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Clinical Trials

Effects of Spectacle Lenses With Aspherical Lenslets on Peripheral Eye Length and Peripheral Refraction in Myopic Children: A 2-Year Randomized Clinical Trial

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Purpose: To investigate changes in peripheral eye length (PEL) and peripheral refraction (PR) in myopic children after wearing spectacle lenses with highly or slightly aspherical lenslets (HAL or SAL) for 2 years.

Methods: We recruited 170 children aged 8 to 13 years with myopia between −0.75 diopters (D) and −4.75 D. Participants were randomized to wear HAL, SAL, or single vision spectacle lenses (SVL). PEL and PR were measured at 0° central and 15° and 30° in the nasal and temporal retina every 6 months for 2 years. The relative PR (RPR) was calculated by subtracting central from peripheral values.

Results: PELs significantly increased with time (all $P < 0.001$), with the greatest elongation in the SVL group and the least in the HAL group. In the SVL and SAL groups, axial length elongated faster than the periphery. Whereas in the HAL group, N30 elongated faster than other PELs, axial length elongated less than the periphery. With time, the PR became more negative (all $P < 0.001$), with the most negative changes in the SVL group and the least negative changes in the HAL group. RPR became more hyperopic in the SVL and SAL groups, but less hyperopic in the HAL group (all $P < 0.001$).

Conclusions: Over the 2-year myopia progression, steeper retina and greater peripheral hyperopic defocus were found in the SVL group. In the SAL group, changes were attenuated. In the HAL group, the retina flattened and peripheral defocus became less hyperopic.

Translational Relevance: HAL and SAL lenses had little impact on PEL elongation.

Introduction

Eye elongation is a hallmark of myopia. Previous magnetic resonance imaging studies found that axial elongation of the eye was greater than width and height elongation when myopia developed and progressed.[1–3] In other words, the eye becomes less oblate or more prolate when myopia develops or progresses because of excessive axial elongation; the prolateness correlates with the degree of myopia.[3,4] A prolate retinal shape can result in relative hyperopic defocus at the periphery. Previous clinical studies have shown varying magnitudes of peripheral hyperopic retinal defocus in human myopic eyes.[5–8] Mutti et al.[9] found that myopic children had more hyperopic relative peripheral refraction (RPR) 2 years before myopia onset than those who remained emmetropic. In addition,

animal studies have shown that introduced peripheral hyperopic defocus can induce myopia development and progression.[10–14] Although these associations have not been fully elucidated, lens designs to decrease peripheral hyperopic retinal defocus or invert hyperopic defocus into myopic defocus have been used as optical interventions for myopia control, based on the hypothesis that a peripheral hyperopic retinal defocus may be the cause for further axial elongation in the myopic eye.

Orthokeratology lenses, multifocal contact lenses, and spectacle lenses like Defocus Incorporated Multiple Segments (DIMS) and highly aspherical lenslets (HAL) were all designed to bring peripheral myopic defocus at the retina.[15–18] Several clinical studies have demonstrated the myopia control efficacy of these lenses; they could significantly slow down the axial length (AL) elongation.[16,17,19–21] However, does the peripheral defocus signal also affect the elongation of the peripheral eye length (PEL)? If so, does it have the same effect of slowing down the elongation of central and PEL, or is it more effective or less effective in the periphery, and therefore changing the expansion pattern of the myopic eyeball?

Our previous study reported that two spectacle lenses with aspherical lenslets of different asphericities showed effective myopia control efficacy for 2 years.[18,21] This study aimed to show the long-term changes in PEL and PR after wearing spectacle lenses with aspherical lenslets for 2 years compared with single vision spectacle lenses (SVLs) to explore the expansion pattern of myopic eyes with simultaneous clear central vision correction and peripheral myopic defocus signal.

Methods

Study Design

The study, designed as a prospective, randomized, controlled, and double-blind trial, was approved by the Ethics Committee of the Eye Hospital of Wenzhou Medical University (Y2018-054). All work was conducted by the tenets of the Declaration of Helsinki. Parents or guardians provided written parental permission and participants provided written assent after explanations of the objectives and possible consequences of the study. The inclusion criteria were age 8 to 13 years, spherical equivalent refraction between –0.75 diopters (D) and –4.75 D, astigmatism of not more than 1.50 D, anisometropia of not more than 1.00 D, no strabismus or other ocular disease, and no myopia control history. The participants were followed up every 6 months for 2 years, and details of the study have been described previously.[18,21] The participants were randomly assigned to wear spectacle lenses with HAL, spectacle lenses with slightly aspherical lenslets (SAL), or SVL.

