• Clinical Research •

Photopic pupil size change in myopic orthokeratology and its influence on axial length elongation

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Abstract

● **AIM:** To explore the photopic pupil size behavior in myopic children undergoing overnight orthokeratology (ortho-k) over 1-year period and its effects on the axial elongation.

● **METHODS:** A total of 202 Chinese myopic children were enrolled in this prospective clinical trial. Ninety-five subjects in ortho-k group and eighty-eight subjects in spectacle group completed the 1-year study. Axial length (AL) was measured before enrollment and every 6mo after the start of ortho-k. The photopic pupil diameter (PPD) was determined using the Pentacam AXL and measured in an examination room with lighting of 300-310 Lx. Stepwise multiple linear regression analysis was used to identify variables contribution to axial elongation.

● **RESULTS:** Compared with spectacle group, the average 1-year axial elongation was significantly slower in the ortho-k group (0.25±0.27 *vs* 0.44±0.23 mm, *P*<0.0001). In ortho-k group, PPDs significantly decreased from 4.21±0.62 mm to 3.94±0.53 mm after 1mo of lens wear (*P*=0.001, Bonferroni correction) and the change lasts for 3-month visit. No significantly change during the other follow-up visits was found (*P*>0.05, Bonferroni correction). The 4.81 mm PPD may be a possible cutoff point in the ortho-k group. Subjects with PPD below or equal to 4.81 mm tended to have smaller axial elongation compared to subjects with PPD above 4.81 mm after 1-year period (*t*=-3.09, *P*=0.003). In ortho-k group, univariate analyses indicated that those with older age, greater degree of myopia, longer AL, smaller baseline PPD ($PPD_{baseline}$) experienced a smaller change in AL. In multivariate analyses, older age, greater AL and smaller $PPD_{baseline}$ were associated with smaller increases in AL. In spectacle group, PPD tended to be stable (*P*>0.05, Bonferroni correction) and did not affect axial growth.

● **CONCLUSION:** PPDs experience significantly decreases at 1-month and 3-month ortho-k treatment. Children with smaller PPD tend to experience slower axial elongation and may benefit more from ortho-k.

● **KEYWORDS:** orthokeratology; myopia; axial length; pupil diameter; accommodation

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INTRODUCTION

Myopia is a globally public health problem associated with increased ocular-related morbidity and enormous healthcare costs[1-3]. In recent decades, it's prevalence in adolescents has already been increasing to 10% to 25% in industrialized societies of the West and 60% to 80% in East Asia, respectively[4-6]. The myopic prevalence will even significantly increase to 50% of the world's population by 2050[5]. Overnight orthokeratology (ortho-k) has been considered an effective and safe myopia-retarding therapy to decrease the increasing prevalence of high myopia and the potentially blinding myopic complications, such as retinal detachment, macula choroidal neovascularization and glaucoma. Although the mechanism of ortho-k remains controversial, most previous studies, including randomized and controlled clinical trials, have demonstrated that ortho-k reduces the axial elongation by 40% to 60% in children when compared with single-vision spectacles or soft contact lenses[7-15].

In the long-term clinical experience, we found the myopia control effect of ortho-k displayed a large inter-individual variability and cannot be precisely predicted. Increased

knowledge of factors related to axial elongation and myopia progression in ortho-k is of great importance, especially for the pre-wear evaluation. If the accurate benefit gained from ortho-k wear could be predicted, we can select different appropriate strategies, such as 0.01% atropine[16], or optimize lens design according to the specific eye characteristics in children to improve the retardation effect of ortho-k and ultimately achieve personalized myopia intervention. Although we have been interested in the predictors of ortho-k treatment for almost 10y, the result is always exciting and controversial. Recently, one study has reported that changes in corneal aberrations could be the inhibitory factor of ortho-k on myopia progression[17]. However, in another research, neither short-term nor long-term changes in corneal aberrations were significantly correlated with the 2-year change in axial elongation[18]. Chen *et al*[19] found large pupil diameters facilitate larger axial retardation effect in myopia treated with ortho-k. However, Downie and Lowe[20] revealed in their study that pupil size appeared not to influence the rate of myopic progression in ortho-k treated eyes. In 2007, a longitudinal study first reported an association between more time outdoors and a reduced risk of myopia onset[21]. After that, a series of observation, from animal experiments to human clinical trials, suggest that outdoor light exposure might be a modifiable risk factor for myopia onset[22-24]. Based on such finding, several years ago, education department has renovated the illumination of classroom in some schools in Shanghai and encourage children to participate in outdoor activities in order to reduce the incidence of myopia. Hence, a photopic condition would more often occurs in daily life conditions in most children and adolescents during ortho-k treatment. Compared with the scotopic pupil diameter (SPD) assessed in Chen *et al*'s research[19], we deduce that photopic pupil diameter (PPD), which was not so stable and would be affected by illumination condition, would be more valuable in predicting myopia control effect in ortho-k treatment.

