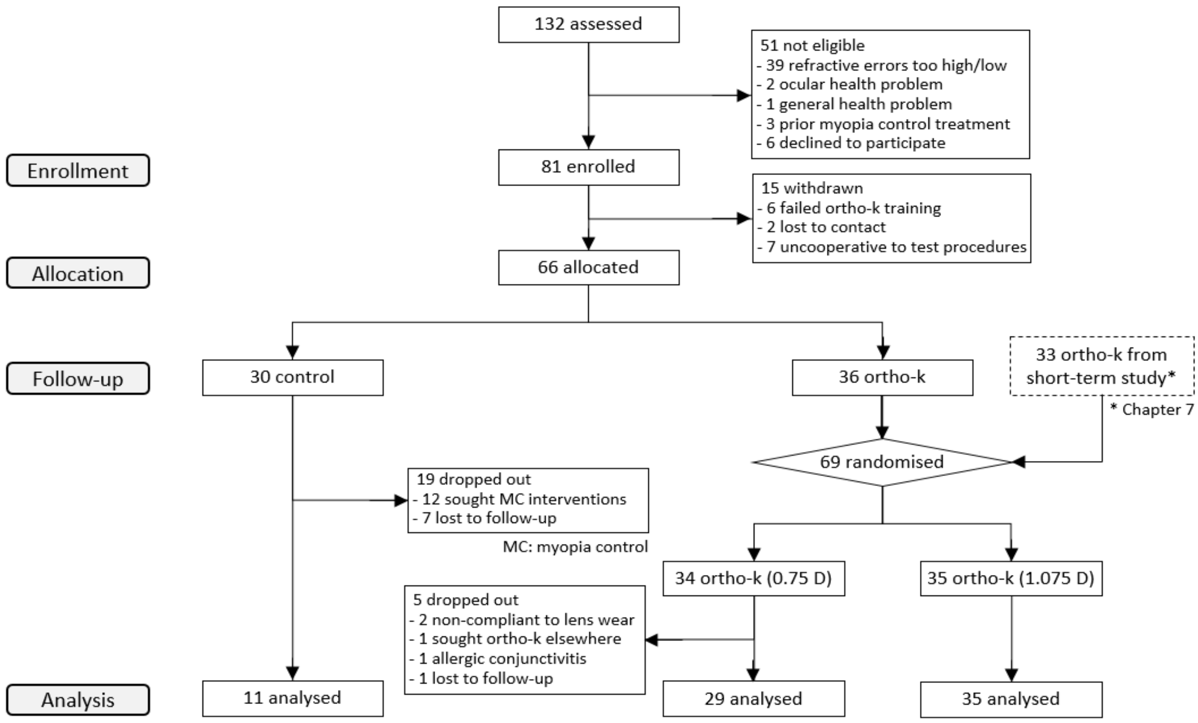


Figure 8.1 Flowchart of the two-year study (ortho-k: orthokeratology).

Since a significant proportion (63%) of the control subjects dropped out of the study, mainly those with significant myopia progression or concerns (40%), the data of the control subjects was not reported in the following sections to avoid any potential bias, from the virtually non-progressing control group. Therefore, the remaining analysis focuses on the comparison between conventional (0.75 D) and increased (1.75 D) compression factor groups.

Table 8.2 shows the baseline demographics, data, and ocular HOAs of the ortho-k subjects. In total, 29 (17 girls, 12 boys) and 35 (21 girls, 14 boys) subjects in the conventional and increased compression factor groups, respectively, completed the study. No significant differences in the age, visual acuities, pre- and post-cycloplegic refraction, and axial length were found between the two ortho-k groups at baseline (all $p > 0.05$). Regarding the baseline ocular HOAs, one ortho-k subject with 0.75 D compression factor was excluded because of missing baseline data. The conventional compression factor group only showed slightly smaller secondary horizontal coma (Z_5^1) (mean differences: 0.003 ± 0.002 μm, $p = 0.03$).

Considering all visits, the pre- and post-cycloplegic refraction and visual acuities were also compared. The differences in myopia, astigmatism, and SER before and after cycloplegia were not clinically significant (all differences ≤ 0.25 D), despite highly statistically significant differences (paired t-tests or Wilcoxon test, where appropriate, all $p < 0.001$). On average, the pre-cycloplegic best-corrected visual acuity was approximately one letter better than that after cycloplegia (mean difference: 0.02 ± 0.07 logMAR; paired t-test, $p < 0.001$). The pre-cycloplegic subjective refraction and visual acuities, from natural pupil size and accommodation status, are presented in the following sections.

Table 8.2 Baseline demographics, data, and ocular higher order aberrations (mean ± SD or median [range]) of the orthokeratology subjects.

	Compression factor		p value
	0.75 D (n = 29)a	1.75 D (n = 35)	
Demographics and data			
Age, y	9.1 ± 1.1	9.4 ± 1.1	0.221
Visual acuities, logMAR			
Unaided	0.63 ± 0.27	0.69 ± 0.29	0.417
Best-corrected	-0.03 ± 0.06	-0.01 ± 0.06	0.330
Pre-cycloplegic refraction, D			
Myopia	2.16 ± 0.74	2.20 ± 0.84	0.857
Astigmatism	0.25 [0.00, 1.25]	0.25 [0.00, 1.50]	0.674†
SER	-2.34 ± 0.76	-2.40 ± 0.91	0.766
Post-cycloplegic refraction, D			
Myopia	2.11 ± 0.77	2.15 ± 0.85	0.854
Astigmatism	0.25 [0.00, 1.50]	0.25 [0.00, 1.50]	0.906†
SER	-2.31 ± 0.80	-2.35 ± 0.92	0.828
Axial length, mm	24.34 ± 0.66	24.52 ± 0.84	0.340
Higher order aberrations, µm			
HO RMS	0.162 [0.106, 0.328]	0.180 [0.057, 0.342]	0.463†
SA RMS	0.055 [0.007, 0.223]	0.045 [-0.010, 0.186]	0.638†
Z_4^0	0.053 [-0.007, 0.223]	0.044 [-0.037, 0.186]	0.447†
Z_6^0	-0.006 [-0.020, 0.020]	-0.006 [-0.017, 0.026]	0.901†
Coma RMS	0.099 [0.034, 0.295]	0.078 [0.021, 0.249]	0.472†
Z_3^{-1}	-0.028 [-0.183, 0.282]	-0.002 [-0.158, 0.241]	0.275†
Z_3^1	0.011 ± 0.055	0.005 ± 0.056	0.660
Z_5^{-1}	0.007 [-0.016, 0.064]	0.010 [-0.020, 0.022]	1.000†
Z_5^1	0.000 ± 0.007	0.004 ± 0.005	**0.034**

SER: spherical equivalent refraction, RMS: root-mean-square value, HO: higher order aberration, SA: spherical aberration.
p values: probability values of unpaired t-tests, except for †Mann-Whitney U tests, for the differences between the two orthokeratology groups.

8.3.1 Changes in refraction and visual acuities

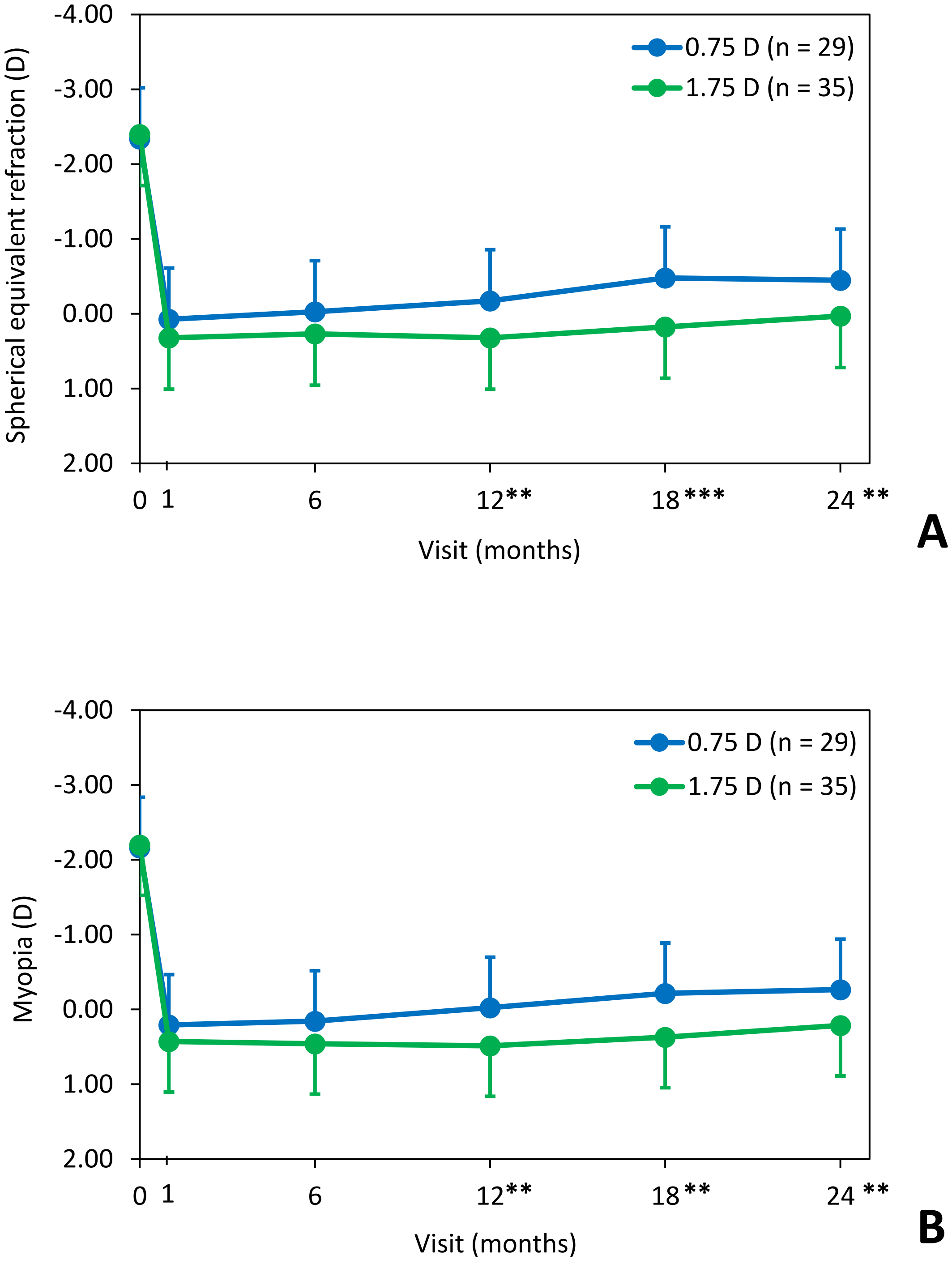


Figure 8.2 Mean (A) spherical equivalent refraction (SER) and (B) myopia of the orthokeratology subjects during the study period. Each error bar represents one standard deviation. Asterisks represent significant differences between the two orthokeratology groups (**$p < 0.01$, ***$p < 0.001$). SER: spherical equivalent refraction, BL: baseline, M: month(s).

Figure 8.2 shows the mean changes in SER of ortho-k subjects during the study period. After receiving the treatment for one month, the SER decreased significantly to emmetropia or low hyperopia on average (Figure 8.2A, both $p < 0.001$). No significant differences in SER between two ortho-k groups were observed at the one-month and six-month visits (mean difference at 1-month: 0.25 ± 0.17 D, 6-month: 0.29 ± 0.17 D, both $p > 0.05$), but the differences were significant at subsequent visits (mean difference at 12-month: 0.49 ± 0.17 D, 18-month: 0.65 ± 0.17 D, 24-month: 0.48 ±.0.17 D, all $p < 0.01$).

On average, subjects fitted with increased compression factor (1.75 D) were slightly over-corrected throughout the whole study period (SER at 1-month: 0.32 ± 0.69 D, 6-month: 0.27 ± 0.69 D, 12-month: 0.32 ± 0.69 D, 18-month: 0.18 ± 0.69 D, 24-month: 0.03 ± 0.69 D) while those with conventional compression factor (0.75 D) were slightly under-corrected at all study visits after one month of lens wear (SER at 1-month: 0.07 ± 0.68 D, 6-month: -0.03 ± 0.68 D, 12-month: -0.17 ± 0.68 D, 18-month: -0.48 ± 0.68 D, 24-month: -0.45 ± 0.68 D).

A similar trend of myopia changes was found. In the ortho-k groups, the subjects with increased compression factor (1.75 D) were slightly more hyperopic than those with conventional compression factor (0.75 D), after one year of ortho-k treatment (Figure 8.2B; mean difference at 1-month: 0.22 ± 0.17 D, 6-month: 0.30 ± 0.17 D, both $p > 0.05$; 12-month: 0.51 ± 0.17 D, 18-month: 0.59 ± 0.17 D, 24-month: 0.48 ± 0.17 D, all $p < 0.01$;). On the other hand, there were no significant changes in astigmatism in both ortho-k groups throughout the study period (p = 0.55).

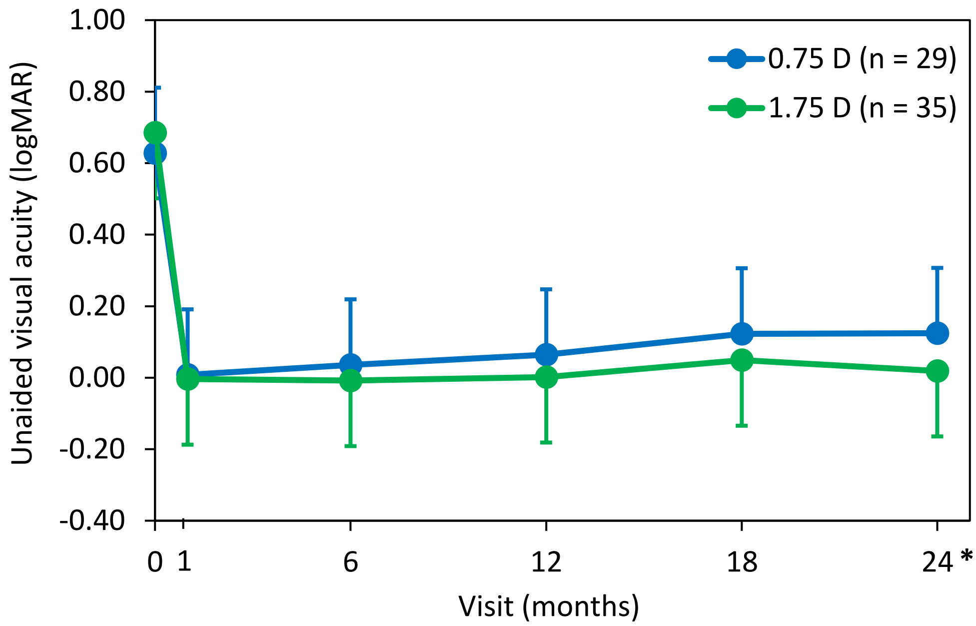


Figure 8.3 Mean unaided visual acuity of the orthokeratology subjects during the study period. Each error bar represents one standard deviation. Asterisk represents significant differences between the two orthokeratology groups (*$p < 0.05$). BL: baseline, M: month(s).

Figure 8.3 shows the unaided visual acuity of the ortho-k subjects. After ortho-k treatment, as expected, the unaided visual acuity significantly improved to approximately zero logMAR at the one-month visit (conventional compression factor: 0.01 ± 0.18 logMAR, increased compression factor: 0.00 ± 0.18 logMAR, both $p < 0.001$). However, there were no significant differences between the two ortho-k groups at all visits (all $p > 0.05$), except for the 24-month visit (conventional compression factor: 0.12 ± 0.18 logMAR, increased compression factor: 0.02 ± 0.18 logMAR, p = 0.03). There were no significant differences in best-corrected visual acuities between all groups throughout the study (all $p > 0.05$).

8.3.2 Changes in axial length

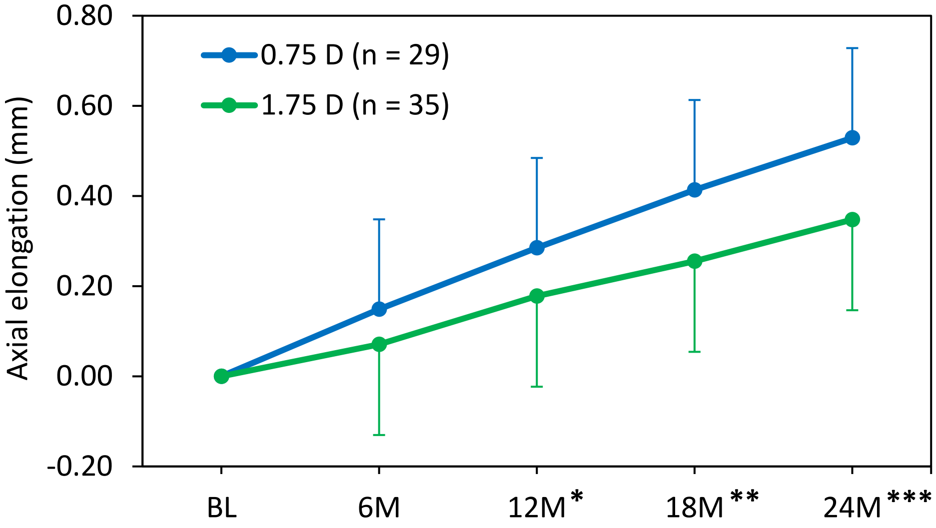


Figure 8.4 Mean axial elongation of the orthokeratology subjects during the study period. Each error bar represents one standard deviation. Asterisks represent significant differences between the two orthokeratology groups (*p < 0.05, **p < 0.01, ***p < 0.001). BL: baseline, M: month(s).

Table 8.3 Mean axial elongation (mm, mean ± SD) of the orthokeratology subjects, compared with the baseline.

Visit	**Compression factor**		**p value†**
	0.75 D (n = 29)	**1.75 D (n = 35)**	
6 month	0.15 ± 0.09	0.07 ± 0.13	0.121
12 months	0.29 ± 0.16	0.18 ± 0.19	**0.035**
18 months	0.41 ± 0.22	0.26 ± 0.24	**0.002**
24 months	0.53 ± 0.29	0.35 ± 0.29	**< 0.001**

†Bonferroni corrected p values.

