Higher-Order Aberrations and Axial Elongation in Myopic Children Treated With Orthokeratology

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PURPOSE. This retrospective longitudinal study aimed to examine the relationship between ocular higher-order aberrations (HOA) and axial eye growth in young myopic children undergoing orthokeratology (ortho-k) treatment.

METHODS. Axial length and ocular HOA, measured under cycloplegia annually over a 2-year period from the right eyes of myopic children, who previously completed ortho-k clinical trials, were retrieved. Linear mixed model analyses were applied to determine the association between ocular HOA, other known confounding variables (age, sex, and refractive error), and axial eye growth.

RESULTS. Data from 103 subjects were analyzed. The root-mean square (RMS) values of total ocular HOA (third to sixth orders combined), spherical (Z_4^0 and Z_6^0 combined), and comatic (Z_3^{-1}, Z_3^1, Z_5^{-1}, and Z_5^1 combined) aberrations increased by approximately 3, 9, and 2 times, respectively, after 2 years of ortho-k treatment. After adjusting for age, sex, and refractive error, higher RMS values of total HOA and spherical aberrations were associated with both longer axial length and slower axial elongation (all $P < 0.01$). For individual Zernike term coefficients, a higher level of positive spherical aberration (Z_4^0) was also associated with longer axial length and slower axial elongation (both $P < 0.01$), after adjusting for baseline HOA.

CONCLUSIONS. Ortho-k for myopia control significantly increases the Zernike coefficients and therefore the RMS values for a range of total ocular HOA terms or metrics in children. These findings suggest the potential role of HOA, particularly spherical aberration, as the possible mechanism of slowing axial elongation in ortho-k treatment.

Keywords: higher-order aberrations, spherical aberration, orthokeratology, axial elongation, myopia progression

Myopia, a common cause of distance vision impairment and uncorrected refractive error, is the second most common cause of blindness worldwide.[1] Its prevalence has been increasing for decades, particularly in East Asian countries.[2] The proportion of the world's population suffering from myopia is estimated to reach 50% by 2050, of whom almost one tenth will become high myopes (≤ -5.00 D),[3] if there is no myopia control intervention. Eyes with longer axial length, common in high myopes,[4] are associated with increased risks of other ocular complications, including cataract, glaucoma, macular diseases, posterior staphyloma, and chorioretinal degenerations.[5] The expenditure on the diagnosis and treatment of these complications can lead to a substantial economic burden to society,[6] and therefore early retardation of myopia progression in children is essential.

According to recent longitudinal studies investigating predominantly young myopic children wearing single-vision spectacles,[7,8] higher levels of the root-mean-square error (RMS) values of both spherical and comatic aberrations were associated with slower axial elongation. With regard to individual Zernike coefficients, Lau et al.[7] showed that more positive spherical aberration and vertical trefoil, and less horizontal trefoil, were associated with slower axial elongation, whereas Hiraoka et al.[8] reported a similar trend for spherical aberration and axial elongation, but only observed a significant correlation with coma, not trefoil. These non-interventional observational studies support the potential role of specific habitual higher-order aberrations (HOA) in the regulation of childhood eye growth and myopia progression. During orthokeratology (ortho-k) treatment, an established effective intervention for myopia control,[9] the cornea is reshaped,[10] which significantly alters the profile of corneal and total ocular HOA.[11] Therefore it is of particular interest to investigate if the changes induced in the ocular HOA profile during ortho-k treatment are associated with axial elongation in children, which may help to further the current understanding of the underlying mechanism of ortho-k for myopia control.