The concept of lenses with aspherical lenslets was described in previous studies.[18,21] The lens contains a 9-mm center optical zone without lenslets for distance refractive error correction. The periphery has 11 concentric ring configurations with contiguous aspherical lenslets to create a volume of nonfocused light in front of the retina. The lenslet-free regions between concentric rings provide distance correction. Every participant was provided with an updated prescription and a pair of new spectacles at each 6-month visit.

Measurements

Cycloplegia was achieved using two drops of 1% cyclopentolate at a 5-minute interval, and measurements were performed at least 30 minutes after administration of the second drop. Measurements of PEL and PR were obtained from the right eye while the left eye was occluded.

PEL were measured using a Lenstar optical biometer (LS 900, Haag-Streit, Koeniz, Switzerland) with an optical apparatus. This novel approach was first described by Mallen et al.[22] The system was composed of a circular goniometer mounted on the headrest bracket to control the peripheral gaze position accurately, a beam splitter placed at 45° in front of the right eye to change the path of light from the target system and to pass the infrared laser beam from the Lenstar. The rotating center of the optical apparatus coincides with the rotation center of the eyeball, that is, 15 mm behind the cornea.[23] In this study, the AL was measured at central and PELs were measured at 15° and 30° horizontal in the nasal (N15, N30) and temporal (T15, T30) retina. Three measurements were recorded and averaged at each location with differences no more than 0.02 mm.

PR was obtained using an open-field Grand Seiko binocular autorefractor (WAM-5500, Rexxam CO. LTD, Kagawa, Japan). The targets were placed on an arc frame 33 cm in front of the right eye; the center of the arc was located at the rotation center of the eyeball, and there were holes every 5° from the center to the nasal and temporal sides. When measuring the corresponding eccentric PR, the corresponding hole on the arc was illuminated with a pen lamp, and the participant was instructed to keep looking at the bright hole. Refractive errors were measured at 0° central, and 15° and 30° in the nasal and temporal retina. Ten readings were recorded and averaged at each location with no more than 1.00 D difference for both sphere and cylin-

der, and the spherical equivalent were calculated as PR. RPR was determined by subtracting the central refraction values from the PR values.

Statistical Analysis

Two-factor repeated-measurements analyses of covariance (RM-ANCOVA) were conducted to compare differences in PEL, PR, and RPR over time and between groups, and baseline AL and sex were included as covariates. The RM-ANCOVA was also done to analyze PEL, PR, and RPR over time in each group. The relationships between AL elongation and PEL, PR, RPR, baseline age, AL, central refraction, and sex were tested using Pearson correlation analysis. Multiple linear regression was used to evaluate factors associated significantly with axial elongation. The data are presented as the mean ± standard deviation. A P value of less than 0.05 was considered statistically significant for two-factor RM-ANCOVA and linear regression. The adjusted significance level was set to 0.01 for PEL, PR, and RPR when analyzed RM-ANCOVA in each group, because they were measured at five retinal eccentricities.

Results

A total of 170 participants were included in the randomization. Of these participants, three were excluded before the lenses were dispensed, nine were lost to follow-up, one missed the 18-month visit, and one did not complete the PEL measurement at baseline; consequently, 156 participants were included in the analysis (Fig. 1). Table 1 shows the baseline