Figure 8.4 and Table 8.3 show the mean axial elongation of ortho-k groups throughout the study period. Subjects in both ortho-k groups showed significant axial elongations over time (both $p < 0.001$). Subjects with increased compression factor showed 53%, 38%, , 38%, and 34% slower axial elongation than those with conventional compression factor at the 6-, 12-, 18-, and 24-month visits, respectively.

8.3.3 Changes in ocular higher order aberrations

In the ortho-k groups, HO RMS, spherical and comatic aberrations RMS increased significantly by approximately three, five, and two times, respectively, after one month of lens wear (Figure 8.5, all $p < 0.05$). Subjects with increased compression factor (1.75 D) demonstrated marginally more HO RMS than those with conventional compression factor (0.75 D) at the 24-month visit only (Figure 8.5A, mean difference: 0.126 ± 0.046 μm, $p = 0.046$). Spherical aberration RMS was also significantly higher in subjects with increased compression factor (Figure 8.5B, mean difference at 12-month: 0.089 ± 0.035 μm, 24-month: 0.086 ± 0.035 μm, both $p < 0.05$). However, no significant differences in comatic aberration RMS were found between the two ortho-k groups at any visit (Figure 8.5C, all $p > 0.05$).

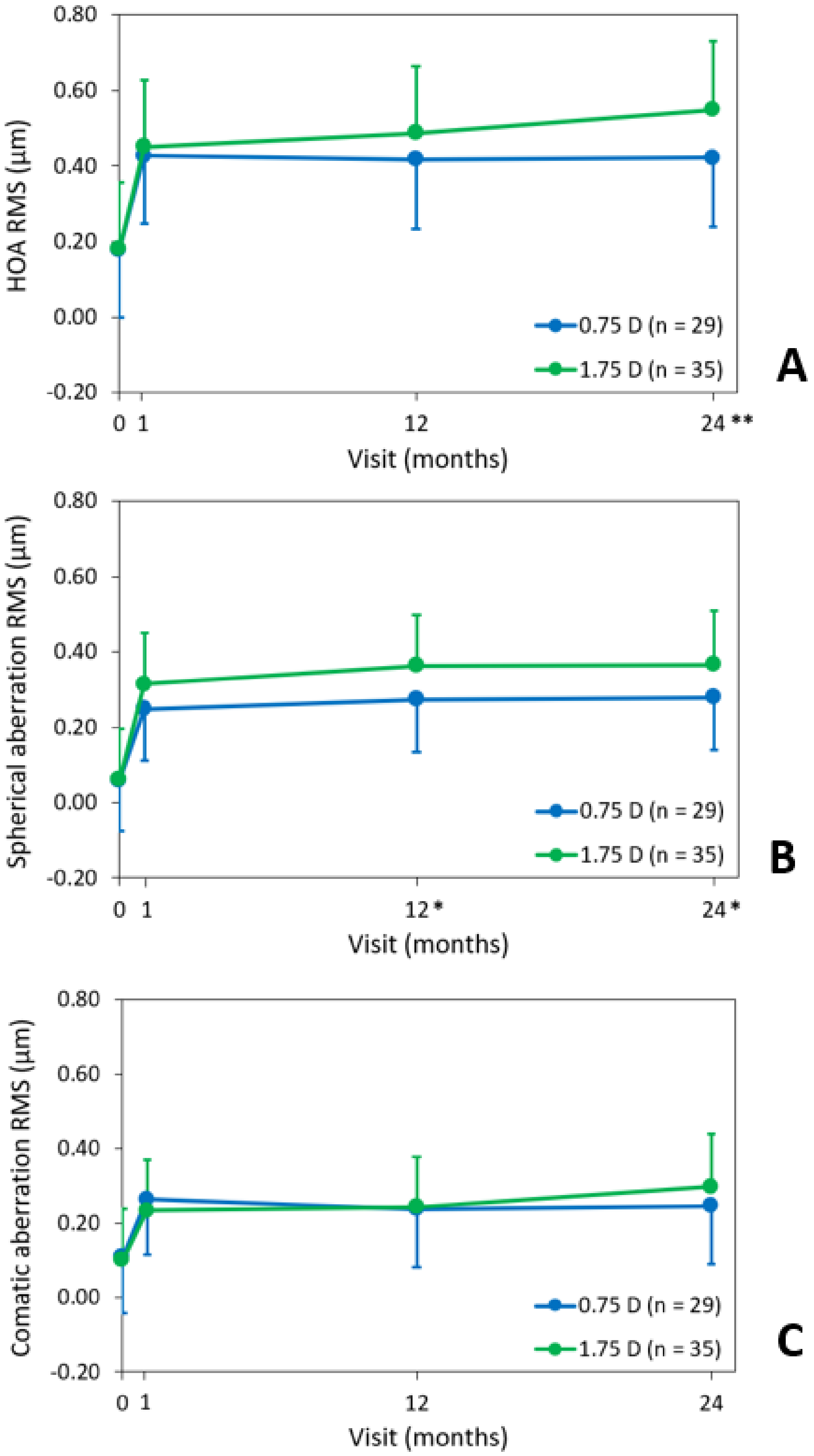


Figure 8.5 Mean (A) HO RMS, (B) spherical aberration RMS, and (C) comatic aberration RMS of the orthokeratology subjects during the study period. Each error bar represents one standard deviation. Asterisks represent significant differences between the two orthokeratology groups (*$p < 0.05$, **$p < 0.01$). RMS: root-mean-square, HO: higher order aberrations, BL: baseline, M: month(s).

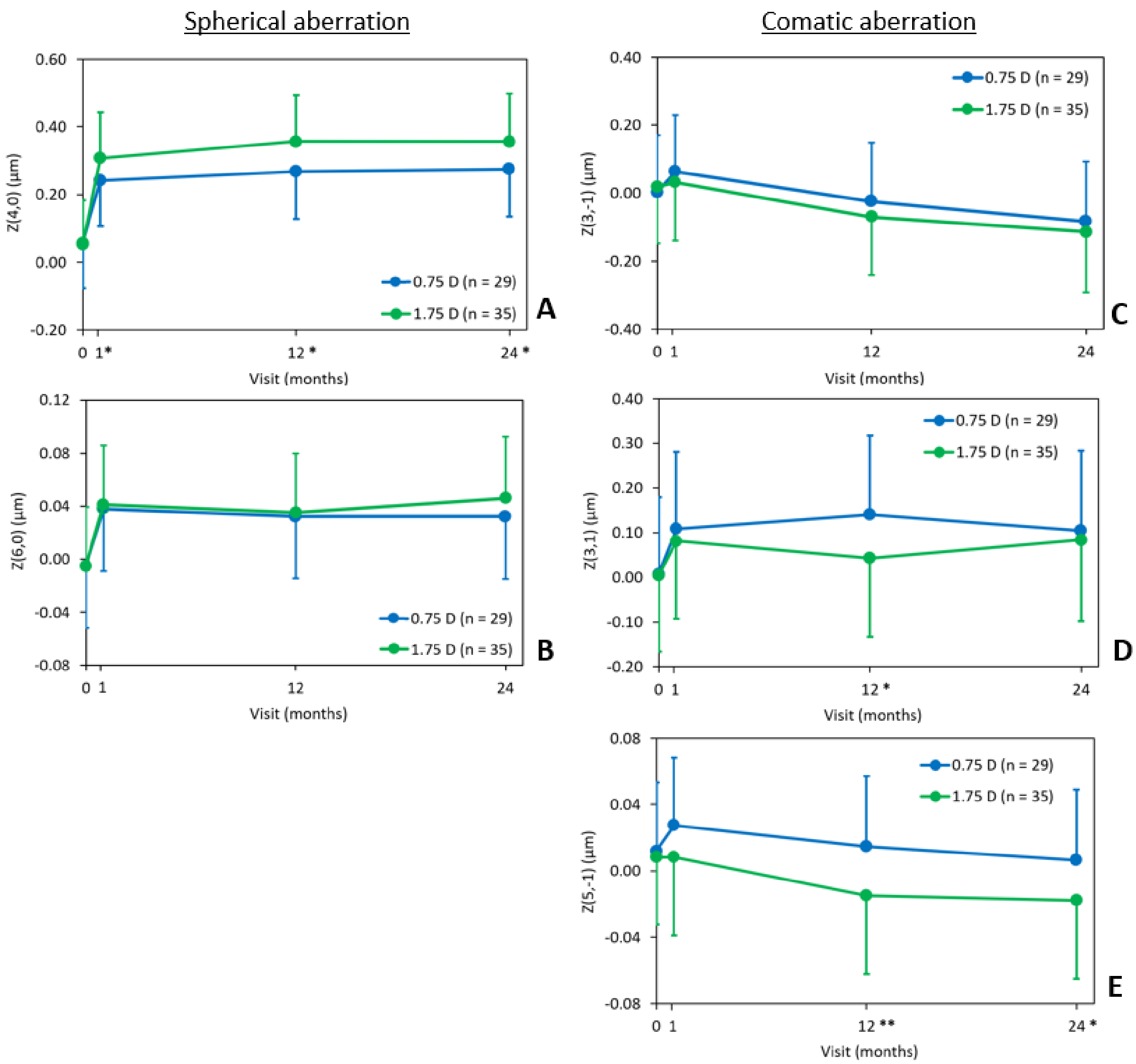


Figure 8.6 Mean (A) primary spherical aberration (Z_4^0), (B) secondary spherical aberration (Z_6^0), (C) primary vertical coma (Z_3^{-1}), (D) primary horizontal coma (Z_3^1) and (E) secondary vertical coma (Z_5^{-1}) of the orthokeratology subjects during the study period. Each error bar represents one standard deviation. Asterisks represent significant differences between the two orthokeratology groups (*p < 0.05, **p < 0.01, ***p < 0.001). Note: the scales are adjusted for corresponding Zernike terms. BL: baseline, M: month(s).

Figure 8.6 illustrates the spherical and comatic Zernike terms which displayed significant changes over time. After ortho-k treatment, the primary spherical aberration (Z_4^0) increased significantly (Figure 8.6A, $p < 0.001$). Subjects with increased compression factor (1.75 D) also demonstrated a greater increase in spherical aberration than those with conventional compression factor (0.75 D), after one month of lens wear and thereafter (all $p < 0.05$). The secondary spherical aberration (Z_6^0) also increased significantly after ortho-k treatment (Figure 8.6B, $p < 0.001$), but no between-group differences were found (all $p > 0.05$).

Considering the comatic aberration terms, the primary vertical coma (Z_3^{-1}) of the ortho-k subjects decreased over time (Figure 8.6C, $p < 0.001$) and was significantly different to the baseline at the 24-month visit ($p = 0.002$). The secondary vertical coma (Z_5^{-1}) slightly increased at the one-month visit and decreased over time (Figure 8.6E, $p = 0.007$). Subjects in the increased compression factor group (1.75 D) had significantly less secondary vertical coma than those in the conventional compression factor group (0.75 D) after the first year visit (both $p < 0.05$). The primary horizontal coma (Z_3^1) increased over time (Figure 8.6D, $p < 0.001$). However, subjects with increased compression factor were significantly less than those with conventional compression factor at the first year visit only ($p = 0.03$). The secondary horizontal coma (Z_5^1), after adjusting for the baseline values, did not change significantly over time and no significant difference between groups were found ($p > 0.05$).

8.3.4 Association between ocular higher order aberrations and axial elongation

Regarding the baseline ocular HOAs, one subject wearing ortho-k lenses with 0.75 D compression factor was excluded because of missing baseline data. Table 8.4 shows the significant ocular HOAs associated with axial length and axial elongation (presented as the interaction between the HOA metric with time) in all the ortho-k treated subjects. In all the models, the axial length increased by approximately 0.31 – 0.36 mm per year ($p < 0.001$). Girls exhibited about 0.50 mm shorter axial length than boys ($p < 0.001$). Every dioptre decrease (more myopic) in residual SER was associated with 0.04 – 0.06 mm longer axial length ($p < 0.05$).

Higher levels of baseline spherical aberration RMS and baseline primary spherical aberration (Z_4^0) were associated with shorter axial length (baseline spherical aberration RMS: $\beta = -0.49$ mm per 0.1 μm, baseline Z_4^0: $\beta = -0.48$ mm per 0.1 μm, both $p \leq 0.01$). Every micron increase in primary spherical aberration (Z_4^0) (across all study visits) was associated with 0.40 mm longer axial length ($p = 0.048$).

Regarding the association between ocular HOAs and axial length, higher levels of HO RMS, comatic aberration RMS, and primary spherical aberration (Z_4^0) were associated with approximately 0.29, 0.43 and 0.28 mm slower axial elongation per year (for each micron increase in the RMS of coefficient value), respectively (all $p < 0.05$). However, there were no associations between other HOA terms or metrics and axial elongation in the ortho-k subjects (all $p > 0.05$).

Table 8.4 Significant fixed effects and parameter estimates of higher order aberrations on axial length and its elongation (interaction with time) in orthokeratology subjects (n = 63).

Parameters	B	p value
Model 1 – HO RMS		
Intercept	24.45	**< 0.001**
Visit	0.36	**< 0.001**
Sex†	-0.62	**0.001**
Residual SER	-0.04	**0.015**
Time by HO RMS	-0.29	**< 0.001**
Model 2 – SA RMS and coma RMS		
Intercept	24.64	**< 0.001**
Visit	0.35	**< 0.001**
Sex†	-0.51	**0.005**
Residual SER	-0.05	**0.006**
Baseline SA RMS	-4.87	**0.010**
Time by coma RMS	-0.43	**0.001**
Model 3 – spherical aberration (Z_4^0 and Z_6^0)		
Intercept	24.63	**< 0.001**
Visit	0.31	**< 0.001**
Sex†	-0.54	**0.002**
Residual SER	-0.06	**0.012**
Baseline Z_4^0	-4.75	**0.006**
Z_4^0 (all visits)	0.40	**0.048**
Time by Z_4^0	-0.28	**0.041**

SER: spherical equivalent refraction, RMS: root-mean-square, HO: higher order aberrations, SA: spherical aberration.
†Parameter estimate for girls.

8.3.5 Predictive values of induced higher order aberrations for axial elongation

The associations between induced HOAs at the one-month visit and axial length or its elongation across all study visits were also investigated (Table 8.5). Since the ocular HOA data of one and four subjects at the baseline and one-month visit were missing, respectively, a total of 59 subjects were analysed in this predictive model. Axial length increased by 0.19-0.26 mm each year ($p < 0.001$). Boys exhibited a longer axial length (boys: $\beta = 0.57 - 0.58$ mm, $p = 0.002$). Every additional 1.00 D of residual SER (more hyperopia/less myopia) was associated with 0.03 mm less axial elongation per year ($p \leq 0.001$).

Higher levels of induced spherical aberration RMS, induced primary spherical aberration (Z_4^0), and induced negative primary vertical coma (Z_3^{-1}) at the one-month visit were associated with slower axial elongation. Every micron increase of induced spherical aberration RMS and induced primary spherical aberration (Z_4^0) were associated with 0.27 and 0.23 mm/y slower axial elongation, respectively, and axial elongation was 0.13 mm/y slower per micron decrease in induced primary vertical coma (Z_3^{-1}) (all $p < 0.05$). No associations between other spherical or comatic aberration terms and axial elongation were found (all $p > 0.05$).

Table 8.5 Significant fixed effects and parameter estimates of the induced higher order aberrations at the one-month visit on axial length and its elongation (interaction with time) in the orthokeratology subjects (n = 59).

Parameters	**ß**	**p value**
Model 1 – HO RMS		
Intercept	24.87	**< 0.001**
Visit	0.23	**< 0.001**
Sex†	-0.57	**0.002**
Time by residual SER	-0.03	**0.001**
Time by ΔHO RMS	-0.08	0.239
Model 2 – SA and coma RMS		
Intercept	24.87	**< 0.001**
Visit	0.26	**< 0.001**
Sex†	-0.57	**0.002**
Time by residual SER	-0.03	**< 0.001**
Time by ΔSA RMS	-0.27	**0.006**
Model 3 – spherical aberration (Z_4^0 and Z_6^0)		
Intercept	24.91	**< 0.001**
Visit	0.26	**< 0.001**
Sex†	-0.58	**0.002**
Time by residual SER	-0.03	**0.001**
Time by ΔZ_4^0	-0.23	**0.011**
Model 4 – comatic aberration (Z_3^{-1}, Z_3^1, Z_5^{-1}, and Z_5^1)		
Intercept	24.83	**< 0.001**
Visit	0.19	**< 0.001**
Sex†	-0.57	**0.002**
Time by residual SER	-0.03	**< 0.001**
Time by ΔZ_3^{-1}	0.13	**0.021**

SER: spherical equivalent refraction, RMS: root-mean-square, HO: higher order aberrations, SA: spherical aberration.
†Parameter estimates for girls, Δchanges relative to one-month visit.

8.4 Discussion

This randomised (among ortho-k groups only) longitudinal study investigated the effect of different compression factors in ortho-k lenses on axial elongation over a two-year period. Increasing the compression factor by 1.00 D significantly increased the induced HOAs, some of which were associated with slower axial elongation and therefore, improved myopia control effectiveness. A higher level of induced HOAs after one month of lens wear, particular spherical aberration, was associated with slower axial elongation over the two-year period.

Ortho-k treatment is proven to be an effective intervention to arrest myopia progression (Si et al., 2015; Sun et al., 2015; Wen et al., 2015; Huang et al., 2016; Li et al., 2016b; Cho and Cheung, 2017b; Li et al., 2017b; Prousali et al., 2019; Guan et al., 2020). Due to the high dropout rate (63%) in the non-randomised control group of the current study, the axial elongation from a randomised clinical trial in Hong Kong (Yam et al., 2018) using atropine eye drops for myopia control was extracted for comparing the effectiveness for ortho-k lenses with conventional (0.75 D) and increased (1.75 D) compression factors. The mean axial elongation of the placebo group was 0.41 ± 0.22 mm at the one-year visit. Comparing with the axial elongations of the ortho-k subjects at the first year visit, the effectiveness of conventional and increased compression factors were 29% and 56%, respectively. Considering the ortho-k subjects in the current study, after two years of treatment, ortho-k lenses with increased compression factor (1.75 D) improved myopia control effectiveness by 34%, compared with the conventional compression factor (0.75 D) group.