Some longitudinal studies have investigated the relationship between HOA and axial elongation after ortho-k treatment. Santodomingo-Rubido et al.[12] analyzed the changes in corneal HOA of 29 children (mean age:

TABLE 1. Description and Baseline Demographics (Mean ± SD or Median [Min, Max]) of Ortho-k Subjects Retrieved from ROMIO,[19] TO-SEE,[20] HM-PRO,[21] and PR (A Subset of Lee and Cho's Study)[22] Studies

Studies	ROMIO	TO-SEE	HM-PRO	PR
Description	Low to moderate myopes	High astigmats	High myopes	Low to moderate myopes
Number of subjects	34	34	7	28
Age, years	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 [−1.00, 0.00]	−1.63 ± 0.60	−0.61 ± 0.40	−0.38 [−1.00, 0.00]
Spherical equivalent refraction, 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

9.6 ± 1.6 years) after 2 years of ortho-k treatment and suggested that despite significant increases in HOA, these changes were not correlated with axial elongation. However, internal aberrations from the posterior cornea or the crystalline lens may partially compensate for the significant increase in corneal HOA during ortho-k treatment. Changes in total ocular spherical aberration RMS or spherical aberration RMS plateau over time in comparison with changes in corneal spherical aberration,[13,14] potentially due to compensatory changes in shape or thickness of the crystalline lens.[11,15] Hence, analyzing corneal HOA only may not provide a comprehensive understanding of the influence of HOA on axial elongation, whereas ocular HOA would more closely reflect the quality of the retinal image.[16] In addition, this study[12] may be underpowered due to the small sample size (n = 29). Hiraoka et al.[13] examined the influence of both corneal and ocular HOA on axial elongation in 55 young myopic children (mean age 10.3 ± 1.4 years) undergoing ortho-k treatment for 1 year. For both corneal and ocular HOA, both spherical and comatic aberrations were negatively associated with axial elongation, with comatic aberrations displaying the strongest correlation. However, in their regression analysis, other confounding factors such as age and sex, which also affect axial elongation,[17] were not accounted for. More recently, Kim et al.[18] investigated various ocular parameters of 17 children (mean age 8.6 ± 0.8 years) and their association with myopia control efficacy in ortho-k. They showed that less peripheral myopia (based on peripheral axial length measurements), more asymmetric optical changes, and comatic aberrations induced by ortho-k, were associated with less axial elongation. However, the limited sample size of 17 participants is likely insufficient for such a multivariate analysis.

To date, only a limited number of studies have examined the influence of ocular HOA on axial elongation in children receiving ortho-k treatment and the potential role of HOA underlying the mechanism of ortho-k for myopia control. The primary aim of this study was therefore to examine the relationship between the change in ocular HOA and axial elongation in young myopic children treated with ortho-k over a 2-year period, while controlling for known confounding variables.

METHODS

Study Design

This retrospective study included data from subjects receiving ortho-k treatment who completed previous 2-year longitudinal clinical trials (ROMIO,[19] TO-SEE,[20] HM-PRO,[21] PR [a subset of Lee & Cho[22] studies]). All previous studies were conducted with written informed consent and in accor-

dance with the tenets of the Declaration of Helsinki and were approved by the Departmental Research Committee of the School of Optometry of The Hong Kong Polytechnic University. All studies were also registered at ClinicalTrials.gov (ROMIO: NCT00962208; TO-SEE: NCT00978692; HM-PRO: NCT00977236; PR: NCT00978679).

Subjects and Procedures

Table 1 summarizes the baseline demographics and refractive errors of the subjects included in this analysis from previous ortho-k studies.[19–22] Young children of different levels of myopia and astigmatism were either partially corrected with ortho-k lenses with residual refractive error corrected with spectacles (HM-PRO[21] study only) or fully corrected with ortho-k lenses (all other studies).

All subjects underwent annual cycloplegic data collection, with the instillation of 1 drop of 0.5% proparacaine, 1% tropicamide, and 1% cyclopentolate, each separated by 5 minutes. The data (cycloplegic subjective refraction, axial length, and ocular aberrations) were obtained by a masked examiner. Cycloplegic subjective refraction was performed following the principle of maximum plus for maximum visual acuity. Axial length was determined, as the average of 5 measurements with a maximum difference of 0.02 mm and a signal-to-noise ratio of more than 3.5, with the IOLMaster 500 (Carl Zeiss Meditec, Dublin, CA, USA). Monochromatic ocular HOA for a wavelength of 555 µm were measured using a Shack-Hartmann aberrometer (Complete Ophthalmic Analysis System [COAS]; Wavefront Sciences Ltd., New Mexico, USA). The average of at least 5 measurements was used for analysis. The acquired data were fitted with a sixth-order Zernike polynomial using a fixed 6-mm pupil diameter. The RMS values of total HOA, spherical, and comatic aberrations were computed as the square root of the sum of squares of corresponding terms (total: from third- to sixth-order terms; spherical aberrations: Z_4^0 and Z_6^0 combined; comatic aberrations: Z_3^{-1}, Z_3^1, Z_5^{-1}, and Z_5^1 combined) as applied in previous analyses of young spectacle-wearing children.[7]