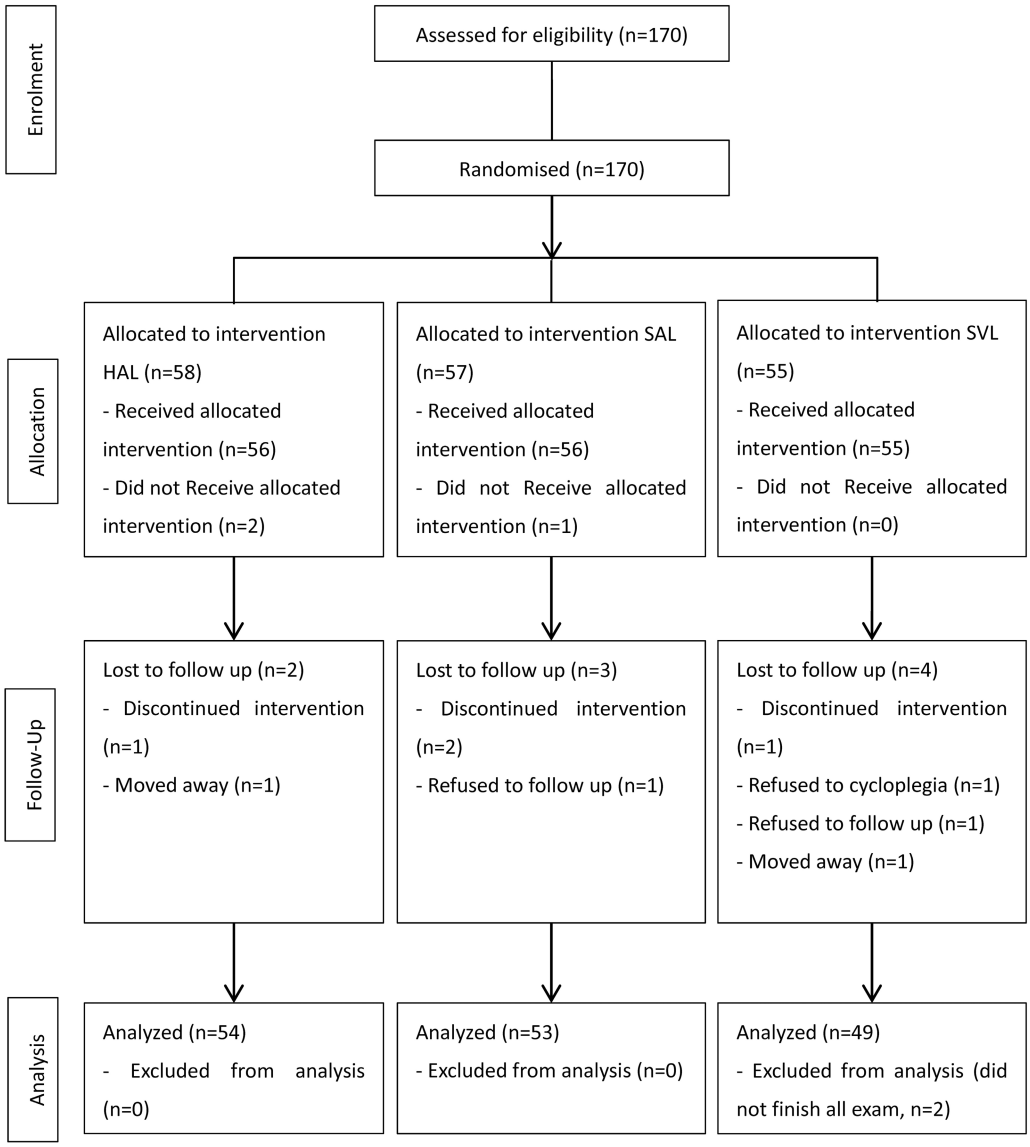

Figure 1. CONSORT flow diagram for the study.

Table 1. Baseline Characteristics of Participants in the Three Groups

Characteristics	HAL	SAL	SVL	ANCOVA or χ^2 Test, *P* Value
No.	54	53	49	
Age	10.65 ± 1.15	10.21 ± 1.21	10.39 ± 1.26	0.17
Sex (M/F)	26/28	17/36	29/20	0.02
Refractive error (SE, D)	−2.70 ± 1.02	−2.28 ± 0.95	−2.44 ± 0.87	0.08
Axial length (mm)	24.76 ± 0.68	24.44 ± 0.75	24.78 ± 0.66	0.02

Data are presented as the mean ± SD.
F, female; M, male; SE, spherical equivalent.