It is well known that ocular HOAs increase after ortho-k treatment (Joslin et al., 2003; Berntsen et al., 2005; Stillitano et al., 2008; Gifford et al., 2013; Lian et al., 2014; Hiraoka et al., 2015). In the current study, the HO RMS, spherical, and comatic aberrations RMS increased by approximately five, seven, and three times, respectively, over a 5-mm pupil size. Spherical aberration (Z_4^0 and Z_6^0) and vertical coma (Z_3^{-1} and Z_5^{-1}) exhibited the largest changes, in line with previous results (Joslin et al., 2003; Berntsen et al., 2005; Hiraoka et al., 2005; Stillitano et al., 2007b; Stillitano et al., 2008; Gifford et al., 2013; Kang et al., 2013; Faria-Ribeiro et al., 2016a; Chen et al., 2017; Santodomingo-Rubido et al., 2017; Kim et al., 2019).

Regarding the association between ocular HOAs and axial elongation, higher levels of HO RMS and comatic aberration RMS were associated with slower axial elongation, after adjusting for other potential confounders, throughout the study period. A similar observation was also noted in spectacle-wearing and ortho-k treated children that, higher levels of HO RMS was associated with slower axial elongation (Chapter 5 and Hiraoka et al. (2017)), whereas the effect of comatic aberration RMS was similarly presented by Hiraoka et al. (2015) and Kim et al. (2019) over a 4-mm pupil. Asymmetric corneal shape across the treatment zone (usually less than 5 mm) may be one of the key HOA terms affecting the ortho-k performance for myopia control. However, further analyses on individual comatic aberration terms did not reveal any relationship with axial elongation in the current study. Since RMS values do not provide any directional cue due to the loss of sign, applying this metric may mask or exaggerate its influence, and this may be the reason for the discrepancy between the findings of the current study and Hiraoka et al. (2015).

When examining the predictive values of induced HOAs at one-month for axial elongation across all study visits, it was noted that spherical aberration RMS, primary spherical aberration (Z_4^0), and negative primary vertical coma (Z_3^{-1}) were significantly associated with slower axial elongation, as similarly found in retrospective analyses of spectacle-wearing and ortho-k children (Chapters 5 and 6). Guo et al. (2008) previously studied contrast sensitivity with and without HOA correction using adaptive optics under certain defocus conditions. They found that ocular HOAs may interact with defocus and result in less deterioration in visual acuity. Further simulations have shown that positive spherical aberration, in combination with hyperopic defocus, which is commonly seen in ortho-k subjects, may have a protective effect against myopia progression (Thibos et al., 2013a). The induced positive spherical aberration, in this case, may produce a better protective effect against axial elongation in providing a better retinal image contrast in the increased compression factor group, compared with the combination of positive spherical aberration.

The significant difference in refractive correction over time was unexpected because no significant difference was observed in the previous one-month study using contralaterally self-controlled study design (Chapter 7). In the current study, there was no significant difference between the two ortho-k group until the first year visit. The most likely reason for this significant difference between the two ortho-k groups arising after one year of treatment is different rates of myopia progression, since the targeted myopia correction of the ortho-k lenses was not changed in order to maintain the same compression factor exerting on the eyes throughout the study period. Careful and routine ortho-k aftercares are therefore necessary for practitioners to monitor the refractive status and axial elongation in children wearing ortho-k lenses.

One limitation of the current study was that the control group was not enrolled through randomisation. A corresponding high dropout rate (40%) due to the concern of myopia progression was similarly observed in another non-randomised ortho-k study (38%) (Chen et al., 2013). This could result in a heavily biased control group for comparisons, and result in a virtually non-progressing control group. As there are numerous myopia control interventions available on the market, a true randomised control group may not feasible in the future. Instead, conventional treatment which is proven to be effective, for example, ortho-k lenses with conventional compression factor, may be regarded as the alternative control group in the future. Cross-over study designs may be another method to "balance" the axial elongation from using control and treatment interventions.

Another limitation was that the residual refraction obtained was not as hyperopic as expected. Since adjusting the targeted refractive correction of the lens would indirectly affect other lens parameters such as alignment curves, changing the lenses with adjusted correction was not performed in this study. The results, however, comparing with the axial elongation of the control group of Yam et al. (2018), revealed that the myopia control effectiveness of ortho-k treatment was feasible in ortho-k subjects wearing lenses of conventional compression factor (0.75 D) and the performance was superior in subjects using lenses of increased compression factor (1.75 D).

8.5 Conclusion

This two-year longitudinal study examined the influence of different compression factors in ortho-k lenses on axial elongation. Increasing the compression factor by 1.00 D significantly increased the induced HOAs, particularly spherical aberration. Given the association between induced HOAs and axial elongation, altering the compression factor of ortho-k lenses may be a feasible method to improve the effectiveness of ortho-k treatment for myopia control.

Paper published from work reported in this chapter:

Wan K, Lau JK, Cheung SW, P Cho. (2020) Orthokeratology with increased compression factor (OKIC): study design and preliminary results. BMJ Open Ophthalmol 5:e000345.

Chapter 9

Conclusions

9.1 Summary

This thesis aims to investigate the relationship between ocular HOAs and axial elongation in spectacle-wearing (Chapter 5) and ortho-k treated (Chapter 6) children. Considering the association analyses performed with adjustment for other confounding factors such as sex, baseline age, baseline SER, a higher level of HOAs (and baseline HOAs) was associated with slower axial elongation. Among all HOA terms, positive spherical aberration appeared to be main factor associated with slower axial elongation.

Despite the significant increases in primary spherical aberration (Z_4^0) and primary comatic aberrations (Z_3^{-1} and Z_3^1) after ortho-k treatment, spherical aberration remains a significant associator with axial elongation (Chapter 6).

Due to these significant associations, the compression factor of ortho-k lenses was increased by 1.00 D in order to alter the induced HOAs and therefore improve the myopia control effectiveness. The short-term study investigated the effect of different compression factors (0.75 and 1.75 D) on the fellow eyes of the subjects over one month (Chapter 7). Increasing the compression factor could result in higher levels of HO RMS, spherical aberration RMS, and primary spherical aberration (Z_4^0), without significant altering the refractive correction of the subjects. However, using choroidal thickness as a biomarker, no significant changes between the eyes were noted. After one week of lens wear, the choroidal thickness increased but the changes approached the repeatability values of the OCT instrument.

The long-term study investigated the influence of different compression factors (0.75 and 1.75 D) on axial elongation over a two-year period (Chapter 8). The high dropout rate and potentially biased control group make it difficult for comparisons. Using the axial elongation in the placebo group from another randomised clinical trial, among the two ortho-k groups with randomised compression factors in the current study, increasing the compression factor by 1.00 D further slowed axial elongation by an additional 34%, when comparing with the conventional compression factor group.

Subjects in the ortho-k group with increased compression factor only demonstrated significant differences in SER, compared with the conventional compression factor group, after six months of lens wear.

Increasing the compression of ortho-k lenses significantly increased the induced HOAs, particularly primary spherical aberration. Given the association of ocular HOAs throughout the study period and induced HOAs at one-month visit with axial elongation, increasing the compression factor by 1.00 D may improve ortho-k effectiveness in slowing axial elongation.

9.2 Limitations

As in most research studies, there were some limitations in the retrospective and prospective experiments. The associations between HOAs and axial elongation in the retrospective and prospective studies were studied over a two-year period. The influence of baseline (in control subjects) or induced HOAs (in ortho-k treated subjects) on axial elongation over a longer period of time is unknown. The effect of baseline or induced HOAs on axial elongation may also diminish over time, and this requires further monitoring of the subjects and investigation until the stabilisation of axial elongation, which is beyond the scope of this study.

Pupil sizes vary between individuals due to differences in age, race, and refractive errors. In the analyses of ocular HOAs, fixed pupil sizes of 6 mm (cycloplegic, Chapters 5 and 6) or 5 mm (non-cycloplegic, Chapters 7 and 8) were used. For the retrospective analyses, a 6-mm pupil size was used consistent with other studies of HOA in children (Hiraoka et al., 2017). For the prospective analyses, a 5-mm pupil size was used to approximate the photopic pupil diameter in children (mean pupil size under photopic [80 cd/m2]: 5.07 ± 0.80 mm; Lam et al. (2013)). Since pupil size varies with luminance, analysing the association between HOAs and axial elongation for a range of different pupil sizes may provide a more comprehensive understanding the visually dependent process of axial elongation. This requires further monitoring and investigation, which is beyond the scope of the current study.

9.3 Future work and potential insights

Increasing the compression factor of ortho-k lenses by 1.00 D appears to be improve the effectiveness of myopia control. Alternative modifications of lens parameters, such as reducing the treatment zone size or steepening the reverse curve, may also alter the levels of induced HOAs, , and potentially improve ortho-k effectiveness for myopia control.

Given the association between HOAs and axial elongation, combining low dose atropine (0.01%) together with ortho-k treatment may be beneficial in magnifying this effect. Vincent et al. (2020) recently investigated the association between HOAs and axial elongation in 53 subjects receiving combined (0.01% atropine with ortho-k, n = 25) and ortho-k (n = 28) treatment. The combined treatment group showed increases in photopic pupil size by around 0.5 mm and induced HO RMS by 70%, whereas some HOA metrics were associated with axial elongation. Therefore, given the association between HOAs and axial elongation in ortho-k treated children, adding treatment with 0.01% atropine to children undergoing ortho-k treatment (possibly with an increased compression factor) may be a useful combination treatment. However, the side effects (potential photophobia, decreased visual acuity, and systemic absorption) need to be taken into account.

The experiments and analyses in the thesis indicated a strong association between spherical aberration and less axial elongation in ortho-k treatment, however, as spherical aberration becomes more negative during accommodation, investigations on the relationship between changes in HOAs and accommodation over natural pupil diameters in subjects undergoing ortho-k treatment may further the current understanding of the optical mechanism involved in slowing axial elongation.

References

Abbott ML, Schmid KL, Strang NC. (1998). Differences in the accommodation stimulus response curves of adult myopes and emmetropes. Ophthalmic Physiol Opt 18:13-20.
Adler D, Millodot M. (2006). The possible effect of undercorrection on myopic progression in children. Clin Exp Optom 89:315-21.
Albarran C, Pons AM, Lorente A, Montes R, Artigas JM. (1997). Influence of the tear film on optical quality of the eye. Cont Lens Anterior Eye 20:129-35.
Alharbi A, La Hood D, Swarbrick HA. (2005). Overnight orthokeratology lens wear can inhibit the central stromal edema response. Invest Ophthalmol Vis Sci 46:2334-40.
Alharbi A, Swarbrick HA. (2003). The effects of overnight orthokeratology lens wear on corneal thickness. Invest Ophthalmol Vis Sci 44:2518-23.
Allen PM, Radhakrishnan H, Price H, Rae S, Theagarayan B, Calver RI, Sailoganathan A, Latham K, O'Leary DJ. (2013). A randomised clinical trial to assess the effect of a dual treatment on myopia progression: the Cambridge anti-myopia study. Ophthalmic Physiol Opt 33:267-76.
Allen PM, Radhakrishnan H, Rae S, Calver RI, Theagarayan BP, Nelson P, Osuobeni E, Sailoganathan A, Price H, O'Leary DJ. (2009). Aberration control and vision training as an effective means of improving accommodation in individuals with myopia. Invest Ophthalmol Vis Sci 50:5120-9.
Alonso-Caneiro D, Read SA, Collins MJ. (2013). Automatic segmentation of choroidal thickness in optical coherence tomography. Biomed Opt Express 4:2795-812.
Amano S, Amano Y, Yamagami S, Miyai T, Miyata K, Samejima T, Oshika T. (2004). Age-related changes in corneal and ocular higher-order wavefront aberrations. Am J Ophthalmol 137:988-92.
Anera RG, Villa C, Jimenez JR, Gutierrez R. (2009). Effect of LASIK and contact lens corneal refractive therapy on higher order aberrations and contrast sensitivity function. J Refract Surg 25:277-84.
Ang M, Flanagan JL, Wong CW, Muller A, Davis A, Keys D, Resnikoff S, Jong M, Wong TY, Sankaridurg P. (2020). Review: myopia control strategies recommendations from the 2018 WHO/IAPB/BHVI meeting on myopia. Br J Ophthalmol. doi: 10.1136/bjophthalmol-2019-315575. [Epub ahead of print]
Applegate RA, Donnelly WJ, Marsack JD, Koenig DE, Pesudovs K. (2007). Three-dimensional relationship between high-order root-mean-square wavefront error, pupil diameter, and aging. J Opt Soc Am A 24:578-87.
Applegate RA, Marsack JD, Ramos R, Sarver EJ. (2003). Interaction between aberrations to improve or reduce visual performance. J Cataract Refract Surg 29:1487-95.
Applegate RA, Sarver EJ, Khemsara V. (2002). Are all aberrations equal? J Refract Surg 18:S556-S62.
Applegate RA, Thibos LN, Bradley A, Marcos S, Roorda A, Salmon TO, Atchison DA. (2000). Reference axis selection: subcommittee report of the OSA Working Group to establish standards for measurement and reporting of optical aberrations of the eye. J Refract Surg 16:S656-8.
Armstrong RA. (2013). Statistical guidelines for the analysis of data obtained from one or both eyes. Ophthalmic Physiol Opt 33:7-14.

Armstrong RA. (2019). Should Pearson's correlation coefficient be avoided? Ophthalmic Physiol Opt 39:316-27.
Artal P, Berrio E, Guirao A, Piers P. (2002). Contribution of the cornea and internal surfaces to the change of ocular aberrations with age. J Opt Soc Am A 19:137-43.
Artal P, Guirao A. (1998). Contributions of the cornea and the lens to the aberrations of the human eye. Opt Lett 23:1713-5.
Artal P, Guirao A, Berrio E, Williams DR. (2001). Compensation of corneal aberrations by the internal optics in the human eye. J Vis 1:1-8.
Atchison DA. (2004). Recent advances in representation of monochromatic aberrations of human eyes. Clin Exp Optom 87:138-48.
Atchison DA. (2005). Recent advances in measurement of monochromatic aberrations of human eyes. Clin Exp Optom 88:5-27.
Atchison DA, Collins MJ, Wildsoet CF, Christensen J, Waterworth MD. (1995). Measurement of monochromatic ocular aberrations of human eyes as a function of accommodation by the Howland aberroscope technique. Vision Res 35:313-23.
Atchison DA, Li SM, Li H, Li SY, Liu LR, Kang MT, Meng B, Sun YY, Zhan SY, Mitchell P, Wang N. (2015). Relative peripheral hyperopia does not predict development and progression of myopia in children. Invest Ophthalmol Vis Sci 56:6162-70.
Atchison DA, Markwell EL. (2008). Aberrations of emmetropic subjects at different ages. Vision Res 48:2224-31.
Atchison DA, Pritchard N, Schmid KL. (2006). Peripheral refraction along the horizontal and vertical visual fields in myopia. Vision Res 46:1450-8.
Atchison DA, Pritchard N, White SD, Griffiths AM. (2005). Influence of age on peripheral refraction. Vision Res 45:715-20.
Atchison DA, Rosen R. (2016). The possible role of peripheral refraction in development of myopia. Optom Vis Sci 93:1042-4.
Atchison DA, Suheimat M, Mathur A, Lister LJ, Rozema J. (2016). Anterior corneal, posterior corneal, and lenticular contributions to ocular aberrations. Invest Ophthalmol Vis Sci 57:5263-70.
Atchison DA, Thibos LN. (2016). Optical models of the human eye. Clin Exp Optom 99:99-106.
Bai Y, Nichols JJ. (2019). In vivo thickness measurement of the lipid layer and the overall tear film by interferometry. Opt Lett 44:2410-3.
Bao J, Le R, Wu J, Shen Y, Lu F, He JC. (2009). Higher-order wavefront aberrations for populations of young emmetropes and myopes. J Optom 2:51-8.
Barr JT, Rah MJ, Meyers W, Legerton J. (2004). Recovery of refractive error after corneal refractive therapy. Eye & Contact Lens 30:247-51.
Batres L, Peruzzo S, Serramito M, Carracedo G. (2020). Accommodation response and spherical aberration during orthokeratology. Graefes Arch Clin Exp Ophthalmol 258:117-27.
Berntsen DA, Barr JT, Mitchell GL. (2005). The effect of overnight contact lens corneal reshaping on higher-order aberrations and best-corrected visual acuity. Optom Vis Sci 82:490-7.
Berntsen DA, Sinnott LT, Mutti DO, Zadnik K. (2012). A randomized trial using progressive addition lenses to evaluate theories of myopia progression in children with a high lag of accommodation. Invest Ophthalmol Vis Sci 53:640-9.
Berntsen DA, Sinnott LT, Mutti DO, Zadnik K, the CLEERE Study Group. (2011). Accommodative lag and juvenile-onset myopia progression in children wearing refractive correction. Vision Res 51:1039-46.
Berrio E, Tabernero J, Artal P. (2010). Optical aberrations and alignment of the eye with age. J Vision 10:34.
Bland JM, Altman D. (1986). Statistical methods for assessing agreement between two methods of clinical measurement. The Lancet 327:307-10.
Borja D, Manns F, Ho A, Ziebarth N, Rosen AM, Jain R, Amelinckx A, Arrieta E, Augusteyn RC, Parel JM. (2008). Optical power of the isolated human crystalline lens. Invest Ophthalmol Vis Sci 49:2541-8.
Brabander JD, Hendricks T, Chateau N, Munnik M, Harms F, Horst Fvd, Bours S, Hendrikse F, Knottnerus A. (2004). Ametropia and higher order aberrations in children 12–13 years of age. Invest Ophthalmol Vis Sci 45:2761.
Brennan NA, Cheng X. (2019). Commonly beld beliefs about myopia that lack a robust evidence base. Eye & Contact Lens 45:215-25.