Statistical Analysis

All statistical analyses were performed using SPSS 23 version (IBM Corp., Armonk, NY, USA). To prevent the inflation of *P*-values when including data from fellow eyes[23] and the influence of mirror symmetry between eyes confounding aberration analyses,[24] only data from right eyes were analyzed. Subjects with missing total HOA data at the baseline visit were excluded. Repeated measures analysis of variance tests, with Bonferroni corrections, were used to compare the changes in spherical equivalent refraction (SER), axial length, and RMS values of total HOA,

spherical, and comatic aberrations, and individual Zernike coefficients between visits.

In order to identify baseline characteristics associated with total HOA RMS, spherical and comatic aberrations RMS, and corresponding Zernike coefficients for particular RMS metrics (spherical aberrations: Z_4^0 and Z_6^0; comatic aberrations: Z_3^{-1}, Z_3^1, Z_5^{-1}, and Z_5^1) at baseline, linear mixed models were used to examine the effects of age, sex, and axial length (similar modelling was repeated for SER to avoid multicollinearity issues) on HOA terms or RMS metrics, with a first-order autoregressive covariance structure and restricted maximum likelihood estimation. Individual subject's slope and intercept were included as random effects using an unstructured covariance matrix to control for intersubject variations.

Regarding the influence of the changes in HOA on axial elongation, the age of the subjects was transformed (using a natural logarithm) to improve the fit of the models.[7,25] To account for sporadic and random missing data in the follow-ups, another linear mixed model was applied to investigate the effect of total HOA RMS on axial elongation. Adjustments for other predictive variables (age, sex, baseline SER, and baseline total HOA RMS) were performed to control for their influence on axial elongation. The model used a first-order autoregressive covariance structure and restricted maximum likelihood estimation. Similar modelling was also applied to investigate the association between HOA terms and metrics and axial elongation; specifically, the specific RMS values for spherical and comatic aberrations, and the corresponding Zernike coefficients (spherical aberrations: Z_4^0 and Z_6^0; comatic aberrations: Z_3^{-1}, Z_3^1, Z_5^{-1}, and Z_5^1). A backward step-wise approach was utilized with the least significant factor removed and the Akaike information criterion was used to compare the goodness of fit between different models.[26]

RESULTS

Data from 103 participants (51 girls and 52 boys; median [range] age 9.1 [6.3–13.0] years) with a median [range] SER of −2.88 [−8.63 to −0.38] D and mean axial length of 24.52 ± 0.80 mm at baseline, were retrieved for analysis. Table 2 summarizes the demographics and ocular HOA at each visit (note that only data available for all visits [baseline, first, second year] are presented). Most parameters, except for age and axial length, were stable at the 1-year visit, with no

further significant changes observed thereafter. After 2 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 RMS values of the total HOA, spherical, and comatic aberrations increased by 0.74 ± 0.56 μm, 0.78 ± 0.51 μm, and 0.17 ± 0.29 μm, respectively (total HOA: F[1.55, 124.17] = 103.32, $P < 0.001$; spherical aberrations: F[1.56, 124.40] = 140.72, $P < 0.001$; comatic aberrations: F[1.75, 139.57] = 19.52, $P < 0.001$).

Regarding the influence of baseline demographics on baseline HOA terms or metrics, using baseline SER in the modelling, girls exhibited more primary vertical coma (Z_3^{-1}: $\beta = 0.07$, $P = 0.04$), whereas more (negative) SER was associated with less primary and secondary horizontal coma (Z_3^1: $\beta = 0.01$ μm/D, p = 0.02; Z_5^1: $\beta = 0.003$ μm/D, $P = 0.01$). In both the modeling using baseline axial length and SER, older children had less secondary vertical coma (Z_5^{-1}: $\beta = -0.01$ μm/year, $0.01 < P < 0.02$). No associations were found for other Zernike terms or specific RMS values (all $P > 0.05$).