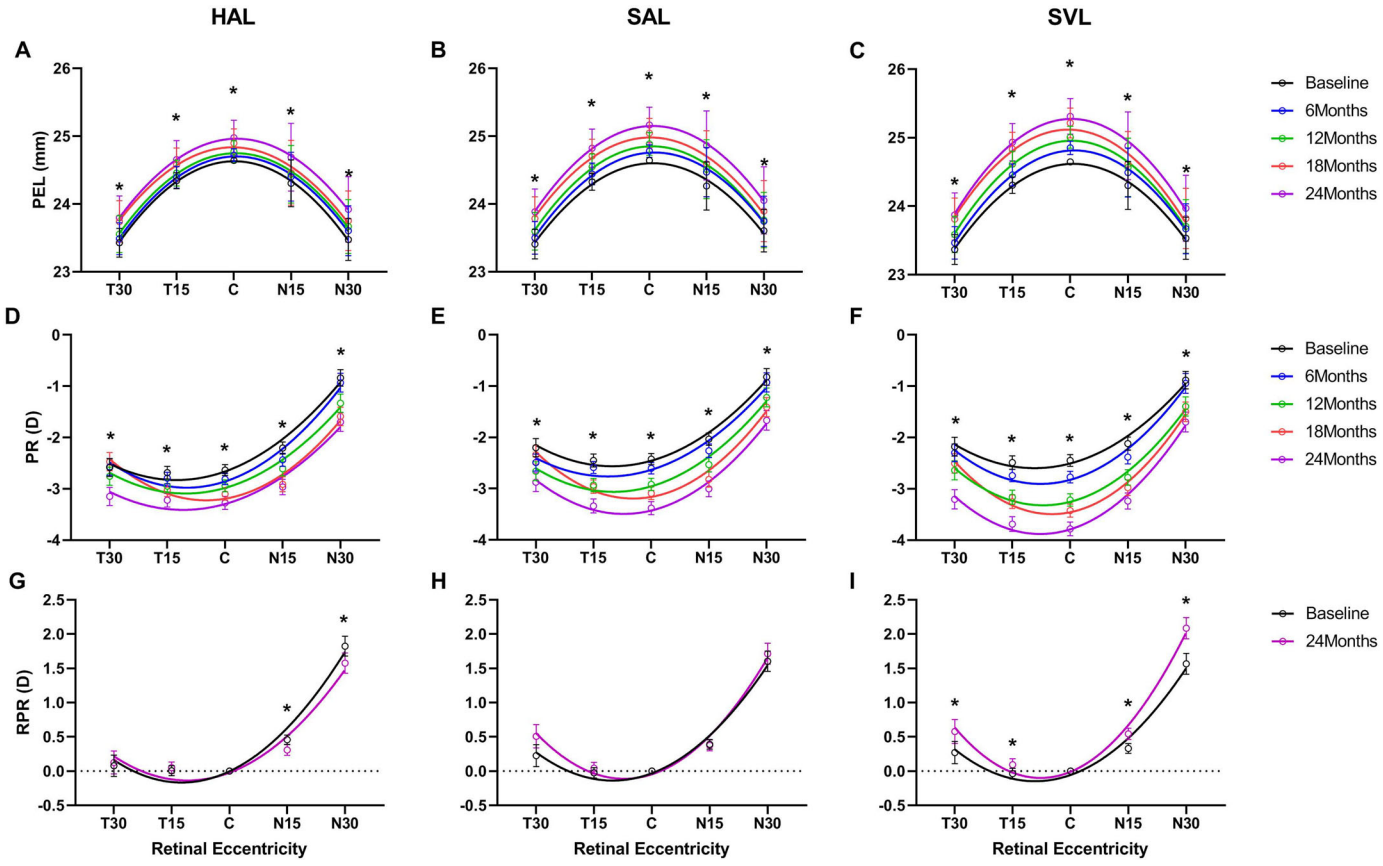

Figure 2. PEL (**A**–**C**), PR (**D**–**F**), and RPR (**G**–**I**) over 2 years. Error bars represent 1 standard error of the mean. *Statistically significant difference over time in the repeated-measure analysis of covariance (**A**–**F**) or *t*-test (**G**–**I**) within the group ($P < 0.01$). C, central; N, nasal retinal; T, temporal retinal.

characteristics of the participants in the three groups; sex ($\chi^2 = 7.66$; $P = 0.02$) and AL ($F_{2,153} = 3.86$; $P = 0.02$) were significantly different between the three groups. Comparisons between groups were adjusted for baseline AL and sex. The 18-month follow-up was delayed by a mean of 3 weeks, from February to March and April 2020, owing to the coronavirus disease 2019 epidemic in China; there were no differences between the three groups ($F_{2,153} = 0.03$; $P = 0.97$). The statistical results of the unadjusted data were consistent with the data adjusted for sex and AL. The statistical results in the text and Figure 2 were from the adjusted data. The unadjusted and adjusted data of changes in PEL and PR are shown in Table 2.

The RM-ANCOVAs adjusted for sex and baseline AL showed significant interactions between time and group for AL, PEL-T15, and PEL-T30 (all $P \leq 0.002$). The main effect of time and group and the interaction between time and group did not show any significance in the PEL-N15 and PEL-N30 (all $P \geq 0.18$). Signif-