The aim of this study was to explore the photopic pupil size behavior in myopic children wearing ortho-k lenses over a 1-year period and its effect on the control of myopic eye growth.

SUBJECTS AND METHODS

Ethical Approval This longitudinal, prospective and nonrandomized study was conducted at Shanghai Eye Disease Prevention & Treatment Center and registered at Clinical-Trials.gov (NCT03516357). The study followed the tenets of the Declaration of Helsinki and was approved by the Ethical Committee of the Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine. All subjects, and their parents, provided signed written informed consent for treatment and were fully informed of the risks and benefits of the treatment.

Subjects A total of 202 patients (92 males and 110 females) were enrolled based on the inclusion criteria listed in Table 1.

Table 1 Inclusion criteria

1 Subjects aged 7-15 years old
2 Spherical equivalent refractive error (SER) between -1.00 and -6.00 D
3 Intraocular pressure (IOP) between 10 and 21 mm Hg
4 With-the- rule astigmatism less than or equal to 1.50 D
5 Best corrected visual acuity ≤0.00 logMAR units in both eyes (Snellen equivalent to 20/20)
6 No other ocular diseases (binocular vision problems, keratoconus, fundus diseases)
7 No history of medications that might affect the progression of myopia
8 No history of contact lens wear

All subjects accepted detailed medical history taking and a series of prescreening ocular examinations, including slit-lamp microscopy of the anterior and posterior segment, cycloplegic manifest refraction, corneal topography (Oculus, Wetzlar, Germany), and binocular vision assessment.

Subjects in the ortho-k group were fitted with 4-zone lenses (Euclid Systems Corporation, Herndon, USA) made of Boston EQUALENS II (oprifocona) with a nominal Dk of 127×10^{-11} (cm^2•mLO_2)/(s•mL•mm Hg), a diameter of 10.6-11.0 mm, an optical center thickness of 0.21-0.23 mm, a wetting angle of 36°. Lenses were fitted according to the instructions recommended by the manufacturer. Final lenses were determined after optimization regarding fluorescein pattern, topographical evaluation, refractive and visual outcomes. The subjects were provided with clear instructions regarding the wearing and maintenance of lenses. Follow-up appointments were promptly planned.

Subjects were instructed to wear ortho-k lenses every night with a minimum of 8h per night and were examined 1, 7, 30 and 90d after beginning ortho-k treatment. After the initial 90d, subjects were examined every 3mo. All examinations were fulfilled within 2h of removing the lens (between 8 and 10 *a.m.*) to minimize the potential influence of diurnal variation. At all follow-up visits, visual acuity, slit lamp examination, manifest refraction, corneal topography was performed. Subjects were also examined whenever an abnormal symptom occurred.

In the spectacle group, examinations were performed every 6mo until the end of the study period.

Measurements Refraction Cycloplegic manifest refraction was performed only at enrollment. One drop of 0.5% tropicamide was instilled in each eye five times at 5-minute intervals, and autorefraction was measured three times after 30min. At the rest follow up visit, only non-cycloplegic subjective refraction were conducted.

Axial length The axial length (AL) was evaluated using the IOL Master (Carl Zeiss Jena GmbH, Jena, Germany). Three consecutive measurements were taken and the average of the 3 was used as a representative value for analysis.

Corneal curvature and photopic pupil diameter The corneal curvature (flat and steep meridians), PPD were determined with Pentacam AXL (Oculus Optikgeräte, Wetzlar, Germany). In order to better match the classroom illumination for students today after the light environment reform in Shanghai, these parameters were measured in a windowless examination room with lighting of approximate 300-310 lx. Moreover, to avoid the potential impact of environment and circadian variation on PPD result, measurements were performed between 8 and 10 a.m. after 15min adaptation in the examination room. These parameters were measured at the time of enrollment and at every follow-up visit. The first 5 data with differences less than 0.50 mm was included and the averaged values were used for sequent analyses.