From the linear mixed model analyses (Model 1, Table 3), as expected, axial length was longer in boys (0.46 mm longer, $P < 0.001$), increased with age ($P < 0.001$), and less so in ortho-k subjects with lower baseline SER (i.e., 0.24 mm shorter per 1 D of SER, $P < 0.001$). After adjusting for baseline HOA (or corresponding RMS values), higher levels of RMS values for total HOA and spherical aberrations were associated with longer axial length (total HOA RMS: $\beta = 0.96$ mm/μm, $P < 0.001$, model 1; spherical aberrations RMS: $\beta = 0.91$ mm/μm, $P = 0.008$, model 2) and slower axial elongation (total HOA RMS: $\beta = -0.43$ mm year^{-1}/μm, $P < 0.001$, model 1; spherical aberrations RMS: $\beta = -0.39$ mm year^{-1}/μm, $P = 0.007$, model 2). When investigating the influence of individual spherical and comatic Zernike coefficients, a higher level of positive spherical aberration (Z_4^0) was associated with longer axial length ($\beta = 0.99$ mm/μm, $P = 0.007$) and slower axial elongation ($\beta = -0.46$ mm year^{-1}/μm, $P = 0.004$, model 3). No associations between the RMS of comatic aberrations or individual comatic Zernike terms and axial length or its elongation were observed (all $P > 0.05$, models 2 and 4).

The Figure shows the wavefront height difference maps (2-year visit minus baseline visit) for 2 representative participants exhibiting relatively fast and slow axial elongation over the 2-year study period. This figure high-

TABLE 2. Demographics and Higher-order Aberrations (Mean ± SD) of the Pooled Population at Different Visits (Note that Only Data from Subjects with Data Available from All Visits are Presented)

	Baseline	First year	Second year
Demographics			
Age, years (n = 91)	9.3 ± 1.3	10.4 ± 1.2	11.4 ± 1.2
Spherical equivalent refraction, 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
Higher-order aberrations, μm (n = 81)			
Total higher-order aberrations RMS	0.31 ± 0.09	1.05 ± 0.64	1.05 ± 0.56
Spherical aberrations RMS	0.09 ± 0.07	0.85 ± 0.55	0.88 ± 0.53
Primary spherical aberration (Z_4^0)	0.06 ± 0.09	0.84 ± 0.54	0.86 ± 0.52
Secondary spherical aberration (Z_6^0)	−0.02 ± 0.02	0.08 ± 0.17	0.07 ± 0.16
Comatic aberrations RMS	0.19 ± 0.11	0.41 ± 0.38	0.36 ± 0.26
Primary vertical coma (Z_3^{-1})	0.11 ± 0.17	−0.04 ± 0.35	−0.08 ± 0.25
Primary horizontal coma (Z_3^1)	−0.02 ± 0.08	0.16 ± 0.37	0.09 ± 0.29
Secondary vertical coma (Z_5^{-1})	0.02 ± 0.03	0.04 ± 0.11	0.05 ± 0.12
Secondary horizontal coma (Z_5^1)	0.00 ± 0.01	0.01 ± 0.15	−0.02 ± 0.13