Table 2. Changes in the PEL (mm) and PR (D) at Follow-ups in the Three Groups

	Unadjusted Data				Adjusted for Sex and Baseline AL			
	6 Months	12 Months	18 Months	24 Months	6 Months	12 Months	18 Months	24 Months
PEL-T30								
HAL	0.06 ± 0.09	0.13 ± 0.19	0.31 ± 0.37	0.37 ± 0.47	0.06 ± 0.12	0.13 ± 0.16	0.31 ± 0.20	0.37 ± 0.25
SAL	0.10 ± 0.09	0.22 ± 0.14	0.45 ± 0.19	0.51 ± 0.22	0.09 ± 0.12	0.19 ± 0.17	0.38 ± 0.20	0.48 ± 0.25
SVL	0.12 ± 0.14	0.16 ± 0.18	0.18 ± 0.22	0.25 ± 0.24	0.10 ± 0.12	0.22 ± 0.16	0.45 ± 0.20	0.51 ± 0.24
PEL-T15								
HAL	0.05 ± 0.11	0.11 ± 0.22	0.24 ± 0.37	0.31 ± 0.48	0.05 ± 0.10	0.11 ± 0.15	0.24 ± 0.21	0.31 ± 0.25
SAL	0.15 ± 0.11	0.31 ± 0.14	0.53 ± 0.20	0.64 ± 0.23	0.12 ± 0.11	0.23 ± 0.15	0.38 ± 0.21	0.50 ± 0.25
SVL	0.09 ± 0.11	0.15 ± 0.15	0.19 ± 0.23	0.23 ± 0.27	0.15 ± 0.11	0.31 ± 0.15	0.53 ± 0.21	0.63 ± 0.25
AL								
HAL	0.08 ± 0.13	0.13 ± 0.24	0.25 ± 0.39	0.34 ± 0.51	0.08 ± 0.10	0.13 ± 0.16	0.25 ± 0.21	0.33 ± 0.26
SAL	0.21 ± 0.11	0.36 ± 0.17	0.57 ± 0.21	0.67 ± 0.25	0.14 ± 0.09	0.24 ± 0.17	0.40 ± 0.22	0.52 ± 0.26
SVL	0.09 ± 0.08	0.15 ± 0.16	0.20 ± 0.22	0.23 ± 0.28	0.21 ± 0.10	0.36 ± 0.16	0.57 ± 0.22	0.67 ± 0.26
PEL-N15								
HAL	0.10 ± 0.20	0.13 ± 0.25	0.15 ± 0.33	0.39 ± 0.58	0.10 ± 0.26	0.13 ± 0.29	0.15 ± 0.37	0.39 ± 0.36
SAL	0.19 ± 0.27	0.26 ± 0.28	0.31 ± 0.41	0.57 ± 0.37	0.20 ± 0.26	0.25 ± 0.29	0.33 ± 0.39	0.60 ± 0.36
SVL	0.21 ± 0.27	0.22 ± 0.33	0.30 ± 0.39	0.28 ± 0.39	0.19 ± 0.26	0.27 ± 0.29	0.31 ± 0.37	0.57 ± 0.36
PEL-N30								
HAL	0.14 ± 0.14	0.20 ± 0.15	0.29 ± 0.29	0.45 ± 0.44	0.13 ± 0.17	0.19 ± 0.18	0.28 ± 0.23	0.44 ± 0.29
SAL	0.14 ± 0.17	0.17 ± 0.19	0.29 ± 0.24	0.45 ± 0.31	0.14 ± 0.17	0.16 ± 0.19	0.29 ± 0.23	0.45 ± 0.29
SVL	0.18 ± 0.14	0.17 ± 0.18	0.2 ± 0.23	0.24 ± 0.29	0.14 ± 0.17	0.17 ± 0.18	0.29 ± 0.22	0.45 ± 0.29
PR-T30								
HAL	0.01 ± 0.75	−0.17 ± 0.88	−0.11 ± 0.98	−0.56 ± 0.78	0.01 ± 0.80	−0.17 ± 0.84	0.11 ± 1.03	−0.56 ± 0.84
SAL	−0.27 ± 0.80	−0.46 ± 0.81	−0.13 ± 1.04	−0.70 ± 0.91	−0.29 ± 0.82	−0.46 ± 0.85	−0.14 ± 1.05	−0.67 ± 0.85
SVL	−0.14 ± 0.85	−0.46 ± 0.78	−0.33 ± 1.03	−1.01 ± 0.80	−0.12 ± 0.81	−0.46 ± 0.84	−0.33 ± 1.04	−1.03 ± 0.85
PR-T15								
HAL	−0.13 ± 0.47	−0.29 ± 0.62	−0.36 ± 0.57	−0.57 ± 0.65	−0.11 ± 0.40	−0.26 ± 0.52	−0.34 ± 0.56	−0.54 ± 0.60
SAL	−0.13 ± 0.42	−0.48 ± 0.48	−0.50 ± 0.45	−0.88 ± 0.57	−0.14 ± 0.40	−0.48 ± 0.53	−0.51 ± 0.57	−0.89 ± 0.61
SVL	−0.26 ± 0.33	−0.68 ± 0.47	−0.78 ± 0.66	−1.21 ± 0.58	−0.25 ± 0.40	−0.68 ± 0.52	−0.76 ± 0.56	−1.20 ± 0.60
PR-C								
HAL	−0.14 ± 0.29	−0.27 ± 0.35	−0.44 ± 0.46	−0.61 ± 0.54	−0.18 ± 0.30	−0.31 ± 0.42	−0.47 ± 0.49	−0.64 ± 0.54
SAL	−0.18 ± 0.28	−0.50 ± 0.37	−0.66 ± 0.42	−0.95 ± 0.50	−0.18 ± 0.31	−0.49 ± 0.43	−0.67 ± 0.50	−0.96 ± 0.55
SVL	−0.32 ± 0.26	−0.77 ± 0.46	−0.98 ± 0.56	−1.34 ± 0.54	−0.32 ± 0.30	−0.77 ± 0.42	−0.98 ± 0.50	−1.33 ± 0.55
PR-N15								
HAL	−0.23 ± 0.63	−0.41 ± 0.63	−0.71 ± 0.64	−0.77 ± 0.69	−0.23 ± 0.48	−0.40 ± 0.51	−0.71 ± 0.62	−0.76 ± 0.62
SAL	−0.22 ± 0.37	−0.48 ± 0.37	−0.77 ± 0.51	−0.96 ± 0.53	−0.23 ± 0.49	−0.50 ± 0.52	−0.79 ± 0.64	−0.97 ± 0.63
SVL	−0.27 ± 0.39	−0.67 ± 0.50	−0.88 ± 0.70	−1.13 ± 0.62	−0.27 ± 0.49	−0.66 ± 0.52	−0.86 ± 0.63	−1.12 ± 0.63
PR-N30								
HAL	−0.09 ± 0.72	−0.48 ± 0.69	−0.74 ± 0.76	−0.86 ± 0.82	−0.09 ± 0.63	−0.49 ± 0.69	−0.75 ± 0.71	−0.86 ± 0.76
SAL	−0.10 ± 0.53	−0.41 ± 0.66	−0.60 ± 0.58	−0.85 ± 0.71	−0.11 ± 0.64	−0.40 ± 0.70	−0.59 ± 0.72	−0.85 ± 0.77
SVL	−0.07 ± 0.61	−0.51 ± 0.71	−0.60 ± 0.78	−0.82 ± 0.70	−0.06 ± 0.64	−0.51 ± 0.70	−0.62 ± 0.72	−0.82 ± 0.76