Brown N. (1973). The change in shape and internal form of the lens of the eye on accommodation. Exp Eye Res 15:441-59.
Brunette I, Bueno JM, Parent M, Hamam H, Simonet P. (2003). Monochromatic aberrations as a function of age, from childhood to advanced age. Invest Ophthalmol Vis Sci 44:5438-46.
Buehren T, Collins MJ. (2006). Accommodation stimulus-response function and retinal image quality. Vision Res 46:1633-45.
Buehren T, Collins MJ, Carney L. (2003). Corneal aberrations and reading. Optom Vis Sci 80:159-66.
Buehren T, Collins MJ, Carney LG. (2005). Near work induced wavefront aberrations in myopia. Vision Res 45:1297-312.
Buehren T, Iskander DR, Collins MJ, Davis B. (2007). Potential higher-order aberration cues for sphero-cylindrical refractive error development. Optom Vis Sci 84:163-74.
Bullimore MA, Brennan NA. (2019). Myopia control: why each diopter matters. Optom Vis Sci 96:463-5.
Bullimore MA, Sinnott LT, Jones-Jordan LA. (2013). The risk of microbial keratitis with overnight corneal reshaping lenses. Optom Vis Sci 90:937-44.
Campbell CE. (2003). Matrix method to find a new set of Zernike coefficients from an original set when the aperture radius is changed. J Opt Soc Am A 20:209-17.
Campbell MC, Kisilak M, Hunter JJ, Bueno JM, King D, Irving EL. (2002). Optical aberrations of the eye and eye growth: why aberrations may be important to understanding refractive error development. J Vision 2:111.
Carkeet A, Luo HD, Tong L, Saw SM, Tan DT. (2002). Refractive error and monochromatic aberrations in Singaporean children. Vision Res 42:1809-24.
Carkeet A, Velaedan S, Tan YK, Lee DY, Tan DT. (2003). Higher order ocular aberrations after cycloplegic and non-cycloplegic pupil dilation. J Refract Surg 19:316-22.
Carvalho LA, Castro JC, Carvalho LA. (2002). Measuring higher order optical aberrations of the human eye: techniques and applications. Braz J Med Biol Res 35:1395-406.
Castejon-Mochon JF, Lopez-Gil N, Benito A, Artal P. (2002). Ocular wave-front aberration statistics in a normal young population. Vision Res 42:1611-7.
Chakraborty R, Read SA, Collins MJ. (2011). Diurnal variations in axial length, choroidal thickness, intraocular pressure, and ocular biometrics. Invest Ophthalmol Vis Sci 52:5121-9.
Chakraborty R, Read SA, Collins MJ. (2012). Monocular myopic defocus and daily changes in axial length and choroidal thickness of human eyes. Exp Eye Res 103:47-54.
Chakraborty R, Read SA, Collins MJ. (2013). Hyperopic defocus and diurnal changes in human choroid and axial length. Optom Vis Sci 90:1187-98.
Chan B, Cho P, Cheung SW. (2008a). Orthokeratology practice in children in a university clinic in Hong Kong. Clin Exp Optom 91:453-60.
Chan B, Cho P, Mountford J. (2008b). The validity of the Jessen formula in overnight orthokeratology: a retrospective study. Ophthalmic Physiol Opt 28:265-8.
Chan KY, Cheung SW, Cho P. (2014). Orthokeratology for slowing myopic progression in a pair of identical twins. Cont Lens Anterior Eye 37:116-9.
Chang CF, Cheng HC. (2019). Effect of orthokeratology lens on contrast sensitivity function and high-order aberrations in children and adults. Eye Contact Lens. doi: 10.1097/ICL.0000000000000667. [Epub ahead of print]
Charm J, Cho P. (2013). High myopia–partial reduction ortho-k: a 2-year randomized study. Optom Vis Sci 90:530-9.
Charman WN. (2005). Wavefront technology: past, present and future. Cont Lens Anterior Eye 28:75-92.
Charman WN, Mountford J, Atchison DA, Markwell EL. (2006). Peripheral refraction in orthokeratology patients. Optom Vis Sci 83:641-8.
Charman WN, Radhakrishnan H. (2010). Peripheral refraction and the development of refractive error: a review. Ophthalmic Physiol Opt 30:321-38.
Chen C, Cheung SW, Cho P. (2013). Myopia control using toric orthokeratology (TO-SEE study). Invest Ophthalmol Vis Sci 54:6510-7.
Chen D, Lam AK, Cho P. (2010a). Posterior corneal curvature change and recovery after 6 months of overnight orthokeratology treatment. Ophthalmic Physiol Opt 30:274-80.

Chen J, Huang W, Zhu R, Jiang J, Li Y. (2018). Influence of overnight orthokeratology lens fitting decentration on corneal topography reshaping. Eye Vis (Lond) 5:5.
Chen Q, Li M, Yuan Y, Me R, Yu Y, Shi G, Ke B. (2017). Interaction between corneal and internal ocular aberrations induced by orthokeratology and its influential factors. Biomed Res Int 2017:3703854.
Chen X, Sankaridurg P, Donovan L, Lin Z, Li L, Martinez A, Holden B, Ge J. (2010b). Characteristics of peripheral refractive errors of myopic and non-myopic chinese eyes. Vision Res 50:31-5.
Chen Y, Zhang J, Morgan IG, He M. (2016a). Identifying children at risk of high myopia using population centile curves of refraction. PLoS One 11:e0167642.
Chen Z, Niu L, Xue F, Qu X, Zhou Z, Zhou X, Chu R. (2012). Impact of pupil diameter on axial growth in orthokeratology. Optom Vis Sci 89:1636-40.
Chen Z, Xue F, Zhou J, Qu X, Zhou X. (2016b). Effects of orthokeratology on choroidal thickness and axial length. Optom Vis Sci 93:1064-71.
Cheng H, Barnett JK, Vilupuru AS, Marsack JD, Kasthurirangan S, Applegate RA, Roorda A. (2004). A population study on changes in wave aberrations with accommodation. J Vis 4:272-80.
Cheng X, Bradley A, Hong X, Thibos LN. (2003a). Relationship between refractive error and monochromatic aberrations of the eye. Optom Vis Sci 80:43-9.
Cheng X, Himebaugh NL, Kollbaum PS, Thibos LN, Bradley A. (2003b). Validation of a clinical Shack-Hartmann aberrometer. Optom Vis Sci 80:587-95.
Cheng X, Xu J, Chehab K, Exford J, Brennan N. (2016). Soft contact lenses with positive spherical aberration for myopia control. Optom Vis Sci 93:353-66.
Cheung SW, Boost MV, Cho P. (2019). Pre-treatment observation of axial elongation for evidence-based selection of children in Hong Kong for myopia control. Cont Lens Anterior Eye 42:392-8.
Cheung SW, Cho P. (2004). Subjective and objective assessments of the effect of orthokeratology – a cross-sectional study. Curr Eye Res 28:121-7.
Cheung SW, Cho P. (2013). Validity of axial length measurements for monitoring myopic progression in orthokeratology. Invest Ophthalmol Vis Sci 54:1613-5.
Cheung SW, Cho P. (2016). Long-term effect of orthokeratology on the anterior segment length. Cont Lens Anterior Eye 39:262-5.
Cheung SW, Cho P, Chui WS, Woo GC. (2007). Refractive error and visual acuity changes in orthokeratology patients. Optom Vis Sci 84:410-6.
Cheung SW, Lam C, Cho P. (2014). Parents' knowledge and perspective of optical methods for myopia control in children. Optom Vis Sci 91:634-41.
Chiang ST, Phillips JR, Backhouse S. (2015). Effect of retinal image defocus on the thickness of the human choroid. Ophthalmic Physiol Opt 35:405-13.
Chiang ST, Chen TL, Phillips JR. (2018). Effect of optical defocus on choroidal thickness in healthy adults with presbyopia. Invest Ophthalmol Vis Sci 59:5188-93.
Cho P, Chan B, Cheung SW, Mountford J. (2012). Do fenestrations affect the performance of orthokeratology lenses? Optom Vis Sci 89:401-10.
Cho P, Cheung SW. (2012). Retardation of myopia in orthokeratology (ROMIO) study: a 2-year randomized clinical trial. Invest Ophthalmol Vis Sci 53:7077-85.
Cho P, Cheung SW. (2017a). Discontinuation of orthokeratology on eyeball elongation (DOEE). Cont Lens Anterior Eye 40:82-7.
Cho P, Cheung SW. (2017b). Protective role of orthokeratology in reducing risk of rapid axial elongation: a reanalysis of data from the ROMIO and TO-SEE studies. Invest Ophthalmol Vis Sci 58:1411-6.
Cho P, Cheung SW, Edwards M. (2005). The longitudinal orthokeratology research in children (LORIC) in Hong Kong: a pilot study on refractive changes and myopic control. Curr Eye Res 30:71-80.
Cho P, Tan Q. (2019). Myopia and orthokeratology for myopia control. Clin Exp Optom 102:364-77.
Choi KY, Yu WY, Lam CHI, Li ZC, Chin MP, Lakshmanan Y, Wong FSY, Do CW, Lee PH, Chan HHL. (2017). Childhood exposure to constricted living space: a possible environmental threat for myopia development. Ophthalmic Physiol Opt 37:568-75.

Choo J, Caroline P, Harlin D. (2004). How does the cornea change under corneal reshaping contact lenses? Eye & Contact Lens 30:211-3.

Choy BNK, You Q, Zhu MM, Lai JSM, Ng ALK, Wong IYH. (2020). Prevalence and associations of myopia in Hong Kong primary school students. Jpn J Ophthalmol. doi: 10.1007/s10384-020-00733-4. [Epub ahead of print]

Chua SY, Sabanayagam C, Cheung YB, Chia A, Valenzuela RK, Tan D, Wong TY, Cheng CY, Saw SM. (2016). Age of onset of myopia predicts risk of high myopia in later childhood in myopic Singapore children. Ophthalmic Physiol Opt 36:388-94.

Chung K, Mohidin N, O'Leary DJ. (2002). Undercorrection of myopia enhances rather than inhibits myopia progression. Vision Res 42:2555-9.

Collins MJ, Buehren T, Bece A, Voetz SC. (2006a). Corneal optics after reading, microscopy and computer work. Acta Ophthalmol Scand 84:216-24.

Collins MJ, Buehren T, Iskander DR. (2006b). Retinal image quality, reading and myopia. Vision Res 46:196-215.

Collins MJ, Wildsoet CF, Atchison DA. (1995). Monochromatic aberrations and myopia. Vision Res 35:1157-63.

Correction of Myopia Evaluation Trial 2 Study Group for the Pediatric Eye Disease Investigator G. (2011). Progressive-addition lenses versus single-vision lenses for slowing progression of myopia in children with high accommodative lag and near esophoria. Invest Ophthalmol Vis Sci 52:2749-57.

Coviltir V, Burcel M, Cherecheanu AP, Ionescu C, Dascalescu D, Potop V, Burcea M. (2019). Update on myopia risk factors and microenvironmental changes. J Ophthalmol 2019.

Dai G-m. (2006). Scaling Zernike expansion coefficients to smaller pupil sizes: a simpler formula. J Opt Soc Am A 23:539-43.

Davis WR, Raasch TW, Mitchell GL, Mutti DO, Zadnik K. (2005). Corneal asphericity and apical curvature in children: a cross-sectional and longitudinal evaluation. Invest Ophthalmol Vis Sci 46:1899-906.

Delshad S, Collins MJ, Read SA, Vincent SJ. (2020). The time course of the onset and recovery of axial length changes in response to imposed defocus. Sci Rep 10:8322.

Dingeldein SA, Klyce SD. (1989). The topography of normal corneas. Arch Ophthalmol 107:512-8.

Dobos MJ, Twa MD, Bullimore MA. (2009). An evaluation of the Bausch & Lomb Zywave aberrometer. Clin Exp Optom 92:238-45.

Donovan L, Sankaridurg P, Ho A, Naduvilath T, Smith EL, Holden BA. (2012). Myopia progression rates in urban children wearing single-vision spectacles. Optom Vis Sci 89:27-32.

Downie LE, Lowe R. (2013). Corneal reshaping influences myopic prescription stability (crimps): an analysis of the effect of orthokeratology on childhood myopic refractive stability. Eye Contact Lens 39:303-10.

Dubbelman M, Sicam VA, van der Heijde RG. (2007). The contribution of the posterior surface to the coma aberration of the human cornea. J Vis 7:10 1-8.

Efron N. (1998). Grading scales for contact lens complications. Ophthalmic Physiol Opt 18:182-6.

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

El Hage S, Leach NE, Miller W, Prager TC, Marsack J, Parker K, Minavi A, Gaume A. (2007). Empirical advanced orthokeratology through corneal topography: the University of Houston clinical study. Eye & Contact Lens 33:224-35.

Fan Q, Guo X, Tideman JW, Williams KM, Yazar S, Hosseini SM, Howe LD, Pourcain BS, Evans DM, Timpson NJ, McMahon G, Hysi PG, Krapohl E, Wang YX, Jonas JB, Baird PN, Wang JJ, Cheng CY, Teo YY, Wong TY, Ding X, Wojciechowski R, Young TL, Parssinen O, Oexle K, Pfeiffer N, Bailey-Wilson JE, Paterson AD, Klaver CC, Plomin R, Hammond CJ, Mackey DA, He M, Saw SM, Williams C, Guggenheim JA, Consortium C. (2016). Childhood gene-environment interactions and age-dependent effects of genetic variants associated with refractive error and myopia: The CREAM Consortium. Sci Rep 6:25853.

Faria-Ribeiro M, Belsue RN, Lopez-Gil N, Gonzalez-Meijome JM. (2016a). Morphology, topography, and optics of the orthokeratology cornea. J Biomed Opt 21:75011.

Faria-Ribeiro M, Navarro R, Gonzalez-Meijome JM. (2016b). Effect of pupil size on wavefront refraction during orthokeratology. Optom Vis Sci 93:1399-408.

Fedtke C, Ehrmann K, Holden BA. (2009). A review of peripheral refraction techniques. Optom Vis Sci 86:429-46.
Felipe-Marquez G, Nombela-Palomo M, Cacho I, Nieto-Bona A. (2015). Accommodative changes produced in response to overnight orthokeratology. Graefes Arch Clin Exp Ophthalmol 253:619-26.
Flaxman SR, Bourne RRA, Resnikoff S, Ackland P, Braithwaite T, Cicinelli MV, Das A, Jonas JB, Keeffe J, Kempen JH, Leasher J, Limburg H, Naidoo K, Pesudovs K, Silvester A, Stevens GA, Tahhan N, Wong TY, Taylor HR, Vision Loss Expert Group of the Global Burden of Disease S. (2017). Global causes of blindness and distance vision impairment 1990-2020: a systematic review and meta-analysis. Lancet Glob Health 5:e1221-e34.
Franssen L, Tabernero J, Coppens JE, van den Berg TJ. (2007). Pupil size and retinal straylight in the normal eye. Invest Ophthalmol Vis Sci 48:2375-82.
French AN, Morgan IG, Burlutsky G, Mitchell P, Rose KA. (2013). Prevalence and 5- to 6-year incidence and progression of myopia and hyperopia in australian schoolchildren. Ophthalmology 120:1482-91.
Fu AC, Qin J, Rong JB, Ji N, Wang WQ, Zhao BX, Lyu Y. (2020). Effects of orthokeratology lens on axial length elongation in unilateral myopia and bilateral myopia with anisometropia children. Cont Lens Anterior Eye 43:73-7.
Fujikado T, Kuroda T, Ninomiya S, Maeda N, Tano Y, Oshika T, Hirohara Y, Mihashi T. (2004). Age-related changes in ocular and corneal aberrations. Am J Ophthalmol 138:143-6.
Gambra E, Sawides L, Dorronsoro C, Marcos S. (2009). Accommodative lag and fluctuations when optical aberrations are manipulated. J Vis 9:4 1-15.
Gardner DJ, Walline JJ, Mutti DO. (2015). Choroidal thickness and peripheral myopic defocus during orthokeratology. Optom Vis Sci 92:579-88.
Gatinel D, Delair E, Abi-Farah H, Hoang-Xuan T. (2005). Distribution and enantiomorphism of higher-order ocular optical aberrations. J Fr Ophtalmol 28:1041-50.
Gaurisankar ZS, van Rijn GA, Lima JEE, Ilgenfritz AP, Cheng Y, Haasnoot GW, Luyten GPM, Beenakker J-WM. (2019). Correlations between ocular biometrics and refractive error: a systematic review and meta-analysis. Acta Ophthalmol 97:735-43.
Ghosh A, Collins MJ, Read SA, Davis BA, Iskander DR. (2011). The influence of downward gaze and accommodation on ocular aberrations over time. J Vis 11:17.
Gifford K, Gifford P, Hendicott PL, Schmid KL. (2017). Near binocular visual function in young adult orthokeratology versus soft contact lens wearers. Cont Lens Anterior Eye 40:184-9.
Gifford KL, Gifford P, Hendicott PL, Schmid KL. (2019). Zone of clear single binocular vision in myopic orthokeratology. Eye Contact Lens 46: 82-90.
Gifford KL, Gifford P, Hendicott PL, Schmid KL. (2020a). Stability of peripheral refraction changes in orthokeratology for myopia. Cont Lens Anterior Eye 43:44-53.
Gifford P, Au V, Hon B, Siu A, Xu P, Swarbrick HA. (2009). Mechanism for corneal reshaping in hyperopic orthokeratology. Optom Vis Sci 86:e306-11.
Gifford P, Li M, Lu H, Miu J, Panjaya M, Swarbrick HA. (2013). Corneal versus ocular aberrations after overnight orthokeratology. Optom Vis Sci 90:439-47.
Gifford P, Swarbrick HA. (2008). Time course of corneal topographic changes in the first week of overnight hyperopic orthokeratology. Optom Vis Sci 85:1165-71.
Gifford P, Swarbrick HA. (2013). Refractive changes from hyperopic orthokeratology monovision in presbyopes. Optom Vis Sci 90:306-13.
Gifford P, Tran M, Priestley C, Maseedupally V, Kang P. (2020b). Reducing treatment zone diameter in orthokeratology and its effect on peripheral ocular refraction. Cont Lens Anterior Eye 43:54-9.
Glasser A, Campbell MC. (1998). Presbyopia and the optical changes in the human crystalline lens with age. Vision Res 38:209-29.
Gong Q, Janowski M, Luo M, Wei H, Chen B, Yang G, Liu L. (2017). Efficacy and adverse effects of atropine in childhood myopia: a meta-analysis. JAMA Ophthalmol 135:624-30.
Gonzalez-Meijome JM, Faria-Ribeiro MA, Lopes-Ferreira DP, Fernandes P, Carracedo G, Queiros A. (2016). Changes in peripheral refractive profile after orthokeratology for different degrees of myopia. Curr Eye Res 41:199-207.
Gonzalez-Mesa A, Villa-Collar C, Lorente-Velazquez A, Nieto-Bona A. (2013). Anterior segment changes produced in response to long-term overnight orthokeratology. Curr Eye Res 38:862-70.