FAST   **SLOW**
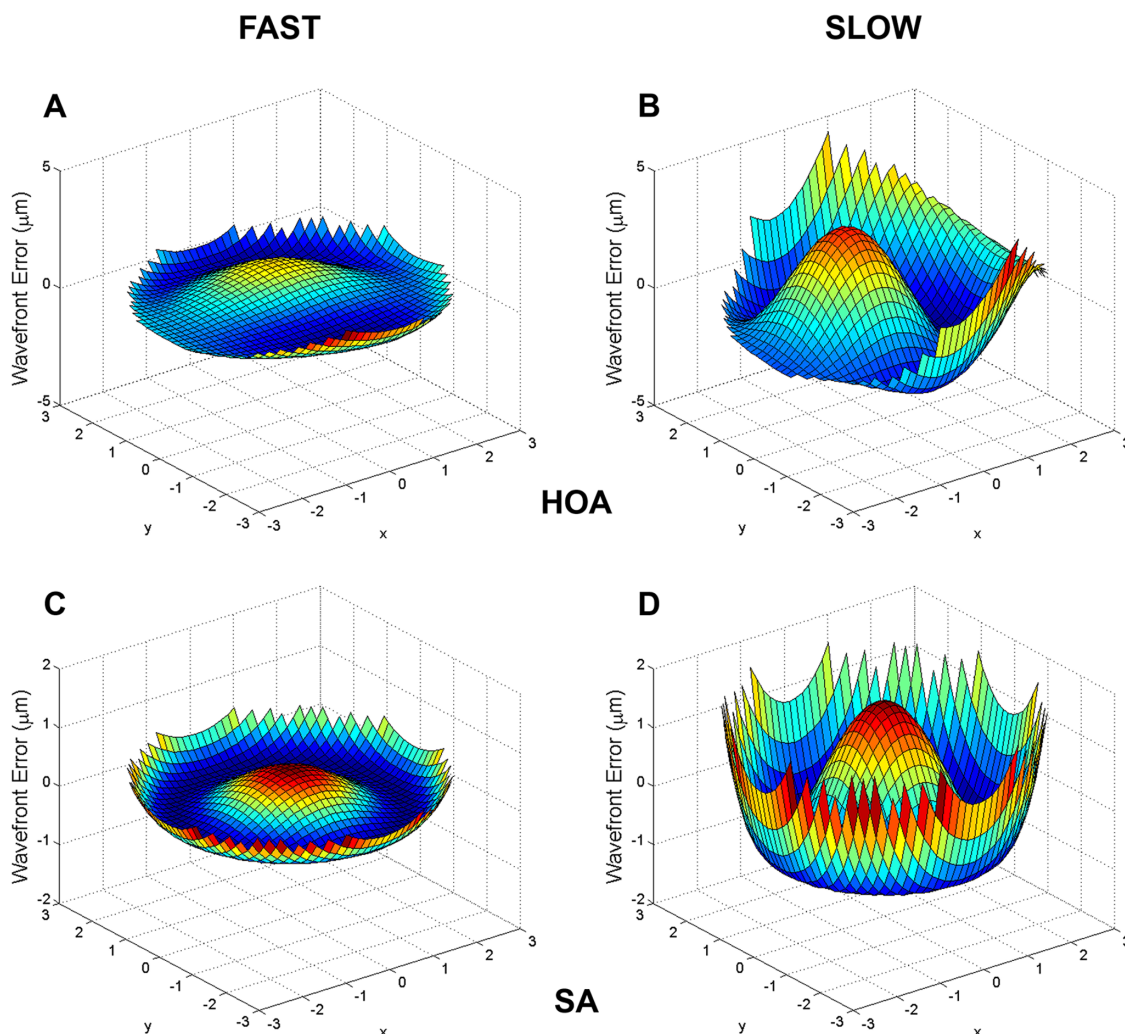
FIGURE. Wavefront height difference maps (2-year visit minus baseline visit) for 2 representative participants exhibiting relatively fast and slow axial elongation over the 2-year study period. Fast: participant 190: 0.64 mm axial elongation, +0.22 µm change in spherical aberration, +0.35 µm change in HOA RMS. Slow: participant 252: 0.05 mm axial elongation, +0.74 µm change in spherical aberration, +1.47 µm change in HOA RMS. Note: the z-axis scale differs for the total ocular higher-order aberration (HOA) plots and the total ocular spherical aberration (SA) plots.

lights the rapid change of wavefront error in spherical pattern towards the edge of the pupil, indicating a higher level of spherical aberration in the participant with relatively slower axial elongation compared with another participant with relatively faster axial elongation.