Data Analysis Use Shapiro-Wilk test to evaluate the normality of the data. For variables that fit a normal distribution, data were presented as the mean and standard deviation (SD) in ortho-k group or spectacle group. Differences on baseline characteristics between two groups were analyzed using the χ^2 or *t* test respectively. AL and PPD changes from baseline were analyzed using repeated measures analysis of variance (ANOVA). If significant differences were found, paired *t* tests with Bonferroni correction were performed to compare the differences. Correlation among variables AL change from baseline, baseline AL, $PPD_{baseline}$, non-contact intraocular pressure (IOP), age, initial spherical equivalent refractive error (SER), initial corneal curvature were explored using scatter plots and Pearson correlation coefficients. Multivariate linear regression was performed to investigate the effect of variables (age; SER; IOP; baseline AL; $PPD_{baseline}$) on AL change. LOWESS was used to curve fit and detect the possible threshold for baseline pupil size in ortho-k group. Significance was set at a *P*-value of <0.05. Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA) and GraphPad Prism (GraphPad Software, San Diego, California USA) were utilized for data analysis and visualization. Only data from the right eyes of the subjects were analyzed.

RESULTS

A total of 202 subjects were eligible for the baseline enrollment, they were allocated to the ortho-k group (100 eyes; 43 males, 57 females) and spectacle group (102 eyes; 49 males, 53 females). During the 1-year follow-up period, 5 and 14 subjects from the ortho-k and spectacle groups were discontinued from the study for various reasons: persistent corneal staining (*n*=2), poor centration (*n*=2), allergic conjunctivitis (*n*=1), lost to follow-up (*n*=4), poor compliance (*n*=2), switch to other myopia control modality (*n*=5), change hospital (*n*=3). Consequently, 95 ortho-k subjects and 88 control subjects completed the 1-year study, the dropout rate was 9.41%. The baseline demographics of the two groups are shown in Table 2.

Table 2 Baseline demographic data of the 183 subjects who completed the study in the ortho-k and the spectacle group

Items	Ortho-k group (*n*=95)	Spectacle group (*n*=88)	*P*[a]
Age (y)	9.89±1.99	9.85±2.19	0.90
M/F ratio	45:40	42:46	0.96
SER (D)	-3.50±1.46	-3.49±1.24	0.99
IOP (mm Hg)	16.01±2.38	15.68±2.25	0.33
PPD (mm)	4.21±0.62	4.11±0.74	0.31
Flatter meridian (D)	42.58±1.23	42.57±1.39	0.95
Steeper meridian (D)	43.76±1.43	43.60±1.49	0.45
AL (mm)	24.92±0.95	24.75±0.87	0.21

SER: Spherical equivalent refractive error; IOP: Intraocular pressure; PPD: Photopic pupil diameter; AL: Axial length. [a]Chi-square test for M/F ratio, unpaired *t*-test for other variables.

Table 3 PPD and AL change over 1-year of ortho-k treatment in both groups

Items	PPD		AL	
	Ortho-k group	Spectacle group	Ortho-k group	Spectacle group
Baseline	4.21±0.62	4.11±0.74	24.92±0.95	24.75±0.87
1wk	4.07±0.54	-	-	-
1mo	3.94±0.53[b]	-	-	-
3mo	4.02±0.54[b]	-	-	-
6mo	4.06±0.55	3.99±0.65	25.04±0.89[b]	24.96±0.86[b]
12mo	4.06±0.63	4.07±0.63	25.17±0.87[b]	25.19±0.85[b]
F	6.60	1.88	68.0	267.6
P[a]	<0.0001	0.16	<0.0001	<0.0001

PPD: Photopic pupil diameter; AL: Axial length. [a]Repeated-measures ANOVA. [b]*P*<0.01 for changes against baseline.

There were no significant differences in baseline characteristics between the two groups.