Data are presented as the mean ± SD.

T, temporal; N, nasal; C, central; AL, axial length; M, male; SE, spherical equivalent.

icant differences between groups were found in the AL and PEL-T15 in all visits except baseline (all $P < 0.001$), which elongated fastest in the SVL group and slowest in the HAL group. PEL-N15, N30, and T30 had no significant differences between groups. RM-ANCOVAs were done in each group, significant differences over time were found in all PELs in all three groups (all $P < 0.001$) (Figs. 2A–C). In the SVL and SAL groups, AL elongated fastest, and the periphery elongated less, resulting in retina steepening; however, in the HAL group, PEL-N30 showed the fastest elongation, PEL-T15 showed the slowest elongation, and AL elongated less than the periphery, thus the retina flattened.

For PR (Figs. 2D–F), significant differences were found over time in all PRs in all three groups (all $P < 0.001$), but no difference was found between groups (all $P \geq 0.31$). For RPR (Figs. 2G–I), the main effect of time and group and the interaction between time and group did not show significance in the RPR-T15 ($F_{8,298} = 0.28$; $P = 0.97$) and RPR-T30 ($F_{8,298} = 1.36$; $P = 0.22$). The interaction showed significances in the

Table 3. Significant Correlations Between 2-Year Changes in AL and Other Parameters at Baseline

		Univariate Analysis		Multivariate Analysis		
Groups	Parameter	Standardized Coefficients β	*P* Value	Standardized Coefficients β	*P* Value	R^2
HAL	Age	−0.27	0.05			
	RPR-T15	0.33	0.02			
	RPR-N15	−0.40	0.003	−0.40	0.003	0.16
SAL	Age	−0.55	<0.001	−0.46	<0.001	0.36
SVL	Age	−0.65	<0.001	−0.53	<0.001	0.61
	RPR-N15	−0.57	<0.001	−0.43	0.001	
	RPR-N30	−0.35	0.01			

N, nasal retina; RPR, relative peripheral refractive; T, temporal retina.

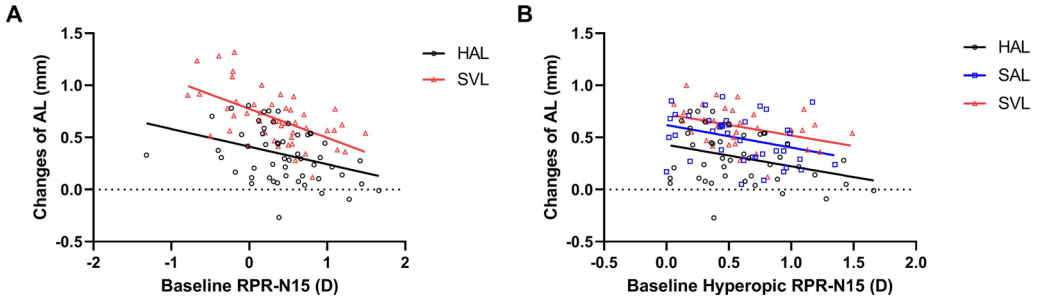

Figure 3. Significant correlations between 2-year axial length (AL) elongation and baseline RPR-N15 (**A**), between 2-year AL elongation and baseline hyperopic RPR-N15 (**B**). N, nasal.