DISCUSSION

The results of this study demonstrate a significant association between ocular HOA, especially spherical aberration, and axial elongation in children undergoing ortho-k treatment, after accounting for known confounding variables. Greater RMS values of total HOA and spherical aberrations, and a higher level of positive spherical aberration (Z_4^0), were associated with slower axial eye growth. The association observed between HOA, which impact on retinal image quality,[27] visual function,[28] and axial elongation found in the current study, provides further insight regarding the potential mechanism underlying the retardation of axial elongation in children treated with ortho-k.

HOA increased dramatically after ortho-k treatment in our subjects, consistent with previous studies,[11,13,14,18,29–31] although the magnitude of change varied substantially with the pupil size analyzed,[32] age of subjects,[35] lens design,[34] and duration of follow-up.[14] For example, Gifford et al.[11] found an approximately doubling in total HOA, spherical, and comatic aberrations (over a 4-mm pupil) in young adults (mean age 21.1 ± 1.8 years) wearing ortho-k for 1 week, whereas Hiraoka et al.[13] reported a tripling in the RMS values for total HOA, spherical, and comatic aberrations (over a 5-mm pupil, up to the fourth order) in their cohort (mean age 10.3 ± 1.4 years) undergoing ortho-k treatment for 1 year. In the participants of this study (mean age 9.1 ± 1.3 years) analyzed over a 6-mm pupil, the total HOA, spherical, and comatic aberrations RMS increased by 3, 9, and 2 times, respectively, after ortho-k treatment. Similar to the findings of Joslin et al.[31] and Chen et al.,[15] primary spherical aberration (Z_4^0) and horizontal coma (Z_3^1) were the most affected individual Zernike coefficients. The increase in positive spherical aberration has been previ-

Table 3. Statistically Significant Fixed Effects and Parameter Estimates (β) of the Influences of Changes in Axial Length

	β	*P*
Model 1 – total HOA RMS		
Intercept	19.00	<0.001
Sex*	−0.46	<0.001
ln(age)	2.33	<0.001
Baseline spherical equivalent refraction	−0.24	<0.001
RMS of total HOA	0.96	<0.001
Time by RMS of total HOA	−0.43	<0.001
Model 2 – specific RMS (spherical and comatic)		
Intercept	19.23	<0.001
Sex*	−0.45	0.002
ln(age)	2.23	<0.001
Baseline spherical equivalent refraction	−0.24	<0.001
RMS of spherical aberrations	0.91	0.008
Time by RMS of spherical aberrations	−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 spherical equivalent refraction	−0.22	<0.001
Baseline primary spherical aberration (Z_4^0)	−1.42	0.012
Baseline secondary spherical aberration (Z_6^0)	9.28	0.012
Primary spherical aberration (Z_4^0)	0.99	0.007
Time by primary spherical aberration (Z_4^0)	−0.46	0.004
Model 4 – comatic Zernike terms (Z_3^{-1}, Z_3^1, Z_5^{-1}, and Z_5^1)		
Intercept	19.51	<0.001
Sex*	−0.49	<0.001
ln(age)	2.03	<0.001
Baseline spherical equivalent refraction	−0.24	<0.001

Other parameters and interactions showing statistical insignificance are not shown.

* Parameter estimate for girls.

ously attributed to the nature of corneal asphericity, as the reverse geometry ortho-k lens flattens the central cornea and changes its shape from prolate to oblate, whereas the increase in comatic aberrations is associated with lens decentration, similar to the change in HOA observed with a decentered LASIK treatment zone.[35] In addition, other researchers have shown that larger increases in spherical and comatic aberration RMS values were associated with more myopic correction[11] (resulting in a greater change in the corneal profile across the treatment zone) and greater lens decentration,[36,37] respectively, during ortho-k treatment.

The association between ocular HOA and axial elongation, with adjustment for other confounders, was similarly analyzed in spectacle-wearing children by Lau et al.,[7] and higher levels of ocular HOA were associated with slower axial elongation. Referring to the beta coefficients in both models of spectacle-wearing[7] and ortho-k treated children in this study, the association between ocular HOA and axial elongation was modest in comparison to the effects of age, sex, and the change in SER. However, following ortho-k treatment, ocular HOA increased significantly by about 3 to 9 times (and 14 times for primary spherical aberration) (Table 2) and consequently the association between ocular HOA and axial elongation in ortho-k treated children also increased compared with spectacle-wearing children (a 3-4 times increase in beta coefficients for models 1 and 2).