After ortho-k treatment, the PPD changed significantly during 1-year period (*P*<0.0001, ANOVA). The biggest decrease (4.21±0.62 mm *vs* 3.94±0.53 mm, *P*=0.001, Bonferroni correction) occurred in 1mo of lens wear and the change lasts for 3-month visit. No significantly changes were observed during the other follow-up visits (*P*>0.05, Bonferroni correction). Whereas in the spectacle group, the PPD showed no significant difference during 1-year period, indicating that PPD tend to be stable in spectacle group (*P*=0.16, ANOVA; Table 3).

During the 1-year period, there was a significant elongation in AL in both the ortho-k and spectacle groups (Table 3). The ortho-k group exhibited less axial elongation than did the spectacle group (6-month: 0.12±0.20 *vs* 0.20±0.15, *F*=8.32, *P*=0.004; 12-month: 0.25±0.27 *vs* 0.44±0.23, *F*=23.64, *P*<0.0001; Figure 1). In total, a 43.18% reduction in axial elongation was estimated at the end of study period.

To be more specific, LOWESS was used to curve fit and detect the possible threshold for baseline pupil size in ortho-k group. As shown in the Figure 2, 4.81 mm may be a possible cutoff point in the ortho-k group. Hence, subjects was further divided into two sub-groups based on the cutoff point (4.81 mm): PPD below or equal to 4.81 mm group and PPD above 4.81mm group. In the ortho-k group, subjects with PPD below or equal to 4.81 mm tended to have smaller axial elongation compared to subjects with PPD above 4.81 mm after 1-year period (t=-3.09, P=0.003; Figure 3, Table 4). AL change in subjects with PPD below or equal to 4.81 mm was 52.27% that of the subjects with PPD above 4.81 mm at 1-year visits. Contrarily, in the spectacle group, PPD was not detected such cutoff value. Correlation among variables AL change from baseline, baseline AL, $PPD_{baseline}$, non-contact IOP, age, initial SER, and initial corneal curvature were explored using scatter plots and Pearson correlation coefficients. The 1-year axial elongation was significantly related to baseline AL, $PPD_{baseline}$, initial age, SER and IOP (All P<0.05). To be more specific, further linear regression analyses of the related variables showed that baseline age, SER, baseline AL and $PPD_{baseline}$ demonstrated a statistically significant relationship with 1-year AL growth in ortho-k group (Figure 4). Other factors, such as IOP, flatter meridian and steeper meridian, were not significantly correlated with the axial elongation (P>0.05). In the spectacle group, age and baseline AL were significantly correlated with the axial elongation (P<0.05).

Since no statistical correlation was observed, flatter meridian, steeper meridian and gender were not included in multivariate analysis. Baseline age, SER, AL, $PPD_{baseline}$, which were potential predictive factors in univariate regression analysis, were included in the multivariate linear regression analysis. The result showed that older age, longer baseline AL, and smaller PPD were significantly associated with less AL elongation in ortho-k group. Decrease in the PPD by 1 unit was related to 0.11 mm reduction in the 1-year AL elongation (P=0.004), holding other factors constant. In the spectacle group, initial age, SER, and baseline AL was significant negatively correlated with axial elongation at 1y (Table 5).

DISCUSSION

Myopia correction with ortho-k contact lens, which uses a specially designed rigid contact lens to submit a stress on the cornea to modify the corneal contour temporarily and eliminate refractive errors, has proven to be a safe and effective procedure. After overnight wearing, it could provide clear vision in wearers without daytime optical correction. Nowadays, ortho-k lens is widely used in children because of its potential effect in slowing myopia progression. In this study, the 1-year axial elongation was 0.25 mm in the ortho-k group and 0.44 mm in the spectacle group. The retardation

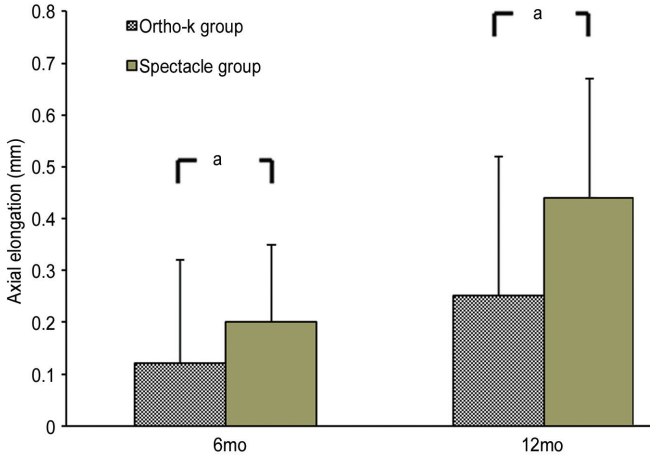

Figure 1 Axial elongation for the subjects in the ortho-k and spectacle group at each follow-up visit ^aP<0.01.