Table 4. The Differences in AL Elongation (mm) Over 2 Years Between Children With Myopic RPR-N15 and Hyperopic RPR-N15 at Baseline in the Three Groups

	Total Participants	HAL Group	SAL Group	SVL Group
Myopic N15	0.67 ± 0.31	0.49 ± 0.23	0.56 ± 0.25	0.89 ± 0.29
Hyperopic N15	0.46 ± 0.25	0.31 ± 0.25	0.49 ± 0.23	0.60 ± 0.19
t-Test, *P* value	<0.001	0.045	0.39	<0.001

Data are presented as the mean ± SD.
C, central; N, nasal; SE, spherical equivalent.

RPR-N15 ($F_{8,298} = 2.76$; $P = 0.007$) and RPR-N30 ($F_{8,298} = 5.93$; $P < 0.001$). Over time, differences were significant in the RPR-N30, RPR-N15, and RPR-T30 in all three groups (all $P < 0.001$), which became more hyperopic in the SVL and SAL groups but less hyperopic in the HAL group. No significant difference in RPRs was found between groups (all $P \geq 0.30$).

The relationships between AL elongation and baseline parameters were tested by Pearson correlation analysis and multiple linear regression, and significant correlations were shown in Table 3. Baseline RPR-N15 was negatively correlated with AL elongation in the SVL and HAL groups (Fig. 3A) (both $P \leq 0.003$). Participants with hyperopic N15 at baseline had less 2-year AL elongation than participants with myopic N15 in the HAL and SVL groups (Table 4). Participants with baseline hyperopic or myopic N15 had no difference in baseline spherical equivalent, AL, age, and sex (all $P \geq 0.051$). After excluding participants with myopic RPR-N15, that is only including participants with hyperopic RPR-N15, a negative correlation between RPR-N15 and AL elongation was found in all three groups (Fig. 3B) (all $P \leq 0.033$).

Discussion

After a 2-year follow-up, PEL and PR showed significant differences over time, and the elongation pattern was different between groups. Compared with

the SVL group, HAL and SAL slow down central and paramacular eye elongation, although they have little effect on peripheral eye elongation. The retina steepened and the RPR became more hyperopic with myopia progression in the SVL group. In the SAL group, the retina also steepened, and the RPR became more hyperopic, but changes were smaller than in the SVL group. For the participants in the HAL group, changes were the opposite; the retina flattened and the RPR became less hyperopic.

In the SVL group, the result showed that axial elongation was faster than the PEL; further into the periphery, the eye elongation was slower, leading to a steepened retina after 2 years of myopia progression. The RPR became more hyperopic with time in the SVL group, which is consistent with the changes of PEL. For test groups, we found a dose-dependent effect of the lenslets asphericity on changes in PEL and refraction. With SAL, the retina steepened and RPR became more hyperopic, which showed the same tendencies as the changes in the SVL group but with a lower magnitude. With HAL, PEL-N30 showed the most elongation, and AL elongation was less than the periphery, which led to retina flattening and decreased peripheral hyperopic RPR, in contrast with the changes observed with SVL. The results of PEL showed that the temporal retina was steeper than the nasal retina, whereas the RPR was more hyperopic in the nasal side, which is contradictory. Results of PEL and refraction in this study were consistent with the previous studies in Chinese children.[24,25] The refraction at temporal retina were measured from the nasal cornea to the temporal retina, and we supposed that PR was not only influenced by retinal steepness, but also the corneal refraction. In our previous study, we found that the nasal corneal power was nearly 1 D larger than temporal corneal power, which means the nasal cornea would bring more myopic defocus assumingly.[23] Therefore, in this study, although there should be more hyperopic defocus in the temporal steeper retina, less hyperopic RPR was found in the temporal side due to more myopic defocus in the nasal cornea.