Greivenkamp JE, Schwiegerling J, Miller JM, Mellinger MD. (1995). Visual acuity modeling using optical raytracing of schematic eyes. Am J Ophthalmol 120:227-40.

Grzybowski A, Kanclerz P, Tsubota K, Lanca C, Saw SM. (2020). A review on the epidemiology of myopia in school children worldwide. BMC Ophthalmol 20:27.

Gu T, Gong B, Lu D, Lin W, Li N, He Q, Wei R. (2019). Influence of corneal topographic parameters in the decentration of orthokeratology. Eye Contact Lens 45:372-6.

Guan M, Zhao W, Geng Y, Zhang Y, Ma J, Chen Z, Peng M, Li Y. (2020). Changes in axial length after orthokeratology lens treatment for myopia: a meta-analysis. Int Ophthalmol 40:255-65.

Guggenheim JA, Zayats T, Prashar A, To CH. (2008). Axes of astigmatism in fellow eyes show mirror rather than direct symmetry. Ophthalmic Physiol Opt 28:327-33.

Guillon M, Dumbleton K, Theodoratos P, Gobbe M, Wooley CB, Moody K. (2016). The effects of age, refractive status, and luminance on pupil size. Optom Vis Sci 93:1093-100.

Guirao A, Redondo M, Artal P. (2000). Optical aberrations of the human cornea as a function of age. J Opt Soc Am A 17:1697-702.

Guo H, Atchison DA, Birt BJ. (2008). Changes in through-focus spatial visual performance with adaptive optics correction of monochromatic aberrations. Vision Res 48:1804-11.

Gwiazda J, Bauer J, Thorn F, Held R. (1995). A dynamic relationship between myopia and blur-driven accommodation in school-aged children. Vision Res 35:1299-304.

Gwiazda J, Deng L, Manny R, Norton TT. (2014). Seasonal variations in the progression of myopia in children enrolled in the correction of myopia evaluation trial. Invest Ophthalmol Vis Sci 55:752-8.

Gwiazda J, Thorn F, Bauer J, Held R. (1993). Myopic children show insufficient accommodative response to blur. Invest Ophthalmol Vis Sci 34:690-4.

Gwiazda J, Thorn F, Held R. (2005). Accommodation, accommodative convergence, and response AC/A ratios before and at the onset of myopia in children. Optom Vis Sci 82:273-8.

Gwiazda JE, Hyman L, Norton TT, Hussein MEM, Marsh-Tootle W, Manny R, Wang Y, Everett D. (2004). Accommodation and related risk factors associated with myopia progression and their interaction with treatment in COMET children. Invest Ophthalmol Vis Sci 45:2143-51.

Han X, Xu D, Ge W, Wang Z, Li X, Liu W. (2018). A comparison of the effects of orthokeratology lens, medcall lens, and ordinary frame glasses on the accommodative response in myopic children. Eye Contact Lens 44:268-71.

Hanumunthadu D, Ilginis T, Restori M, Sagoo MS, Tufail A, Balaggan KS, Patel PJ. (2017). Repeatability of swept-source optical coherence tomography retinal and choroidal thickness measurements in neovascular age-related macular degeneration. Br J Ophthalmol 101:603-8.

Haque S, Fonn D, Simpson T, Jones L. (2004). Corneal and epithelial thickness changes after 4 weeks of overnight corneal refractive therapy lens wear, measured with optical coherence tomography. Eye Contact Lens 30:189-93.

Haque S, Fonn D, Simpson T, Jones L. (2007). Corneal refractive therapy with different lens materials, part 1: corneal, stromal, and epithelial thickness changes. Optom Vis Sci 84:343-8.

Hartwig A, Atchison DA. (2012). Analysis of higher-order aberrations in a large clinical population. Invest Ophthalmol Vis Sci 53:7862-70.

Hartwig A, Atchison DA, Radhakrishnan H. (2013). Higher-order aberrations and anisometropia. Curr Eye Res 38:215-9.

Harvitt DM, Bonanno JA. (1999). Re-evaluation of the oxygen diffusion model for predicting minimum contact lens Dk/t values needed to avoid corneal anoxia. Optom Vis Sci 76:712-9.

Hashemi H, Khabazkhoob M, Jafarzadehpur E, Yekta A, Emamian MH, Shariati M, Fotouhi A. (2015). Higher order aberrations in a normal adult population. J Curr Ophthalmol 27:115-24.

He JC, Burns SA, Marcos S. (2000). Monochromatic aberrations in the accommodated human eye. Vision Res 40:41-8.

He JC, Gwiazda J, Thorn F, Held R. (2003). Wave-front aberrations in the anterior corneal surface and the whole eye. J Opt Soc Am A 20:1155-63.

He JC, Sun P, Held R, Thorn F, Sun X, Gwiazda JE. (2002). Wavefront aberrations in eyes of emmetropic and moderately myopic school children and young adults. Vision Res 42:1063-70.
He M, Du Y, Liu Q, Ren C, Liu J, Wang Q, Li L, Yu J. (2016). Effects of orthokeratology on the progression of low to moderate myopia in chinese children. BMC Ophthalmol 16:126.
Hepsen IF, Evereklioglu C, Bayramlar H. (2001). The effect of reading and near-work on the development of myopia in emmetropic boys: a prospective, controlled, three-year follow-up study. Vision Res 41:2511-20.
Hiraoka T, Kakita T, Okamoto F, Oshika T. (2015). Influence of ocular wavefront aberrations on axial length elongation in myopic children treated with overnight orthokeratology. Ophthalmology 122:93-100.
Hiraoka T, Kakita T, Okamoto F, Takahashi H, Oshika T. (2012). Long-term effect of overnight orthokeratology on axial length elongation in childhood myopia: a 5-year follow-up study. Invest Ophthalmol Vis Sci 53:3913-9.
Hiraoka T, Kotsuka J, Kakita T, Okamoto F, Oshika T. (2017). Relationship between higher-order wavefront aberrations and natural progression of myopia in schoolchildren. Sci Rep 7:7876.
Hiraoka T, Matsumoto Y, Okamoto F, Yamaguchi T, Hirohara Y, Mihashi T, Oshika T. (2005). Corneal higher-order aberrations induced by overnight orthokeratology. Am J Ophthalmol 139:429-36.
Hiraoka T, Mihashi T, Okamoto C, Okamoto F, Hirohara Y, Oshika T. (2009a). Influence of induced decentered orthokeratology lens on ocular higher-order wavefront aberrations and contrast sensitivity function. J Cataract Refract Surg 35:1918-26.
Hiraoka T, Okamoto C, Ishii Y, Kakita T, Okamoto F, Oshika T. (2008a). Time course of changes in ocular higher-order aberrations and contrast sensitivity after overnight orthokeratology. Invest Ophthalmol Vis Sci 49:4314-20.
Hiraoka T, Okamoto C, Ishii Y, Kakita T, Okamoto F, Takahashi H, Oshika T. (2009b). Patient satisfaction and clinical outcomes after overnight orthokeratology. Optom Vis Sci 86:875-82.
Hiraoka T, Okamoto C, Ishii Y, Kakita T, Oshika T. (2007). Contrast sensitivity function and ocular higher-order aberrations following overnight orthokeratology. Invest Ophthalmol Vis Sci 48:550-6.
Hiraoka T, Okamoto C, Ishii Y, Okamoto F, Oshika T. (2009c). Recovery of corneal irregular astigmatism, ocular higher-order aberrations, and contrast sensitivity after discontinuation of overnight orthokeratology. Br J Ophthalmol 93:203-8.
Hiraoka T, Okamoto C, Ishii Y, Takahira T, Kakita T, Oshika T. (2008b). Mesopic contrast sensitivity and ocular higher-order aberrations after overnight orthokeratology. Am J Ophthalmol 145:645-55.
Hiraoka T, Sekine Y, Okamoto F, Mihashi T, Oshika T. (2018). Safety and efficacy following 10-years of overnight orthokeratology for myopia control. Ophthalmic Physiol Opt 38:281-9.
Holden BA, Fricke TR, Wilson DA, Jong M, Naidoo KS, Sankaridurg P, Wong TY, Naduvilath TJ, Resnikoff S. (2016). Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. Ophthalmology 123:1036-42.
Hoogerheide J, Rempt F, Hoogenboom WP. (1971). Acquired myopia in young pilots. Ophthalmologica 163:209-15.
Hoseini-Yazdi H, Vincent SJ, Collins MJ, Read SA. (2019). Regional alterations in human choroidal thickness in response to short-term monocular hemifield myopic defocus. Ophthalmic Physiol Opt 39:172-82.
Howland HC, Howland B. (1977). A subjective method for the measurement of monochromatic aberrations of the eye. J Opt Soc Am 67:1508-18.
Hsu CC, Huang N, Lin PY, Fang SY, Tsai DC, Chen SY, Tsai CY, Woung LC, Chiou SH, Liu CJ. (2017). Risk factors for myopia progression in second-grade primary school children in Taipei: a population-based cohort study. Br J Ophthalmol 101:1611-7.
Hu JR, Yan ZH, Liu CF, Huang LN. (2004). Higher-order aberrations in myopic and astigmatism eyes. Chin J Ophthalmol 40:13-6.
Hu Y, Wen C, Li Z, Zhao W, Ding X, Yang X. (2019). Areal summed corneal power shift is an important determinant for axial length elongation in myopic children treated with overnight orthokeratology. Br J Ophthalmol 103:1571-5.

Huang HM, Chang DST, Wu PC. (2015). The association between near work activities and myopia in children—a systematic review and meta-analysis. PLoS One 10:e0140419.
Huang J, Wen D, Wang Q, McAlinden C, Flitcroft I, Chen H, Saw SM, Chen H, Bao F, Zhao Y, Hu L, Li X, Gao R, Lu W, Du Y, Jinag Z, Yu A, Lian H, Jiang Q, Yu Y, Qu J. (2016). Efficacy comparison of 16 interventions for myopia control in children: a network meta-analysis. Ophthalmology 123:697-708.
Iribarren R, Cortinez MF, Chiappe JP. (2009). Age of first distance prescription and final myopic refractive error. Ophthalmic Epidemiol 16:84-9.
Iskander DR, Davis BA, Collins MJ, Franklin R. (2007). Objective refraction from monochromatic wavefront aberrations via Zernike power polynomials. Ophthalmic Physiol Opt 27:245-55.
Jensen H. (1995). Myopia in teenagers. An eight-year follow-up study on myopia progression and risk factors. Acta Ophthalmol Scand 73:389-93.
Jessen GN. (1962). World wide summary of contact lens techniques. Am J Optom Arch Am Acad Optom 39:680-2.
Jin WQ, Huang SH, Jiang J, Mao XJ, Shen MX, Lian Y. (2018). Short term effect of choroid thickness in the horizontal meridian detected by spectral domain optical coherence tomography in myopic children after orthokeratology. Int J Ophthalmol 11:991-6.
Johnson KL, Carney LG, Mountford JA, Collins MJ, Cluff S, Collins PK. (2007). Visual performance after overnight orthokeratology. Cont Lens Anterior Eye 30:29-36.
Joslin CE, Wu SM, McMahon TT, Shahidi M. (2003). Higher-order wavefront aberrations in corneal refractive therapy. Optom Vis Sci 80:805-11.
Kakita T, Hiraoka T, Oshika T. (2011). Influence of overnight orthokeratology on axial elongation in childhood myopia. Invest Ophthalmol Vis Sci 52:2170-4.
Kang P. (2018). Optical and pharmacological strategies of myopia control. Clin Exp Optom 101:321-32.
Kang P, Gifford P, Swarbrick H. (2013). Can manipulation of orthokeratology lens parameters modify peripheral refraction? Optom Vis Sci 90:1237-48.
Kang P, Swarbrick H. (2011). Peripheral refraction in myopic children wearing orthokeratology and gas-permeable lenses. Optom Vis Sci 88:476-82.
Kang P, Swarbrick H. (2013). Time course of the effects of orthokeratology on peripheral refraction and corneal topography. Ophthalmic Physiol Opt 33:277-82.
Kang P, Swarbrick H. (2016). New perspective on myopia control with orthokeratology. Optom Vis Sci 93:497-503.
Kang P, Watt K, Chau T, Zhu J, Evans BJW, Swarbrick H. (2018). The impact of orthokeratology lens wear on binocular vision and accommodation: a short-term prospective study. Cont Lens Anterior Eye 41:501-6.
Kang SY, Kim BK, Byun YJ. (2007). Sustainability of orthokeratology as demonstrated by corneal topography. Korean J Ophthalmol 21:74-8.
Karimian F, Feizi S, Doozande A. (2010). Higher-order aberrations in myopic eyes. J Ophthalmic Vis Res 5:3-9.
Kelly JE, Mihashi T, Howland HC. (2004). Compensation of corneal horizontal/vertical astigmatism, lateral coma, and spherical aberration by internal optics of the eye. J Vis 4:262-71.
Kim J, Lim DH, Han SH, Chung TY. (2019). Predictive factors associated with axial length growth and myopia progression in orthokeratology. PLoS One 14:e0218140.
Kim WK, Kim BJ, Ryu IKH, Kim JK, Kim SW. (2018). Corneal epithelial and stromal thickness changes in myopic orthokeratology and their relationship with refractive change. PLoS One 13:e0203652-e.
Kim YS, Lee SY, Park SH. (2017). Longitudinal changes in refractive error in a pediatric referral population in korea. J Pediatr Ophthalmol Strabismus 54:43-51.
King-Smith PE, Fink BA, Fogt N, Nichols KK, Hill RM, Wilson GS. (2000). The thickness of the human precorneal tear film: evidence from reflection spectra. Invest Ophthalmol Vis Sci 41:3348-59.
Kirwan C, O'Keefe M, Soeldner H. (2006). Higher-order aberrations in children. Am J Ophthalmol 141:67-70.
Klein SA, Garcia DD. (2000). Line of sight and alternative representations of aberrations of the eye. J Refract Surg 16:S630-5.

Kobayashi Y, Yanai R, Chikamoto N, Chikama T, Ueda K, Nishida T. (2008). Reversibility of effects of orthokeratology on visual acuity, refractive error, corneal topography, and contrast sensitivity. Eye Contact Lens 34:224-8.

Koomen M, Tousey R, Scolnik R. (1949). The spherical aberration of the eye. J Opt Soc Am 39:370-6.

Koomson NY, Amedo AO, Opoku-Baah C, Ampeh PB, Ankamah E, Bonsu K. (2016). Relationship between reduced accommodative lag and myopia progression. Optom Vis Sci 93:683-91.

Koretz JF, Cook CA, Kaufman PL. (2002). Aging of the human lens: changes in lens shape upon accommodation and with accommodative loss. J Opt Soc Am A 19:144-51.

Kuroda T, Fujikado T, Maeda N, Oshika T, Hirohara Y, Mihashi T. (2002a). Wavefront analysis of higher-order aberrations in patients with cataract. J Cataract Refract Surg 28:438-44.

Kuroda T, Fujikado T, Ninomiya S, Maeda N, Hirohara Y, Mihashi T. (2002b). Effect of aging on ocular light scatter and higher order aberrations. J Refract Surg 18:S598-S602.

Kwan WC, Yip SP, Yap MK. (2009). Monochromatic aberrations of the human eye and myopia. Clin Exp Optom 92:304-12.

Lam AK, Chan R, Pang PC. (2001). The repeatability and accuracy of axial length and anterior chamber depth measurements from the IOLmaster. Ophthalmic Physiol Opt 21:477-83.

Lam AK, Leung SY, Hon Y, Shu-Ho L, Wong KY, Tiu PK, Lam DC. (2018). Influence of short-term orthokeratology to corneal tangent modulus: a randomized study. Curr Eye Res 43:474-81.

Lam CS, Tang WC, Tse DY, Tang YY, To CH. (2014). Defocus Incorporated Soft Contact (DISC) lens slows myopia progression in Hong Kong Chinese schoolchildren: a 2-year randomised clinical trial. British Journal of Ophthalmology 98:40-5.

Lam DS, Fan DS, Lam RF, Rao SK, Chong KS, Lau JT, Lai RY, Cheung EY. (2008). The effect of parental history of myopia on children's eye size and growth: results of a longitudinal study. Invest Ophthalmol Vis Sci 49:873-6.

Lee EJ, Lim DH, Chung TY, Hyun J, Han J. (2018). Association of axial length growth and topographic change in orthokeratology. Eye Contact Lens 44:292-8.

Lee TT, Cho P. (2013a). Rebound of refractive errors after discontinuation of orthokeratology treatment-a case report. Cont Lens Anterior Eye 36:e18-e9.

Lee TT. (2015). Peripheral refraction and peripheral eye length in myopic progression and myopic control. [Doctoral dissertation, The Hong Kong Polytechnic University]

Lee TT, Cho P. (2010). Discontinuation of orthokeratology and myopic progression. Optom Vis Sci 87:1053-6.

Lee TT, Cho P. (2012). Repeatability of relative peripheral refraction in untreated and orthokeratology-treated eyes. Optom Vis Sci 89:1477-86.

Lee TT, Cho P. (2013b). Relative peripheral refraction in children: twelve-month changes in eyes with different ametropias. Ophthalmic Physiol Opt 33:283-93.

Lee YY, Lo CT, Sheu SJ, Yin LT. (2015). Risk factors for and progression of myopia in young Taiwanese men. Ophthalmic Epidemiol 22:66-73.

Leo SW, Scientific Bureau of World Society of Paediatric O, Strabismus. (2017). Current approaches to myopia control. Curr Opin Ophthalmol 28:267-75.