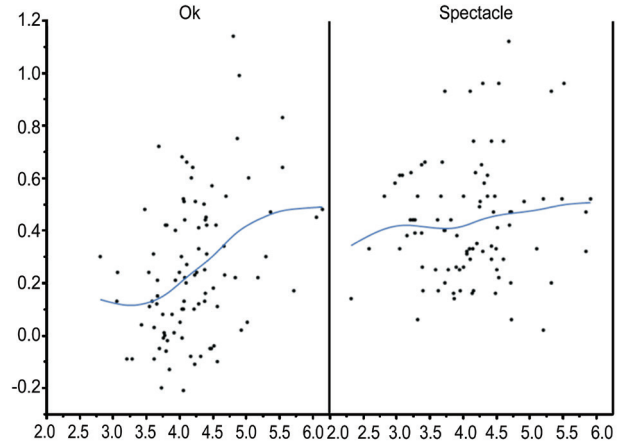

Figure 2 Use LOWESS to fit a smooth curve between pupil diameter and 1-year axial elongation in the ortho-k and the spectacle group (It was found that 4.81 was the possible cutoff point for the ortho-k group, and no cutoff point was found in the spectacle group).

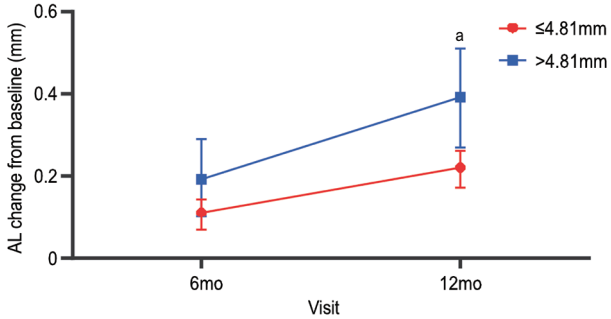

Figure 3 One-year axial elongation for the subjects in the ortho-k group at each follow-up visit ^aP<0.01.

Table 4 Axial elongation in 2 subgroup in the ortho-k group at each visit

Group	6mo	12mo
PPD≤4.81 mm (n=81)	0.10±0.17	0.21±0.25
PPD>4.81 mm (n=14)	0.23±0.32	0.44±0.29
t	-1.48	-3.09
P	0.16	0.003

PPD: Photopic pupil diameter.