Based on a series of simulations combining different magnitudes of coefficients for specific HOA terms that vary during accommodation in down gaze (spherical aberration, trefoil along 30 degrees and vertical coma),[38] Buehren

et al.[39] proposed that the magnitude and sign of HOA, especially spherical aberration, may provide a directional cue to the retina, which could lead to compensatory eye growth to optimize image quality. Spherical aberration values of −0.2 to −0.3 µm or less (more negative) for a 5-mm pupil required clinically significant changes (at least 0.25 D) in the best sphere correction to optimize the retinal image quality. Thibos et al.[40] also performed computational modelling and investigated the coupling effect of the sign of spherical aberration and defocus on retinal image quality. They reported that positive spherical aberration may have a protective effect against myopia progression because, in combination with hyperopic defocus that is often present in young myopes with a lag of accommodation during near work,[41,42] this improved the retinal image quality in comparison with the combination of negative spherical aberration and hyperopic defocus. In addition, from Tarrant et al.[43] study investigating the predictive values of certain optical quality metrics in defining the plane of best focus, using accommodative and HOA data obtained from emmetropic and myopic adults, defocus alone may not be a good measure. They indicated the importance of the interaction between defocus and spherical aberration on affecting the retinal image quality. The significant increase in HOA, particularly spherical aberration, due to ortho-k may therefore be linked mechanistically to the slowed axial elongation with this treatment in myopic children.

Since baseline HOA may affect axial elongation as observed in spectacle-wearing children,[7] linear mixed models were also performed on specific HOA terms or metrics measured at baseline. These analyses revealed that the majority of HOA terms and metrics (except for primary and secondary horizontal coma) were not significantly associated with sex, age, and axial length (or SER) at baseline in our cohort of subjects, similar to those reported in a review by Little et al.[44] More importantly, in the modelling presented in the current study, baseline HOA terms or metrics, and baseline SER were included as fixed factors and any potential influence of these factors were accounted for in the statistical models.

Santodomingo-Rubido et al.[12] reported no correlations between corneal HOA and axial elongation in children undergoing ortho-k. However, corneal HOA do not accurately represent the true retinal image quality (i.e., derived from the ocular HOA) due the partial compensatory changes observed in the internal optics of the eye.[45,46] Hiraoka et al.[13] and Kim et al.[18] applied multiple linear regressions and generalized estimating equations to identify significant factors associated with axial elongation after performing simple correlations between predictors and axial elongation. They showed that higher levels of comatic aberrations RMS were significantly associated with slower axial elongation. However, potentially significant terms may be missed using correlation analyses without statistical adjustments for other known confounders. Multicollinearity may also be a limiting factor in some of their modelling which included both second-order Zernike coefficients (defocus and astigmatism) and spherical equivalent refractive error (highly correlated variables) as predictors of axial elongation.

In addition, in order to compare the average changes in primary spherical aberration (Z_4^0) across previous studies[13,18] and the current study, data were extracted from Kim et al.[18] and Hiraoka et al.[13] (using WebPlotDigitizer, https://automeris.io/WebPlotDigitizer/ and rescaled to a 6-mm pupil diameter).[47] Over a 6-mm pupil diameter, the

mean change in ocular primary spherical aberration after 2 years of ortho-k treatment was +0.80 μm in the current study compared with +0.51 μm in Hiraoka et al.[13], and +0.34 μm in Kim et al.[18] These differences in the change in primary spherical aberration (Z_4^0) between the studies may be a result of lens design (given that compression factor appears to influence spherical aberration),[48] ethnicity, or some other factors, and likely explain the different reported associations between eye growth and changes in spherical aberration.