Leveziel N, Marillet S, Dufour Q, Lichtwitz O, Bentaleb Y, Pelen F, Ingrand P, Bourne R. (2020). Prevalence of macular complications related to myopia - results of a multicenter evaluation of myopic patients in eye clinics in France. Acta Ophthalmol 98:e245-e51.

Levy Y, Segal O, Avni I, Zadok D. (2005). Ocular higher-order aberrations in eyes with supernormal vision. Am J Ophthalmol 139:225-8.

Li F, Jiang ZX, Hao P, Li X. (2016a). A meta-analysis of central corneal thickness changes with overnight orthokeratology. Eye Contact Lens 42:141-6.

Li J, Yang C, Xie W, Zhang G, Li X, Wang S, Yang X, Zeng J. (2017a). Predictive role of corneal Q-value differences between nasal-temporal and superior-inferior quadrants in orthokeratology lens decentration. Medicine 96:e5837-e.

Li SM, Kang MT, Wu SS, Liu LR, Li H, Chen Z, Wang N. (2016b). Efficacy, safety and acceptability of orthokeratology on slowing axial elongation in myopic children by meta-analysis. Curr Eye Res 41:600-8.

Li SM, Li SY, Kang MT, Zhou Y, Liu LR, Li H, Wang YP, Zhan SY, Gopinath B, Mitchell P, Wang N, Anyang Childhood Eye Study G. (2015a). Near work related parameters and myopia in Chinese children: the Anyang Childhood Eye Study. PLoS One 10:e0134514.

Li SY, Li SM, Zhou YH, Liu LR, Li H, Kang MT, Zhan SY, Wang N, Millodot M. (2015b). Effect of undercorrection on myopia progression in 12-year-old children. Graefes Arch Clin Exp Ophthalmol 253:1363-8.

Li T, Zhou X, Chen Z, Zhou X, Chu R, Hoffman MR. (2012). Relationship between ocular wavefront aberrations and refractive error in Chinese school children. Clin Exp Optom 95:399-403.

Li X, Friedman IB, Medow NB, Zhang C. (2017b). Update on orthokeratology in managing progressive myopia in children: efficacy, mechanisms, and concerns. J Pediatr Ophthalmol Strabismus 54:142-8.

Li Y, Bao FJ. (2014). Interocular symmetry analysis of bilateral eyes. J Med Eng Technol 38:179-87.

Li YJ, Choi JA, Kim H, Yu SY, Joo CK. (2011). Changes in ocular wavefront aberrations and retinal image quality with objective accommodation. J Cataract Refract Surg 37:835-41.

Li Z, Cui D, Hu Y, Ao S, Zeng J, Yang X. (2017c). Choroidal thickness and axial length changes in myopic children treated with orthokeratology. Cont Lens Anterior Eye.

Li Z, Hu Y, Cui D, Long W, He M, Yang X. (2018). Change in subfoveal choroidal thickness secondary to orthokeratology and its cessation: a predictor for the change in axial length. Acta Ophthalmol 97:e454-59.

Lian Y, Shen M, Huang S, Yuan Y, Wang Y, Zhu D, Jiang J, Mao X, Wang J, Lu F. (2014). Corneal reshaping and wavefront aberrations during overnight orthokeratology. Eye Contact Lens 40:161-8.

Lian Y, Shen M, Jiang J, Mao X, Lu P, Zhu D, Chen Q, Wang J, Lu F. (2013). Vertical and horizontal thickness profiles of the corneal epithelium and bowman's layer after orthokeratology. Invest Ophthalmol Vis Sci 54:691-6.

Liang J, Grimm B, Goelz S, Bille JF. (1994). Objective measurement of wave aberrations of the human eye with the use of a Hartmann–Shack wave-front sensor. J Opt Soc Am A 11:1949-57.

Liang J, Williams DR. (1997). Aberrations and retinal image quality of the normal human eye. J Opt Soc Am A 14:2873-83.

Lin MC, Graham AD, Fusaro RE, Polse KA. (2002). Impact of rigid gas-permeable contact lens extended wear on corneal epithelial barrier function. Invest Ophthalmol Vis Sci 43:1019-24.

Little JA, McCullough SJ, Breslin KM, Saunders KJ. (2014). Higher order ocular aberrations and their relation to refractive error and ocular biometry in children. Invest Ophthalmol Vis Sci 55:4791-800.

Llorente L, Barbero S, Cano D, Dorronsoro C, Marcos S. (2004). Myopic versus hyperopic eyes: axial length, corneal shape and optical aberrations. J Vis 4:288-98.

Logan NS, Wolffsohn JS. (2020). Role of un-correction, under-correction and over-correction of myopia as a strategy for slowing myopic progression. Clini Exp Optom 103:133-7.

Lombardo M, Lombardo G, Serrao S. (2006). Interocular high-order corneal wavefront aberration symmetry. J Opt Soc Am A 23:777-87.

Lopez-Gil N, Fernandez-Sanchez V. (2010). The change of spherical aberration during accommodation and its effect on the accommodation response. J Vis 10:12.

Lopez-Gil N, Fernandez-Sanchez V, Legras R, Montes-Mico R, Lara F, Nguyen-Khoa JL. (2008). Accommodation-related changes in monochromatic aberrations of the human eye as a function of age. Invest Ophthalmol Vis Sci 49:1736-43.

Low W, Dirani M, Gazzard G, Chan YH, Zhou HJ, Selvaraj P, Au Eong KG, Young TL, Mitchell P, Wong TY, Saw SM. (2010). Family history, near work, outdoor activity, and myopia in Singapore Chinese preschool children. Br J Ophthalmol 94:1012-6.

Luo M, Ma S, Liang N. (2014). Clinical efficacy of toric orthokeratology in myopic adolescent with moderate to high astigmatism. Eye Sci 29:209-13, 18.

Lyall DA, Srinivasan S, Gray LS. (2013). Changes in ocular monochromatic higher-order aberrations in the aging eye. Optom Vis Sci 90:996-1003.

Maduka Okafor FC, Okoye OI, Eze BI. (2009). Myopia: a review of literature. Niger J Med 18:134-8.

Marcos S, Sawides L, Gambra E, Dorronsoro C. (2008). Influence of adaptive-optics ocular aberration correction on visual acuity at different luminances and contrast polarities. J Vision 8:1.

Martinez AA, Sankaridurg PR, Naduvilath TJ, Mitchell P. (2009). Monochromatic aberrations in hyperopic and emmetropic children. J Vis 9:23 1-14.

Maseedupally V, Gifford P, Lum E, Swarbrick H. (2013). Central and paracentral corneal curvature changes during orthokeratology. Optom Vis Sci 90:1249-58.

McAlinden C, Khadka J, Pesudovs K. (2011). Statistical methods for conducting agreement (comparison of clinical tests) and precision (repeatability or reproducibility) studies in optometry and ophthalmology. Ophthalmic Physiol Opt 31:330-8.

McCrann S, Flitcroft I, Lalor K, Butler J, Bush A, Loughman J. (2018). Parental attitudes to myopia: a key agent of change for myopia control? Ophthalmic Physiol Opt 38:298-308.

McLellan JS, Marcos S, Burns SA. (2001). Age-related changes in monochromatic wave aberrations of the human eye. Invest Ophthalmol Vis Sci 42:1390-5.

Mika R, Morgan B, Cron M, Lotoczky J, Pole J. (2007). Safety and efficacy of overnight orthokeratology in myopic children. Optometry 78:225-31.

Millodot M. (1981). Effect of ametropia on peripheral refraction. Am J Optom Physiol Opt 58:691-5.

Modis L, Jr., Langenbucher A, Seitz B. (2004). Evaluation of normal corneas using the scanning-slit topography/pachymetry system. Cornea 23:689-94.

Morgan IG, Rose KA. (2019). Myopia: is the nature-nurture debate finally over? Clin Exp Optom 102:3-17.

Morgan MW, Jr. (1952). Relationship between accommodation and convergence. AMA Arch Ophthalmol 47:745-59.

Mountford J. (1998). Retention and regression of orthokeratology with time. Int Contact Lens Clin 25:59-64.

Mutti DO, Hayes JR, Mitchell GL, Jones LA, Moeschberger ML, Cotter SA, Kleinstein RN, Manny RE, Twelker JD, Zadnik K, the CLEERE Study Group. (2007). Refractive error, axial length, and relative peripheral refractive error before and after the onset of myopia. Invest Ophthalmol Vis Sci 48:2510-9.

Mutti DO, Mitchell GL, Hayes JR, Jones LA, Moeschberger ML, Cotter SA, Kleinstein RN, Manny RE, Twelker JD, Zadnik K, the CLEERE Study Group. (2006). Accommodative lag before and after the onset of myopia. Invest Ophthalmol Vis Sci 47:837-46.

Mutti DO, Mitchell GL, Jones-Jordan LA, Cotter SA, Kleinstein RN, Manny RE, Twelker JD, Zadnik K, Group ftCS. (2017). The response AC/A ratio before and after the onset of myopia. Invest Ophthalmol Vis Sci 58:1594-602.

Mutti DO, Sholtz RI, Friedman NE, Zadnik K. (2000). Peripheral refraction and ocular shape in children. Invest Ophthalmol Vis Sci 41:1022-30.

Mutti DO, Sinnott LT, Mitchell GL, Jones-Jordan LA, Moeschberger ML, Cotter SA, Kleinstein RN, Manny RE, Twelker JD, Zadnik K, the CLEERE Study Group. (2011). Relative peripheral refractive error and the risk of onset and progression of myopia in children. Invest Ophthalmol Vis Sci 52:199-205.

Na M, Yoo A. (2018). The effect of orthokeratology on axial length elongation in children with myopia: contralateral comparison study. Jpn J Ophthalmol 62:327-34.

Naidoo KS, Fricke TR, Frick KD, Jong M, Naduvilath TJ, Resnikoff S, Sankaridurg P. (2019). Potential lost productivity resulting from the global burden of myopia: systematic review, meta-analysis, and modeling. Ophthalmology 126:338-46.

Namba H, Kawasaki R, Narumi M, Sugano A, Homma K, Nishi K, Murakami T, Kato T, Kayama T, Yamashita H. (2015). Ocular higher-order wavefront aberrations in the Japanese adult population: the Yamagata study (Funagata). Invest Ophthalmol Vis Sci 56:90-7.

Namba H, Kawasaki R, Sugano A, Murakami T, Nishitsuka K, Kato T, Kayama T, Yamashita H. (2017). Age-related changes in ocular aberrations and the Yamagata Study (Funagata). Cornea 36 Suppl 1:S34-S40.

Navarro R, Santamaria J, Bescos J. (1985). Accommodation-dependent model of the human eye with aspherics. J Opt Soc Am A 2:1273-81.

Neil Charman W, Radhakrishnan H. (2010). Peripheral refraction and the development of refractive error: a review. Ophthalmic Physiol Opt 30:321-38.

Nichols JJ, Marsich MM, Nguyen M, Barr JT, Bullimore MA. (2000). Overnight orthokeratology. Optom Vis Sci 77:252-9.

Nieto-Bona A, Gonzalez-Mesa A, Nieto-Bona MP, Villa-Collar C, Lorente-Velazquez A. (2011a). Long-term changes in corneal morphology induced by overnight orthokeratology. Curr Eye Res 36:895-904.

Nieto-Bona A, Gonzalez-Mesa A, Nieto-Bona MP, Villa-Collar C, Lorente-Velazquez A. (2011b). Short-term effects of overnight orthokeratology on corneal cell morphology and corneal thickness. Cornea 30:646-54.

Ninomiya S, Fujikado T, Kuroda T, Maeda N, Tano Y, Oshika T, Hirohara Y, Mihashi T. (2002). Changes of ocular aberration with accommodation. Am J Ophthalmol 134:924-6.

Norton TT, Siegwart JT, Jr., Amedo AO. (2006). Effectiveness of hyperopic defocus, minimal defocus, or myopic defocus in competition with a myopiagenic stimulus in tree shrew eyes. Invest Ophthalmol Vis Sci 47:4687-99.

Oberholzer, M., Gillan, W., & Rubin, A. (2014). Mirror symmetry of higher order aberrations between right and left eyes. African Vis Eye Health 73:39-44.

O'Neal MR, Polse KA, Sarver MD. (1984). Corneal response to rigid and hydrogel lenses during eye closure. Invest Ophthalmol Vis Sci 25:837-42.

Ommani A, Hutchings N, Thapa D, Lakshminarayanan V. (2014). Pupil scaling for the estimation of aberrations in natural pupils. Optom Vis Sci 91:1175-82.

Oshika T, Klyce SD, Applegate RA, Howland HC. (1999). Changes in corneal wavefront aberrations with aging. Invest Ophthalmol Vis Sci 40:1351-5.

Oshika T, Okamoto C, Samejima T, Tokunaga T, Miyata K. (2006). Contrast sensitivity function and ocular higher-order wavefront aberrations in normal human eyes. Ophthalmology 113:1807-12.

Osmanbasoglu OA, Alkin Z, Ozkaya A, Ozpinar Y, Yazici AT, Demirok A. (2013). Diurnal choroidal thickness changes in normal eyes of Turkish people measured by spectral domain optical coherence tomography. J Ophthalmol 2013:687165.

Owens H, Garner LF, Craig JP, Gamble G. (2004). Posterior corneal changes with orthokeratology. Optom Vis Sci 81:421-6.

Papadogiannis P, Romashchenko D, Unsbo P, Lundström L. (2020). Lower sensitivity to peripheral hypermetropic defocus due to higher order ocular aberrations. Ophthalmic Physiol Opt 40:300-7.

Papamastorakis G, Panagopoulou S, Tsilimbaris MK, Pallikaris IG, Plainis S. (2015). Ocular higher-order aberrations in a school children population. J Optom 8:93-100.

Paquin MP, Hamam H, Simonet P. (2002). Objective measurement of optical aberrations in myopic eyes. Optom Vis Sci 79:285-91.

Pärssinen O, Hemminki E, Klemetti A. (1989). Effect of spectacle use and accommodation on myopic progression: final results of a three-year randomised clinical trial among schoolchildren. Br J Ophthalmol 73:547-51.

Paune J, Cardona G, Quevedo L. (2012). Toric double tear reservoir contact lens in orthokeratology for astigmatism. Eye Contact Lens 38:245-51.

Paune J, Morales H, Armengol J, Quevedo L, Faria-Ribeiro M, Gonzalez-Meijome JM. (2015). Myopia control with a novel peripheral gradient soft lens and orthokeratology: a 2-year clinical trial. Biomed Res Int 2015:507572.

Phillips JR. (2005). Monovision slows juvenile myopia progression unilaterally. British Journal of Ophthalmology 89:1196-200.

Philip K, Martinez A, Ho A, Conrad F, Ale J, Mitchell P, Sankaridurg P. (2012). Total ocular, anterior corneal and lenticular higher order aberrations in hyperopic, myopic and emmetropic eyes. Vision Res 52:31-7.

Philip K, Sankaridurg P, Holden B, Ho A, Mitchell P. (2014). Influence of higher order aberrations and retinal image quality in myopisation of emmetropic eyes. Vision Res 105:233-43.

Philip K, Sankaridurg PR, Ale JB, Naduvilath TJ, Mitchell P. (2018). Profile of off-axis higher order aberrations and its variation with time among various refractive error groups. Vision Res 153:111-23.

Plainis S, Ginis HS, Pallikaris A. (2005). The effect of ocular aberrations on steady-state errors of accommodative response. J Vis 5:466-77.

Plainis S, Pallikaris I. (2008). Ocular monochromatic aberration statistics in a large emmetropic population. Journal of Modern Optics 55:759-72.

Porter J, Guirao A, Cox IG, Williams DR. (2001). Monochromatic aberrations of the human eye in a large population. J Opt Soc Am A 18:1793-803.

Price H, Allen PM, Radhakrishnan H, Calver R, Rae S, Theagarayan B, Sailoganathan A, O'Leary DJ. (2013). The Cambridge Anti-myopia Study: variables associated with myopia progression. Optom Vis Sci 90:1274-83.

Prousali E, Haidich AB, Fontalis A, Ziakas N, Brazitikos P, Mataftsi A. (2019). Efficacy and safety of interventions to control myopia progression in children: an overview of systematic reviews and meta-analyses. BMC Ophthalmol 19:106.

Queirós A, Amorim-de-Sousa A, Lopes-Ferreira D, Villa-Collar C, Gutiérrez ÁR, González-Méijome JM. (2018). Relative peripheral refraction across 4 meridians after orthokeratology and LASIK surgery. Eye and Vision 5:12.

Queiros A, Gonzalez-Meijome JM, Jorge J, Villa-Collar C, Gutierrez AR. (2010). Peripheral refraction in myopic patients after orthokeratology. Optom Vis Sci 87:323-9.

Queirós A, González-Méijome JM, Villa-Collar C, Gutiérrez AR, Jorge J. (2010). Local steepening in peripheral corneal curvature after corneal refractive therapy and LASIK. Optom Vis Sci 87:432-9.

Queiros A, Lopes-Ferreira D, Gonzalez-Meijome JM. (2016). Astigmatic peripheral defocus with different contact lenses: review and meta-analysis. Curr Eye Res 41:1005-15.

Queirós A, Villa-Collar C, Gutiérrez AR, Jorge J, González-Méijome JM. (2012). Quality of life of myopic subjects with different methods of visual correction using the nei rql-42 questionnaire. Eye & Contact Lens 38:116-21.

Radhakrishnan H, Charman WN. (2007). Age-related changes in ocular aberrations with accommodation. J Vision 7:11.

Radhakrishnan H, Pardhan S, Calver RI, O'Leary DJ. (2004). Unequal reduction in visual acuity with positive and negative defocusing lenses in myopes. Optom Vis Sci 81:14-7.

Rah MJ, Jackson JM, Jones LA, Marsden HJ, Bailey MD, Barr JT. (2002). Overnight orthokeratology: preliminary results of the lenses and overnight orthokeratology (LOOK) study. Optom Vis Sci 79:598-605.

Rahman W, Chen FK, Yeoh J, Patel P, Tufail A, Da Cruz L. (2011). Repeatability of manual subfoveal choroidal thickness measurements in healthy subjects using the technique of enhanced depth imaging optical coherence tomography. Invest Ophthalmol Vis Sci 52:2267-71.