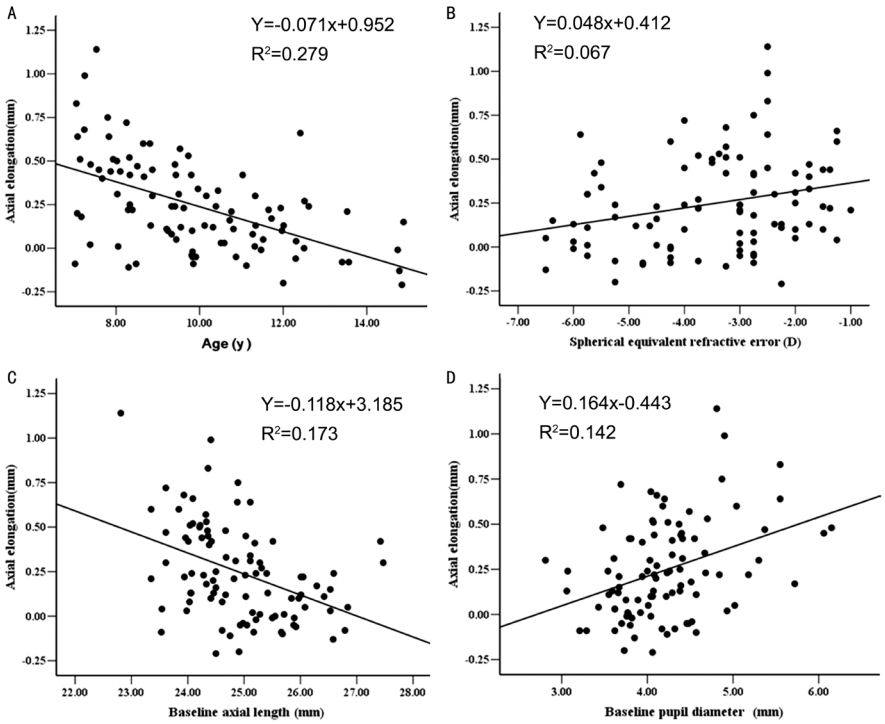

Figure 4 Simple linear regressions between 1-year axial elongation and baseline age (A), SER (B), AL (C), pupil diameter (D) of ortho-k subjects SER: Spherical equivalent refractive error; AL: Axial length.

Table 5 Multivariable regression analysis of different independent variables on 1-year axial elongation

Items	Ortho-k group				Spectacle group			
	β	95%CI	t	P	β	95%CI	t	P
Age	-1.18[a]	-2.09 to -0.26	-2.55	0.01	-0.74[a]	-1.48 to -0.002	2.18	0.0495
SER	-0.16	-0.39 to 0.07	-1.35	0.18	-0.33[b]	-0.51 to -0.14	-1.99	0.0008
IOP	-0.01	-0.02 to 0.01	-0.68	0.50	-0.02	-0.04 to 0	-3.48	0.06
AL	-0.56[b]	-0.94 to -0.17	-2.89	0.005	-0.30[a]	-0.59 to -0.01	-1.93	0.04
$PPD_{baseline}$	0.11[b]	0.04 to 0.19	2.98	0.004	0.03	-0.03 to 0.08	-2.09	0.34
Age*AL	0.05[a]	0.01 to 0.09	2.42	0.02	0.03[a]	0.001 to 0.06	0.97	0.04
Age*SER	0.02	-0.01 to 0.04	1.41	0.16	0.03[b]	0.01 to 0.05	2.06	0.0012

SER: Spherical equivalent refractive error; AL: Axial length; IOP: Intraocular pressure; $PPD_{baseline}$: Baseline photopic pupil diameter. [a]P<0.05; [b]P<0.01.

effect in AL growth of ortho-k was 43.18%, indicating that ortho-k treatment was a promising optical intervention to prevent the development of myopia in Chinese children.

The size of the pupil not only determines the amount of light entering the eye, but also determines the exposure of the surrounding retina, which is considered to be an important mechanism for regulating the speed of myopia development[25]. At the same time, the pupil diameter is also related to some important visual feedback mechanisms, such as aberrations[26-27] and accommodative functions[28]. Recently, a study done by Chen *et al*[19] found that larger SPD possess more advantageous myopia control effect in ortho-k treated children. This result prompted pupil diameter to receive more emphasis and become a vital predictor of the myopia control benefit before wearing ortho-k contact lens. However, until now, articles explore the photopic pupil size behavior in children wearing ortho-k lenses are still rare. To our knowledge, this was the first study to investigate the long-term PPD change during ortho-k treatment and showed significant pupil constriction after 1-month of overnight ortho-k contact lens wear. This pupillary regulation has two probable explanation. First, myopia showed less accommodation demands with or without corrective eyeglasses during near work, compared with emmetropia. This accommodation requirement can be alleviated when refractive correction strategy switch from spectacles to contact lenses[29]. Although we did not directly measure the accommodative response, Yang *et al*[30] have found an elevated accommodation function

after ortho-k treatment. As Yuda *et al*[31] points out, over a period of accommodation training, the pupil diameter decreased in far accommodation. In this regard, we speculated that the repetitive and effective accommodation training induced by ortho-k, subsequently enhanced accommodative function, contribute to the pupil constriction during ortho-k treatment. Second, an earlier study has confirmed that a blurred image may induce pupillary constriction[31]. The dramatic and irregular changes in corneal morphology, especially in the early stage of ortho-k, lead to an increase in corneal and ocular higher order aberrations (HOAs)[17] and a decrease in contrast sensitivity function[32], modulation transfer function cutoff values (MTF_{cutoff}) and Strehl ratio (SR)[33]. The ortho-k-induced decline in optical quality, which result in a blurred image on retina, elicits miosis to compensate for the deterioration of optical quality. In the present study, the pupil constriction effect was gradually attenuated and pupil diameters eventually did not change after 1-year ortho-k therapy. Hence, we speculate that this pupillary regulation is probably an ocular adaptation response toward the improved accommodation function and decreased vision quality after ortho-k. However, the real accommodative function and visual quality was not monitored in this study, further short-term and long-term research is required to investigate ortho-k-induced changes to PPD, accommodative function and visual quality and their interaction comprehensively.