Pupil size is another potential factor affecting axial elongation in ortho-k treated eyes.[49,50] Chen et al.[49] investigated the association between axial elongation and pupil size in 25 children treated with ortho-k and reported an association between slower axial elongation and larger pupil size (compared to the average sample mean). Faria-Ribeiro et al.[50] analyzed the influence of pupil sizes from 3 to 6 mm in simulated eye models and suggested that the effectiveness of myopia control may be enhanced in eyes with larger pupils due to increased exposure to peripheral defocus. Therefore, not only the change in corneal optics (e.g., more positive spherical aberration), but the natural pupil size may also influence axial elongation and the extent of myopia control. Variations in the pupil size used for HOA analyses may also explain some inconsistencies observed between studies. For example, Hiraoka et al.[13] performed HOA analysis using a 4-mm pupil, which was smaller than the average photopic pupil size of young children reported in a previous study (5.4 mm)[51] and may therefore underestimate the true increase in HOA induced by changes in the mid-peripheral cornea towards the edge of the treatment zone. However, little is known about the effect of treatment zone size on axial elongation in children treated with ortho-k and further investigations with adjustment for other known covariates are warranted.

Other researchers have also attempted to control axial elongation by altering the ocular HOA profile. Allen et al.[52] attempted to arrest myopia progression by using contact lenses that altered the patient's primary spherical aberration to −0.1 μm over a 5-mm pupil, because this had previously been shown to improve accommodation, that is, reduce accommodation lags, in adults.[53] However, they were unable to show any significant myopia control with these lenses over a 2-year period. On the other hand, Sankaridurg et al.[54] recently showed a modest myopia control effect in subjects wearing extended depth-of-focus contact lenses (+1.75 D and +1.25 D; 25%–28% slower) modulated by HOA (details not provided) and center distance multifocal lens designs (23%–32% slower), compared with single-vision control lenses, in 508 children (mean age 10.4 ± 1.3 years) over a 2-year period. Cheng et al.[55] also demonstrated a moderate effect with soft contact lenses of higher positive spherical aberrations (about 0.175 μm for a 5-mm aperture) in 127 children (mean age 9.2 ± 1.1 years). Axial elongation in the treated eyes were 65% (0.11 mm) and 39% (0.14 mm) shorter than the control eyes after 6 and 12 months, respectively. However, the magnitude of spherical aberration induced by these soft contact lenses was much smaller, compared with the amount induced by ortho-k treatment (0.39 μm increase in Z_4^0 in this study [rescaled for a 5-mm pupil size]). Because the "minimum effective dose" of positive spherical aberration required to alter axial elongation in children remains unknown, further investigation of the relationship between spherical aberration and axial elongation for other optical interventions for myopia control is also warranted. A recent study[48] investigated the changes in ocular HOA with ortho-k lens wear after adjusting the compression factor (also known as Jessen factor) of a specific brand of ortho-k lens (Menicon Z Night or Menicon Z Night Toric lenses; NKL Contactlenzen B.V., Emmen, The Netherlands). The study showed that increasing the compression factor by 1.00 D significantly increased the primary spherical aberration (Z_4^0), RMS values of spherical aberrations, and total HOA by 40–50%, without significantly inducing more refractive changes or compromising vision in photopic conditions. It would be of interest to determine if the intentional modification of the amount of ocular HOA, particularly spherical aberration, can improve myopia control efficacy in ortho-k treatment.

One limitation of our study is that the numbers of children with different refractive errors (low and high myopia, high astigmatism) were not large enough to conduct separate analyses on the association between ocular HOA and axial elongation in different refractive error groups treated with ortho-k. As a result, all subjects were pooled together to provide a general understanding of the association between HOA and axial eye growth with ortho-k treatment. Because emmetropization is a complex, multifactorial process, other possible confounding factors such as pupil size,[49,50] parental myopia,[56] outdoor activities,[57] and living conditions[58] should also be evaluated in future studies (or controlled for with statistical modeling).

In conclusion, this study investigated the relationship between ocular HOA and axial elongation in young subjects wearing ortho-k lenses and found that higher levels of total HOA RMS, spherical aberration RMS, and positive primary spherical aberration were associated with slower axial elongation, after adjusting for confounders, such as age, baseline refraction, and baseline HOA. The increase in ocular HOA, notably spherical aberration, and its association with slower axial elongation, may be the mechanism of ortho-k in myopia control. Optical treatments that optimize the ocular HOA profile without significantly compromising visual function may yield a superior myopia control outcome.

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