Ramamurthy D, Lin Chua SY, Saw SM. (2015). A review of environmental risk factors for myopia during early life, childhood and adolescence. Clin Exp Optom 98:497-506.

Randleman JB, Lynn MJ, Perez-Straziota CE, Weissman HM, Kim SW. (2015). Comparison of central and peripheral corneal thickness measurements with scanning-slit, Scheimpflug and Fourier-domain ocular coherence tomography. Br J Ophthalmol 99:1176-81.

Read SA, Alonso-Caneiro D, Vincent SJ, Collins MJ. (2015). Longitudinal changes in choroidal thickness and eye growth in childhood. Invest Ophthalmol Vis Sci 56:3103-12.

Read SA, Collins MJ, Sander BP. (2010). Human optical axial length and defocus. Invest Ophthalmol Vis Sci 51:6262-9.

Reinstein DZ, Gobbe M, Archer TJ, Couch D, Bloom B. (2009). Epithelial, stromal, and corneal pachymetry changes during orthokeratology. Optom Vis Sci 86:E1006-E14.

Rempt F, Hoogerheide J, Hoogenboom WP. (1971). Peripheral retinoscopy and the skiagram. Ophthalmologica 162:1-10.

Ren Q, Yue H, Zhou Q. (2016). Effects of orthokeratology lenses on the magnitude of accommodative lag and accommodativeconvergence/accommodation. Zhong Nan Da Xue Xue Bao Yi Xue Ban 41:169-73.

Rocha KM, Nose W, Bottos K, Bottos J, Morimoto L, Soriano E. (2007). Higher-order aberrations of age-related cataract. J Cataract Refract Surg 33:1442-6.

Rosén R, Lundström L, Unsbo P. (2012a). Sign-dependent sensitivity to peripheral defocus for myopes due to aberrations. Invest Ophthalmol Vis Sci 53:7176-82.

Rosén R, Lundström L, Unsbo P, Atchison DA. (2012b). Have we misinterpreted the study of Hoogerheide et al. (1971)? Optom Vis Sci 89:1235-7.

Rudnicka AR, Kapetanakis VV, Wathern AK, Logan NS, Gilmartin B, Whincup PH, Cook DG, Owen CG. (2016). Global variations and time trends in the prevalence of childhood myopia, a systematic review and quantitative meta-analysis: implications for aetiology and early prevention. Br J Ophthalmol 100:882-90.

Sachdev N, Ormonde SE, Sherwin T, McGhee CN. (2004). Higher-order aberrations of lenticular opacities. J Cataract Refract Surg 30:1642-8.
Salmon TO, Thibos LN. (2002). Videokeratoscope-line-of-sight misalignment and its effect on measurements of corneal and internal ocular aberrations. J Opt Soc Am A 19:657-69.
Salmon TO, van de Pol C. (2005). Evaluation of a clinical aberrometer for lower-order accuracy and repeatability, higher-order repeatability, and instrument myopia. Optometry 76:461-72.
Salmon TO, van de Pol C. (2006). Normal-eye Zernike coefficients and root-mean-square wavefront errors. J Cataract Refract Surg 32:2064-74.
Sander BP, Collins MJ, Read SA. (2014). The effect of topical adrenergic and anticholinergic agents on the choroidal thickness of young healthy adults. Exp Eye Res 128:181-9.
Sander BP, Collins MJ, Read SA. (2018). The interaction between homatropine and optical blur on choroidal thickness. Ophthalmic Physiol Opt 38:257-65.
Sanfilippo PG, Hewitt AW, Hammond CJ, Mackey DA. (2010). The heritability of ocular traits. Surv Ophthalmol 55:561-83.
Sankaridurg P, Bakaraju RC, Naduvilath T, Chen X, Weng R, Tilia D, Xu P, Li W, Conrad F, Smith EL, Ehrmann K. (2019). Myopia control with novel central and peripheral plus contact lenses and extended depth of focus contact lenses: 2 year results from a randomised clinical trial. Ophthalmic Physiol Opt 39:294-307.
Sankaridurg P, Conrad F, Tran H, Zhu J. (2018). Controlling progression of myopia: optical and pharmaceutical strategies. Asia Pac J Ophthalmol (Phila) 7:405-14.
Sankaridurg PR, Holden BA. (2014). Practical applications to modify and control the development of ametropia. Eye (Lond) 28:134-41.
Santodomingo-Rubido J, Villa-Collar C, Gilmartin B, Gutierrez-Ortega R. (2012). Myopia control with orthokeratology contact lenses in Spain: refractive and biometric changes. Invest Ophthalmol Vis Sci 53:5060-5.
Santodomingo-Rubido J, Villa-Collar C, Gilmartin B, Gutierrez-Ortega R. (2013a). Factors preventing myopia progression with orthokeratology correction. Optom Vis Sci 90:1225-36.
Santodomingo-Rubido J, Villa-Collar C, Gilmartin B, Gutierrez-Ortega R. (2014). Short-term changes in ocular biometry and refraction after discontinuation of long-term orthokeratology. Eye Contact Lens 40:84-90.
Santodomingo-Rubido J, Villa-Collar C, Gilmartin B, Gutiérrez-Ortega R. (2013b). Myopia control with orthokeratology contact lenses in Spain: a comparison of vision-related quality-of-life measures between orthokeratology contact lenses and single-vision spectacles. Eye & Contact Lens 39:153-7.
Santodomingo-Rubido J, Villa-Collar C, Gilmartin B, Gutiérrez-Ortega R. (2018). Short-term and long-term changes in corneal power are not correlated with axial elongation of the eye induced by orthokeratology in children. Eye & contact lens 44:260-7.
Santodomingo-Rubido J, Villa-Collar C, Gilmartin B, Gutierrez-Ortega R, Sugimoto K. (2017). Long-term efficacy of orthokeratology contact lens wear in controlling the progression of childhood myopia. Curr Eye Res 42:713-20.
Santodomingo-Rubido J, Villa-Collar C, Gilmartin B, Gutierrez-Ortega R, Suzaki A. (2017). Short- and long-term changes in corneal aberrations and axial length induced by orthokeratology in children are not correlated. Eye Contact Lens 43:358-63.
Santolaria-Sanz E, Cervino A, Gonzalez-Meijome JM. (2016). Corneal aberrations, contrast sensitivity, and light distortion in orthokeratology patients: 1-year results. J Ophthalmol 2016:8453462.
Santolaria E, Cervino A, Queiros A, Brautaset R, Gonzalez-Meijome JM. (2013). Subjective satisfaction in long-term orthokeratology patients. Eye Contact Lens 39:388-93.
Santolaria Sanz E, Cervino A, Queiros A, Villa-Collar C, Lopes-Ferreira D, Gonzalez-Meijome JM. (2015). Short-term changes in light distortion in orthokeratology subjects. Biomed Res Int 2015:278425.
Sanz Diez P, Yang LH, Lu MX, Wahl S, Ohlendorf A. (2019). Growth curves of myopia-related parameters to clinically monitor the refractive development in Chinese schoolchildren. Graefes Arch Clin Exp Ophthalmol 257:1045-53.
Saw SM, Nieto FJ, Katz J, Schein OD, Levy B, Chew SJ. (2000). Factors related to the progression of myopia in Singaporean children. Optom Vis Sci 77:549-54.

Saw SM, Shih-Yen EC, Koh A, Tan D. (2002). Interventions to retard myopia progression in children: an evidence-based update. Ophthalmology 109:415-21.

Schaeffel F, Glasser A, Howland HC. (1988). Accommodation, refractive error and eye growth in chickens. Vision Res 28:639-57.

Schwiegerling J. (2002). Scaling Zernike expansion coefficients to different pupil sizes. J Opt Soc Am A 19:1937-45.

Scotto R, Bagnis A, Papadia M, Cutolo CA, Risso D, Traverso CE. (2017). Comparison of central corneal thickness measurements using ultrasonic pachymetry, anterior segment OCT and noncontact specular microscopy. J Glaucoma 26:860-5.

Seidemann A, Schaeffel F, Guirao A, Lopez-Gil N, Artal P. (2002). Peripheral refractive errors in myopic, emmetropic, and hyperopic young subjects. J Opt Soc Am A 19:2363-73.

Shaw AJ, Collins MJ, Davis BA, Carney LG. (2008). Corneal refractive changes due to short-term eyelid pressure in downward gaze. J Cataract Refract Surg 34:1546-53.

Si JK, Tang K, Bi HS, Guo DD, Guo JG, Wang XR. (2015). Orthokeratology for myopia control: a meta-analysis. Optom Vis Sci 92:252-7.

Smith EL. (2011). Prentice award lecture 2010: a case for peripheral optical treatment strategies for myopia. Optom Vis Sci 88:1029-44.

Smith EL, Hung LF. (1999). The role of optical defocus in regulating refractive development in infant monkeys. Vision Res 39:1415-35.

Smith EL, Hung LF, Huang J. (2009). Relative peripheral hyperopic defocus alters central refractive development in infant monkeys. Vision Res 49:2386-92.

Smith EL, Hung LF, Huang J, Arumugam B. (2013). Effects of local myopic defocus on refractive development in monkeys. Optom Vis Sci 90:1176-86.

Smith EL, Hung LF, Huang J, Blasdel TL, Humbird TL, Bockhorst KH. (2010). Effects of optical defocus on refractive development in monkeys: Evidence for local, regionally selective mechanisms. Invest Ophthalmol Vis Sci 51:3864-73.

Smith EL, Kee CS, Ramamirtham R, Qiao-Grider Y, Hung LF. (2005). Peripheral vision can influence eye growth and refractive development in infant monkeys. Invest Ophthalmol Vis Sci 46:3965-72.

Smith EL, Ramamirtham R, Qiao-Grider Y, Hung LF, Huang J, Kee CS, Coats D, Paysse E. (2007). Effects of foveal ablation on emmetropization and form-deprivation myopia. Invest Ophthalmol Vis Sci 48:3914-22.

Smith G, Cox MJ, Calver R, Garner LF. (2001). The spherical aberration of the crystalline lens of the human eye. Vision Res 41:235-43.

Smolek MK, Klyce SD, Sarver EJ. (2002). Inattention to nonsuperimposable midline symmetry causes wavefront analysis error. Arch Ophthalmol 120:439-47.

Sng CC, Lin XY, Gazzard G, Chang B, Dirani M, Lim L, Selvaraj P, Ian K, Drobe B, Wong TY, Saw SM. (2011). Change in peripheral refraction over time in Singapore Chinese children. Invest Ophthalmol Vis Sci 52:7880-7.

Soni PS, Nguyen TT, Bonanno JA. (2003). Overnight orthokeratology: visual and corneal changes. Eye Contact Lens 29:137-45.

Soni PS, Nguyen TT, Bonanno JA. (2004). Overnight orthokeratology: refractive and corneal recovery after discontinuation of reverse-geometry lenses. Eye Contact Lens 30:254-62; discussion 63-4.

Sorbara L, Fonn D, Simpson T, Lu F, Kort R. (2005). Reduction of myopia from corneal refractive therapy. Optom Vis Sci 82:512-8.

Sridharan R, Swarbrick H. (2003). Corneal response to short-term orthokeratology lens wear. Optom Vis Sci 80:200-6.

Stillitano I, Schor P, Lipener C, Hofling-Lima AL. (2007a). Stability of wavefront aberrations during the daytime after 6 months of overnight orthokeratology corneal reshaping. J Refract Surg 23:978-83.

Stillitano I, Schor P, Lipener C, Hofling-Lima AL. (2008). Long-term follow-up of orthokeratology corneal reshaping using wavefront aberrometry and contrast sensitivity. Eye Contact Lens 34:140-5.

Stillitano IG, Chalita MR, Schor P, Maidana E, Lui MM, Lipener C, Hofling-Lima AL. (2007b). Corneal changes and wavefront analysis after orthokeratology fitting test. Am J Ophthalmol 144:378-86.

Sun JT, An M, Yan XB, Li GH, Wang DB. (2018). Prevalence and related factors for myopia in school-aged children in qingdao. J Ophthalmol 2018:9781987.
Sun Y, Wang L, Gao J, Yang M, Zhao Q. (2017a). Influence of overnight orthokeratology on corneal surface shape and optical quality. J Ophthalmol 2017:3279821.
Sun Y, Xu F, Zhang T, Liu M, Wang D, Chen Y, Liu Q. (2015). Orthokeratology to control myopia progression: a meta-analysis. PLoS One 10:e0124535.
Sun YY, Li SM, Li SY, Kang MT, Liu LR, Meng B, Zhang FJ, Millodot M, Wang N. (2017b). Effect of uncorrection versus full correction on myopia progression in 12-year-old children. Graefes Arch Clin Exp Ophthalmol 255:189-95.
Swarbrick HA, Alharbi A, Watt K, Lum E, Kang P. (2015). Myopia control during orthokeratology lens wear in children using a novel study design. Ophthalmology 122:620-30.
Swarbrick HA, Kang P, Peguda R. (2020). Corneal total and epithelial thickness measured by sonogage ultrasound pachometry and high-resolution optical coherence tomography. Optom Vis Sci 97:346-50.
Swarbrick HA, Wong G, O'Leary DJ. (1998). Corneal response to orthokeratology. Optom Vis Sci 75:791-9.
Tabernero J, Benito A, Alcon E, Artal P. (2007). Mechanism of compensation of aberrations in the human eye. J Opt Soc Am A 24:3274-83.
Tahhan N, Du Toit R, Papas E, Chung H, La Hood D, Holden AB. (2003). Comparison of reverse-geometry lens designs for overnight orthokeratology. Optom Vis Sci 80:796-804.
Tan CS, Ouyang Y, Ruiz H, Sadda SR. (2012). Diurnal variation of choroidal thickness in normal, healthy subjects measured by spectral domain optical coherence tomography. Invest Ophthalmol Vis Sci 53:261-6.
Tarrant J, Liu Y. Wildsoet CF. (2009). Orthokeratology can decrease the accommodative lag in myopes. Invest Ophthalmol Vis Sci, 50, 4294.
Tarrant J, Roorda A, Wildsoet CF. (2010). Determining the accommodative response from wavefront aberrations. J Vis 10:4.
Tedja MS, Wojciechowski R, Hysi PG, Eriksson N, Furlotte NA, Verhoeven VJM, Iglesias AI, Meester-Smoor MA, Tompson SW, Fan Q, Khawaja AP, Cheng CY, Hohn R, Yamashiro K, Wenocur A, Grazal C, Haller T, Metspalu A, Wedenoja J, Jonas JB, Wang YX, Xie J, Mitchell P, Foster PJ, Klein BEK, Klein R, Paterson AD, Hosseini SM, Shah RL, Williams C, Teo YY, Tham YC, Gupta P, Zhao W, Shi Y, Saw WY, Tai ES, Sim XL, Huffman JE, Polasek O, Hayward C, Bencic G, Rudan I, Wilson JF, Joshi PK, Tsujikawa A, Matsuda F, Whisenhunt KN, Zeller T, van der Spek PJ, Haak R, Meijers-Heijboer H, van Leeuwen EM, Iyengar SK, Lass JH, Hofman A, Rivadeneira F, Uitterlinden AG, Vingerling JR, Lehtimaki T, Raitakari OT, Biino G, Concas MP, Schwantes-An TH, Igo RP, Jr., Cuellar-Partida G, Martin NG, Craig JE, Gharahkhani P, Williams KM, Nag A, Rahi JS, Cumberland PM, Delcourt C, Bellenguez C, Ried JS, Bergen AA, Meitinger T, Gieger C, Wong TY, Hewitt AW, Mackey DA, Simpson CL, Pfeiffer N, Parssinen O, Baird PN, Vitart V, Amin N, van Duijn CM, Bailey-Wilson JE, Young TL, Saw SM, Stambolian D, MacGregor S, Guggenheim JA, Tung JY, Hammond CJ, Klaver CCW. (2018). Genome-wide association meta-analysis highlights light-induced signaling as a driver for refractive error. Nat Genet 50:834-48.
Thapa D, Fleck A, Lakshminarayanan V, Bobier WR. (2011). Ocular wavefront aberration and refractive error in pre-school children. Journal of Modern Optics 58:1681-9.
Theagarayan B, Radhakrishnan H, Allen PM, Calver RI, Rae SM, O'Leary DJ. (2009). The effect of altering spherical aberration on the static accommodative response. Ophthalmic Physiol Opt 29:65-71.
Thibos LN. (2000). Principles of Hartmann-Shack aberrometry. J Refract Surg 16:S563-5.
Thibos LN. (2001). Wavefront data reporting and terminology. J Refract Surg 17:S578-83.
Thibos LN. (2013). The 2012 charles prentice medal lecture: wavefront measurement of refractive state. Optom Vis Sci 90:911-23.
Thibos LN, Applegate RA, Schwiegerling JT, Webb R, science VSTMV, its a. (2002a). Standards for reporting the optical aberrations of eyes. J Refract Surg 18:S652-60.
Thibos LN, Bradley A, Liu T, Lopez-Gil N. (2013a). Spherical aberration and the sign of defocus. Optom Vis Sci 90:1284-91.