Whether pupil diameter was the factor that suppress myopia progression in children treated with ortho-k is still controversial. A study done by Chen *et al*[19] demonstrated the relationship between the basic SPD and regulation effect, found that larger SPD turned out to have less myopia progression in ortho-k treated eye. However, in two latter studies, no association was found between pupil size and myopia control effect in eyes undergoing ortho-k treatment[20,34]. In the current study, $PPD_{baseline}$ showed significant correlations with axial elongation. Unexpectedly, we got exactly the opposite result that smaller $PPD_{baseline}$ experienced smaller axial elongation in ortho-k lens wearers. At the end of the 1-year period, AL change in the ortho-k subjects with PPD below or equal to 4.81 mm was approximately half that of the ortho-k subjects with PPD above 4.81 mm. The different result can be attributed to that we measured the PPD, while Chen *et al*[19] assessed the SPD in their study. Due to the SPD cannot reflect the real state of daily life conditions, Chen *et al*[19] deduced the PPD in their study from the scotopic one, according to the research of Alfonso *et al*[35] that the average difference between photopic and mesopic pupil size was approximately 1.5 mm and finally draw the conclusion that children with relatively larger pupils would benefit more myopia control effect from ortho-k treatment[34]. However, in the article of Alfonso *et al*[35], they also revealed that there is no potential mutual predictive ability between PPD and SPD because the photopic value only explains 48.1% of the variability in the mesopic value, Hence, any prediction of mesopic pupil size from photopic values would be inaccurate. They recommended to measure photopic and scotopic pupil size respectively in order to obtain reliable value. Considering that photopic pupil size is unstable, we got 5 repeatable PPD data for each eye under uniform illumination conditions and used the averaged values for analyses in order to obtain an unbiased value of pupil diameter. Therefore, the result of the current study that AL is prone to increase slowly in subjects with a photopic small pupil diameter by ortho-k was convincing.

The exact mechanism responsible for the development of myopia has not been determined. A rapidly growing research revealed that the onset and progression of myopia should be a complex and multifactorial process. One of the current hypotheses is peripheral defocus theory[36-38], which have been shown in animal studies that peripheral myopic defocus could modulate not only peripheral ocular growth, but also axial growth[39]. However, recent investigations in humans have failed to find the correlation between peripheral refraction and myopia progression[40]. The peripheral myopic shift induced by ortho-k has the following characteristics: first, the range and power of the peripheral defocus across the retina caused by ortho-k remained stable, as the corneal morphology stabilizes after 1mo of ortho-k lens wear. Second, the typical treatment zone (central flattened area) of ortho-k was approximately 5.5 mm diameter[41-42], the reverse curve area (mid-peripheral steepened area) will appear further away. Hence, the ortho-k lens-induced shift was more evident in the far periphery than in the near periphery. Faria-Ribeiro *et al*[27] found, as the pupil diameter dilates from 3 to 6 mm, peripheral refraction in eyes treated with ortho-k suffers a significant myopic shift, and further speculate it contribute to the positive influence in regulation effects. However, during most part of the waking cycle, whether from daylight or artificial sources, eyes are normally exposed to photopic levels of ambient lighting, which make pupil constrict to a more modest diameter[43]. In the current study, most dynamics pupil diameters were less than 5 mm with photopic illumination conditions of 300 Lx, Thus, it seems that the power of myopic shift in peripheral refraction caused by pupil dilation is limited.

On the other hand, the aberration also increases as the pupil diameter increases. It has been postulated that high levels of axial ocular aberration, which result in poor quality of the retinal image, might be precursors to myopia development[43]. Numerous studies have investigated the relationships between HOAs and AL[44-45], refractive error[45], and axial eye growth[26], the result remains equivocal. Several researchers support

the idea that HOAs have no impact on the emmetropization process[26,43]. On the contrary, to date, Lau *et al*[46] reported that less myopia development was observed in subjects with more positive spherical aberrations. Recently, Hiraoka *et al*[17] showed that higher levels of corneal HOAs were associated with less axial elongation during ortho-k treatment. As we all known, the values of aberration depend on pupil diameter and it was usually small for 3 mm pupil diameter and increase rapidly as the pupil dilates beyond about 4 mm diameter increases[43]. However, in these studies, HOAs were all measured over a fixed pupil size of 6 mm, which may not be a realistic pupil size for children across a range of visual tasks and environments. Exposure to photopic illumination conditions, such as bright outdoor lighting, pupil diameter is likely to reduce to under 3-4 mm and may result in HOAs of negligible magnitude. As in the current study, most PPD was 3.0 to 5.0 mm with lighting of 300 Lx. Hence, it has been suggested to measure the value with real pupil diameter. Smaller pupil size could increase the depth of focus[47], and decreases a spherical aberration; accommodation lag during near work[48], as well as the corneal multifocality, and asymmetric corneal shape induced by treatment zone decentration, thus erase the blur retinal signals, which would stimulate myopia progression during ortho-k. It seems also reasonable to conclude that pupil-related peripheral myopic shift, which has positive effect on myopia control of ortho-k, may be strengthened by improvement of visual quality induced by pupil miosis. In the present study, subjects with smaller PPDs gain a more pronounced myopia control effect. Further studies were needed to clarify the change of aberrations under normal viewing conditions and its relationship with myopia progression.

At present, a number of characteristics, including age, initial degree of myopia, and corneal morphology, has been proved to be important factors affecting the myopia control effect of ortho-k. However, even the above-mentioned baseline demographics and ocular biometrics of patients are the same, obvious individual differences can still be observed clinically. More recently, studies focus on changes in corneal power profile, including areal summed corneal power shift (ASCPS; central 4 mm area)[49], apex-peripheral refractive power difference[50], summed corneal power change (SCPC, the sum of relative corneal power change within the area of 7.2 mm diameter)[42], were also associated with axial elongation after ortho-k wear. Thus, the effect of inhibiting axial growth of the ortho-k can not only be predicted, but also modified by optimizing the lens design. In the current study, we found that PPD is an independent factor for the myopia control effect of ortho-k. Smaller PPD associated with slower myopia progression. Based on our research, PPD can not only be used to guide patient selection, but also predict myopia control effects before wearing ortho-k lens. It is also a factor that can be modified manually, some possible interventions that help to obtain long-time smaller PPD, such as drugs (mydriatics), more outdoor activities, and brighter indoor lighting, may be attempted to enhance the axial growth suppression effect in ortho-k treated eyes. In addition, the lens design can be individually adjusted according to the patient's pupil diameter. A novel ortho-k design concept, reducing optical zone size and introducing reverse curve into pupil size region, leading to more retinal area being exposed to the peripheral myopic defocus might help to improve the ortho-k lens myopia control effect.

There are some limitations in our study. First, although the most accurate and reliable instrument for measuring pupil performance at present is the dynamic pupilometer, in this study, we used Pentacam to measure the pupil diameter, mainly because Pentacam is clinically applied to almost every wearer's pre-wear inspection. All patients using the same measurement method will be more comparable. This is also conducive to rapid predicting the myopia control effect of wearing ortho-k. Considering that pupil size is affected by factors such as light, accommodation and cognitive activity, which may cause a larger fluctuation in pupil size measurement. In the current study, adequate indoor light environment adaptation time, sufficient measurement times can minimize measurement errors. Further investigation, using a dynamic pupilometer to measure PPD change during ortho-k is warranted. Second, the follow-up period of the study was relatively short (1-year). Given that ortho-k is always widely conducted on children for a long period for purpose of slowing the progression of myopia, further studies with longer follow-up designs are needed to assess the pupil diameter behavior in myopic children population. Third, we did not measure SPD, peripheral refraction and ocular aberration at the same time. Further studies, including more potential factors, are needed to clarify the effect of pupil diameter on the development of myopia during ortho-k.

In conclusion, PPDs experience significantly decrease at 1-month and 3-month ortho-k treatment. At the end of 1-year period, PPDs change with ortho-k are not different with baseline. Children with smaller PPDs tend to experience slower axial elongation and may benefit more from ortho-k treatment, which may be attribute to the appropriate foveal visual signal induced by smaller PPDs.

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