Thibos LN, Bradley A, Lopez-Gil N. (2013b). Modelling the impact of spherical aberration on accommodation. Ophthalmic Physiol Opt 33:482-96.
Thibos LN, Hong X, Bradley A, Applegate RA. (2004). Accuracy and precision of objective refraction from wavefront aberrations. J Vis 4:329-51.
Thibos LN, Hong X, Bradley A, Cheng X. (2002b). Statistical variation of aberration structure and image quality in a normal population of healthy eyes. J Opt Soc Am A 19:2329-48.
Tian Y, Tarrant J, Wildsoet CF. (2011). Optical and biometric characteristics of anisomyopia in human adults. Ophthalmic Physiol Opt 31:540-9.
Ticak A, Walline JJ. (2013). Peripheral optics with bifocal soft and corneal reshaping contact lenses. Optom Vis Sci 90:3-8.
Tideman JWL, Polling JR, Vingerling JR, Jaddoe VWV, Williams C, Guggenheim JA, Klaver CCW. (2018). Axial length growth and the risk of developing myopia in European children. Acta Ophthalmol 96:301-9.
Touzeau O, Allouch C, Borderie V, Kopito R, Laroche L. (2003). Correlation between refraction and ocular biometry. J Fr Ophtalmol 26:355-63.
Troilo D. (1992). Neonatal eye growth and emmetropisation – a literature review. Eye (Lond) 6:154-60.
Troilo D, Totonelly K, Harb E. (2009). Imposed anisometropia, accommodation, and regulation of refractive state. Optom Vis Sci 86:E31-9.
Tsai WS, Wang JH, Lee YC, Chiu CJ. (2019). Assessing the change of anisometropia in unilateral myopic children receiving monocular orthokeratology treatment. J Formos Med Assoc 118:1122-8.
Tsukiyama J, Miyamoto Y, Higaki S, Fukuda M, Shimomura Y. (2008). Changes in the anterior and posterior radii of the corneal curvature and anterior chamber depth by orthokeratology. Eye Contact Lens 34:17-20.
Tutt R, Bradley A, Begley C, Thibos LN. (2000). Optical and visual impact of tear break-up in human eyes. Invest Ophthalmol Vis Sci 41:4117-23.
Twa MD, Schulle KL, Chiu SJ, Farsiu S, Berntsen DA. (2016). Validation of macular choroidal thickness measurements from automated SD-OCT image segmentation. Optom Vis Sci 93:1387-98.
Uhlhorn SR, Borja D, Manns F, Parel JM. (2008). Refractive index measurement of the isolated crystalline lens using optical coherence tomography. Vision Res 48:2732-8.
Van Meter WS, Musch DC, Jacobs DS, Kaufman SC, Reinhart WJ, Udell IJ, American Academy of O. (2008). Safety of overnight orthokeratology for myopia: a report by the American Academy of Ophthalmology. Ophthalmology 115:2301-13 e1.
VanderVeen DK, Kraker RT, Pineles SL, Hutchinson AK, Wilson LB, Galvin JA, Lambert SR. (2019). Use of orthokeratology for the prevention of myopic progression in children: a report by the American Academy of Ophthalmology. Ophthalmology 126:623-36.
Vasudevan B, Esposito C, Peterson C, Coronado C, Ciuffreda KJ. (2014). Under-correction of human myopia – is it myopigenic?: a retrospective analysis of clinical refraction data. J Optom 7:147-52.
Vaz S, Falkmer T, Passmore AE, Parsons R, Andreou P. (2013). The case for using the repeatability coefficient when calculating test–retest reliability. PLoS One 8:e73990.
Verhoeven VJ, Hysi PG, Wojciechowski R, Fan Q, Guggenheim JA, Hohn R, MacGregor S, Hewitt AW, Nag A, Cheng CY, Yonova-Doing E, Zhou X, Ikram MK, Buitendijk GH, McMahon G, Kemp JP, Pourcain BS, Simpson CL, Makela KM, Lehtimaki T, Kahonen M, Paterson AD, Hosseini SM, Wong HS, Xu L, Jonas JB, Parssinen O, Wedenoja J, Yip SP, Ho DW, Pang CP, Chen LJ, Burdon KP, Craig JE, Klein BE, Klein R, Haller T, Metspalu A, Khor CC, Tai ES, Aung T, Vithana E, Tay WT, Barathi VA, Chen P, Li R, Liao J, Zheng Y, Ong RT, Doring A, Evans DM, Timpson NJ, Verkerk AJ, Meitinger T, Raitakari O, Hawthorne F, Spector TD, Karssen LC, Pirastu M, Murgia F, Ang W, Mishra A, Montgomery GW, Pennell CE, Cumberland PM, Cotlarciuc I, Mitchell P, Wang JJ, Schache M, Janmahasatian S, Igo RP, Jr., Lass JH, Chew E, Iyengar SK, Gorgels TG, Rudan I, Hayward C, Wright AF, Polasek O, Vatavuk Z, Wilson JF, Fleck B, Zeller T, Mirshahi A, Muller C, Uitterlinden AG, Rivadeneira F, Vingerling JR, Hofman A, Oostra BA, Amin N, Bergen AA, Teo YY, Rahi JS, Vitart V, Williams C, Baird PN, Wong TY, Oexle K, Pfeiffer N, Mackey DA, Young TL, van Duijn CM, Saw SM, Bailey-Wilson JE, Stambolian D, Klaver CC, Hammond CJ. (2013). Genome-wide meta-analyses of

multiancestry cohorts identify multiple new susceptibility loci for refractive error and myopia. Nat Genet 45:314-8.

Villa-Collar C, Gonzalez-Meijome JM, Queiros A, Jorge J. (2009). Short-term corneal response to corneal refractive therapy for different refractive targets. Cornea 28:311-6.

Vincent SJ, Collins MJ, Read SA, Carney LG, Yap MK. (2011). Interocular symmetry in myopic anisometropia. Optom Vis Sci 88:1454-62.

Voke J. (2010). Understanding the basics of ocular aberrations. Optometry Today 50:41-5.

Walline JJ. (2015). Myopia control: a review. Eye Contact Lens 42:3-8.

Walline JJ, Jones LA, Sinnott LT. (2009). Corneal reshaping and myopia progression. Br J Ophthalmol 93:1181-5.

Wallman J, Winawer J. (2004). Homeostasis of eye growth and the question of myopia. Neuron 43:447-68.

Walsh G, Charman WN, Howland HC. (1984). Objective technique for the determination of monochromatic aberrations of the human eye. J Opt Soc Am A 1:987-92.

Wan XH, Li SM, Xiong Y, Liang YB, Li J, Wang FH, Li J, Jhanji V, Wang NL. (2014). Ocular monochromatic aberrations in a rural Chinese adult population. Optom Vis Sci 91:68-75.

Wang B, Naidu RK, Qu X. (2017). Factors related to axial length elongation and myopia progression in orthokeratology practice. PLoS One 12:e0175913.

Wang D, Chun RK, Liu M, Lee RP, Sun Y, Zhang T, Lam C, Liu Q, To CH. (2016). Optical defocus rapidly changes choroidal thickness in schoolchildren. PLoS One 11:e0161535.

Wang J, Fonn D, Simpson TL, Sorbara L, Kort R, Jones L. (2003a). Topographical thickness of the epithelium and total cornea after overnight wear of reverse-geometry rigid contact lenses for myopia reduction. Invest Ophthalmol Vis Sci 44:4742-6.

Wang J, Yang D, Bi H, Du B, Lin W, Gu T, Zhang B, Wei R. (2018). A new method to analyze the relative corneal refractive power and its association to myopic progression control with orthokeratology. Transl Vis Sci Technol 7:17.

Wang L, Dai E, Koch DD, Nathoo A. (2003b). Optical aberrations of the human anterior cornea. J Cataract Refract Surg 29:1514-21.

Wang L, Koch DD. (2003). Ocular higher-order aberrations in individuals screened for refractive surgery. J Cataract Refract Surg 29:1896-903.

Wang L, Santaella RM, Booth M, Koch DD. (2005). Higher-order aberrations from the internal optics of the eye. J Cataract Refract Surg 31:1512-9.

Wang Y, Zhao K, Jin Y, Niu Y, Zuo T. (2003c). Changes of higher order aberration with various pupil sizes in the myopic eye. J Refract Surg 19:S270-4.

Watson AB, Ahumada AJ, Jr. (2008). Predicting visual acuity from wavefront aberrations. J Vis 8:17 1-9.

Webb R. (1992). Zernike polynomial description of ophthalmic surfaces. Ophthalmic and Visual Optics 3:28-31.

Wei RH, Lim L, Chan WK, Tan DT. (2006). Higher order ocular aberrations in eyes with myopia in a Chinese population. J Refract Surg 22:695-702.

Weizhong L, Zhikuan Y, Wen L, Xiang C, Jian G. (2008). A longitudinal study on the relationship between myopia development and near accommodation lag in myopic children. Ophthalmic Physiol Opt 28:57-61.

Wen D, Huang J, Chen H, Bao F, Savini G, Calossi A, Chen H, Li X, Wang Q. (2015). Efficacy and acceptability of orthokeratology for slowing myopic progression in children: a systematic review and meta-analysis. J Ophthalmol 2015:360806.

Wenbo L, Congxia B, Hui L. (2017). Genetic and environmental-genetic interaction rules for the myopia based on a family exposed to risk from a myopic environment. Gene 626:305-8.

Werkmeister RM, Alex A, Kaya S, Unterhuber A, Hofer B, Riedl J, Bronhagl M, Vietauer M, Schmidl D, Schmoll T, Garhofer G, Drexler W, Leitgeb RA, Groeschl M, Schmetterer L. (2013). Measurement of tear film thickness using ultrahigh-resolution optical coherence tomography. Invest Ophthalmol Vis Sci 54:5578-83.

Williams D, Yoon GY, Porter J, Guirao A, Hofer H, Cox I. (2000). Visual benefit of correcting higher order aberrations of the eye. J Refract Surg 16:S554-9.

Wilson BJ, Decker KE, Roorda A. (2002). Monochromatic aberrations provide an odd-error cue to focus direction. J Opt Soc Am 19:833-9.

Wlodyga R, Harris D. (1993). Accelerated orthokeratology techniques and procedures manual, Part 1. National Eye Research Foundation, Chicago:1-7.

Wolffsohn JS, Calossi A, Cho P, Gifford K, Jones L, Jones D, Guthrie S, Li M, Lipener C, Logan NS, Malet F, Peixoto-de-Matos SC, Gonzalez-Meijome JM, Nichols JJ, Orr JB, Santodomingo-Rubido J, Schaefer T, Thite N, van der Worp E, Tarutta E, Iomdina E, Ali BM, Villa-Collar C, Abesamis-Dichoso C, Chen C, Pult H, Blaser P, Parra Sandra Johanna G, Iqbal F, Ramos R, Carrillo Orihuela G, Boychev N. (2020). Global trends in myopia management attitudes and strategies in clinical practice - 2019 update. Cont Lens Anterior Eye 43:9-17.

Wolffsohn JS, Calossi A, Cho P, Gifford K, Jones L, Li M, Lipener C, Logan NS, Malet F, Matos S, Meijome JM, Nichols JJ, Orr JB, Santodomingo-Rubido J, Schaefer T, Thite N, van der Worp E, Zvirgzdina M. (2016). Global trends in myopia management attitudes and strategies in clinical practice. Cont Lens Anterior Eye 39:106-16.

Wolffsohn JS, Kollbaum PS, Berntsen DA, Atchison DA, Benavente A, Bradley A, Buckhurst H, Collins M, Fujikado T, Hiraoka T, Hirota M, Jones D, Logan NS, Lundstrom L, Torii H, Read SA, Naidoo K. (2019). IMI - clinical myopia control trials and instrumentation report. Invest Ophthalmol Vis Sci 60:M132-M60.

Wu LJ, You QS, Duan JL, Luo YX, Liu LJ, Li X, Gao Q, Zhu HP, He Y, Xu L, Jonas JB, Wang W, Guo XH. (2015). Prevalence and associated factors of myopia in high-school students in Beijing. PLoS One 10:e0120764.

Wu PC, Chen CT, Chang LC, Niu YZ, Chen ML, Liao LL, Rose K, Morgan IG. (2020). Increased time outdoors is followed by reversal of the long-term trend to reduced visual acuity in Taiwan primary school students. Ophthalmology. doi: 10.1016/j.ophtha.2020.01.054. [Epub ahead of print]

Wu PC, Chen CT, Lin KK, Sun CC, Kuo CN, Huang HM, Poon YC, Yang ML, Chen CY, Huang JC, Wu PC, Yang IH, Yu HJ, Fang PC, Tsai CL, Chiou ST, Yang YH. (2018). Myopia prevention and outdoor light intensity in a school-based cluster randomized trial. Ophthalmology 125:1239-50.

Wu R, Stapleton F, Swarbrick HA. (2009). Residual corneal flattening after discontinuation of long-term orthokeratology lens wear in asian children. Eye Contact Lens 35:333-7.

Wu X, Gao G, Jin J, Hua W, Tao L, Xu S, Tao F. (2016). Housing type and myopia: the mediating role of parental myopia. BMC Ophthalmol 16:151.

Xiong S, Sankaridurg P, Naduvilath T, Zang J, Zou H, Zhu J, Lv M, He X, Xu X. (2017). Time spent in outdoor activities in relation to myopia prevention and control: a meta-analysis and systematic review. Acta Ophthalmol 95:551-66.

Yam JC, Jiang Y, Tang SM, Law AK, Chan JJ, Wong E, Ko ST, Young AL, Tham CC, Chen LJ. (2018). Low-concentration atropine for myopia progression (LAMP) study: a randomized, double-blinded, placebo-controlled trial of 0.05%, 0.025%, and 0.01% atropine eye drops in myopia control. Ophthalmology 126:113-24.

Yam JC, Tang SM, Kam KW, Chen LJ, Yu M, Law AK, Yip BH, Wang YM, Cheung CYL, Ng DSC, Young AL, Tham CC, Pang CP. (2020). High prevalence of myopia in children and their parents in Hong Kong Chinese population: the Hong Kong Children Eye Study. Acta Ophthalmol. doi:10.1111/aos.14350. [Epub ahead of print]

Yang Y, Wang L, Li P, Li J. (2018). Accommodation function comparison following use of contact lens for orthokeratology and spectacle use in myopic children: a prospective controlled trial. Int J Ophthalmol 11:1234-8.

Yang YR, Zhao JL, Xiao F, Zhao HX, Dai Y. (2019). Effect of high-order aberrations on pattern-reversal visual evoked potentials. Vision Res 161:52-9.

Yazar S, Hewitt AW, Forward H, McKnight CM, Tan A, Mountain JA, Mackey DA. (2014). Comparison of monochromatic aberrations in young adults with different visual acuity and refractive errors. J Cataract Refract Surg 40:441-9.

Vincent SJ, Tan Q, Ng AL, Cheng GP, Woo VC, Cho P. (2020). Higher order aberrations and axial elongation in combined 0.01% atropine with orthokeratology for myopia control. Ophthalmic and Physiological Optics 40:728-37.

Yoon JH, Swarbrick HA. (2013). Posterior corneal shape changes in myopic overnight orthokeratology. Optom Vis Sci 90:196-204.

You X, Wang L, Tan H, He X, Qu X, Shi H, Zhu J, Zou H. (2016). Near work related behaviors associated with myopic shifts among primary school students in the Jiading district of Shanghai: a school-based one-year cohort study. PLoS One 11:e0154671.

Yu LH, Jin WQ, Mao XJ, Jiang J. (2020). Effect of orthokeratology on axial length elongation in moderate myopic and fellow high myopic eyes of children. Clin Exp Optom. doi:10.1111/cxo.13067. [Epub ahead of print]

Zadnik K. (1997). Myopia development in childhood. Optom Vis Sci 74:603-8.

Zadnik K, Manny RE, Yu JA, Mitchell GL, Cotter SA, Quiralte JC, Shipp MD, Friedman NE, Kleinstein RN, Walker TW. (2003). Ocular component data in schoolchildren as a function of age and gender. Optom Vis Sci 80:226-36.

Zadnik K, Mutti DO, Mitchell GL, Jones LA, Burr D, Moeschberger ML. (2004). Normal eye growth in emmetropic schoolchildren. Optom Vis Sci 81:819-28.

Zadok D, Levy Y, Segal O, Barkana Y, Morad Y, Avni I. (2005). Ocular higher-order aberrations in myopia and skiascopic wavefront repeatability. J Cataract Refract Surg 31:1128-32.

Zhang J, Li J, Li X, Li F, Wang T. (2020). Redistribution of the corneal epithelium after overnight wear of orthokeratology contact lenses for myopia reduction. Cont Lens Anterior Eye 43:232-7.

Zhang M, Li L, Chen L, Lee J, Wu J, Yang A, Chen C, Xu D, Lam DSC, Sharma A, Griffiths S, Gao Y, Congdon N. (2010). Population density and refractive error among Chinese children. Invest Ophthalmol Vis Sci 51:4969-76.

Zhang N, Liu L, Yang B, Ma W, Wang X, Ye W, Yang X, Lam CSY. (2018). Higher-order aberrations in children and adolescents of Southwest China. Optom Vis Sci 95:53-9.

Zhang N, Yang XB, Zhang WQ, Liu LQ, Dong GJ, Chen TW, Liao M, Liao X. (2013). Relationship between higher-order aberrations and myopia progression in schoolchildren: a retrospective study. Int J Ophthalmol 6:295.

Zhang X, Qu X, Zhou X. (2015). Association between parental myopia and the risk of myopia in a child. Exp Ther Med 9:2420-8.

Zhao PF, Li SM, Lu J, Song HM, Zhang J, Zhou YH, Wang NL. (2017). Effects of higher-order aberrations on contrast sensitivity in normal eyes of a large myopic population. Int J Ophthalmol 10:1407-11.

Zhong X, Chen X, Xie RZ, Yang J, Li S, Yang X, Gong X. (2009). Differences between overnight and long-term wear of orthokeratology contact lenses in corneal contour, thickness, and cell density. Cornea 28:271-9.

Zhong Y, Chen Z, Xue F, Miao H, Zhou X. (2015). Central and peripheral corneal power change in myopic orthokeratology and its relationship with 2-year axial length change. Invest Ophthalmol Vis Sci 56:4514-9.

Zhong Y, Chen Z, Xue F, Zhou J, Niu L, Zhou X. (2014). Corneal power change is predictive of myopia progression in orthokeratology. Optom Vis Sci 91:404-11.

Zhou WJ, Zhang YY, Li H, Wu YF, Xu J, Lv S, Li G, Liu SC, Song SF. (2016). Five-year progression of refractive errors and incidence of myopia in school-aged children in Western China. J Epidemiol 26:386-95.

Zhou XY, Wang L, Zhou XT, Yu ZQ. (2015). Wavefront aberration changes caused by a gradient of increasing accommodation stimuli. Eye (Lond) 29:115-21.

Zhu M, Feng H, Zhu J, Qu X. (2014a). The impact of amplitude of accommodation on controlling the development of myopia in orthokeratology. Zhonghua Yan Ke Za Zhi 50:14-9.

Zhu MJ, Feng HY, He XG, Zou HD, Zhu JF. (2014b). The control effect of orthokeratology on axial length elongation in Chinese children with myopia. BMC Ophthalmol 14:141.