Only the AL and PEL-T15 showed significant differences between groups, which means HAL and SAL slowed mainly central AL elongation and did not affect peripheral eye elongation. Fung et al.[26] investigated the effects of peripheral myopic defocus on retinal activities by global flash multifocal electroretinogram. They found that the central (8°) and paramacular (8°–18°) retina showed an enhanced retinal response under the strong stimulus of defocus (+7.5 D), whereas the perimacular (18°–30°) retina did not show a differential response. Moreover, a weak stimulus of defocus (+2.5 D) resulted in no significant enhancements at any macular regions. Our study drew the same conclusion that peripheral defocus influenced only the central macula, and higher lenslet asphericity (HAL) had a better effect. Moreover, changes in the RPR were more likely caused by changes in retinal steepness. In our previous study, wearing orthokeratology lenses for 1 year was also found to flatten the retina and decrease peripheral hyperopic defocus.[23] Zhang et al.[25,27] also found decreases in the RPR in the perimacular region after wearing DIMS for 2 years and 3 years, but they did not investigate the changes in PEL. The BLINK study recently reported on the effects of multifocal contact lenses on peripheral eye elongation.[28] They also found that wearing center-distance contact lenses with +2.50 D addition showed either similar or less elongation at the fovea compared with the periphery, and the retina flattened as a result. According to these studies on children, we speculated that lens designs based on peripheral myopic defocus theory mainly slow down the central and paramacular eye elongation, the myopic defocus caused did not result in peripheral slowing of growth as much as it did central slowing of growth, perhaps suggesting the signal from myopic defocus throughout the periphery was integrated across the retina affecting central growth versus slowing local growth. The eyeball expansion pattern changed consequently, make the retina flattened and decrease peripheral hyperopic defocus.

There are several hypotheses about the mechanism of action of myopic defocus lenses. Animal studies have shown that the effects of myopic defocus were mediated by mechanisms that integrate visual signals in a local, regionally selective manner.[29,30] Neither this study nor previous studies on myopia control lenses can support this hypothesis. The interventional lenses (HAL and SAL) used in this study were designed to provide different myopic defocus signals at different eccentricities. It is possible that the same defocus amount may have different effects at different eccentricities, but the results of the current study cannot verify this conclusion because we cannot detect the actual defocus amount at the retina, nor detecting the retinal function at different eccentricities through electroretinography. Future animal research is needed to validate this theory. The eye shape factor is also a hypothesis from animal researches, stating that the more the eye deviates from emmetropia, the greater the response to defocus signals. However, in the multiple linear regression, we did not find that children with a longer eye AL had a better myopia control effect with HAL and SAL (Table 3). The mechanism

of defocus signals in humans and animals may be different.

Previous studies have shown that a more hyperopic defocus in the periphery was supposed to promote myopia.[9–14] However, in this study, participants with baseline more hyperopic defocus at N15 had less myopia progression. Zhang et al.[31] found a similar relationship between RPR-N10, RPR-N20, and AL elongation in participants with DIMS but not in participants with SVL. However, the measurement of RPR-N15 was not as reliable as other points because of the nerve head. The impact of RPR-N15 on myopia progression or intervention efficacy to slow down myopia remains unclear and requires further investigation.

The design of concentric rings of contiguous aspherical lenslets exposes both the horizontal and vertical retina to the defocus, but different areas of the retina may have different responses to the defocus. A limitation in this study is that we did not measure the vertical PEL and refraction to make a complete description of the eye changes; such vertical measurements could be added in further studies. Another limitation is that we only measured five points and one is at the optic nerve head (N15). The measurement of N15 may not be accurate enough because of the optic nerve head. The aim of the study was to pay more attention to the influence of peripheral defocus on peripheral elongation and the overall expansion pattern of the eyeball. Therefore, we considered that the inaccuracy of a single point in N15 did not affect the overall results.

Conclusions

In the SVL group, the retina steepened and the peripheral retinal defocus became more hyperopic with 2-year myopia progression. The peripheral myopic defocus induced by aspherical lenslets only slowed the central eye elongation, and the peripheral eye elongated as usual. In the SAL group, the retina steepened and peripheral hyperopic defocus increased, but with less magnitude than in the SVL group. Participants with HAL had faster PEL elongation than axial elongation, resulting in a flattened retina and peripheral hyperopic defocus decreased.

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Availability of Data and Materials: The datasets used and analyzed for the present study are available from the corresponding authors upon reasonable request.

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Author Contributions: Bao and Chen had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and Design: Bao, Chen.

Acquisition, Analysis, or Interpretation of Data: Huang, Li, Zhou, Wu, Zhang, Bao, Chen.

Drafting the Manuscript: Huang.

Critical Revision of the Manuscript for Important Intellectual Content: Huang, Li, Zhou, Wu, Zhang, Yang, Spiegel, Drobe, Chen, Bao.

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References

1. Atchison DA, Pritchard N, Schmid KL, Scott DH, Jones CE, Pope JM. Shape of the retinal surface in emmetropia and myopia. *Invest Ophthalmol Vis Sci*. 2005;46(8):2698–2707.
2. Cheng HM, Singh OS, Kwong KK, Xiong J, Woods BT, Brady TJ. Shape of the myopic eye as seen with high-resolution magnetic resonance imaging. *Ophthalmol Vis Sci*. 1992;69(9):698–701.
3. Atchison DA, Jones CE, Schmid KL, et al. Eye shape in emmetropia and myopia. *Invest Ophthalmol Vis Sci*. 2004;45(10):3380–3386.
4. Matsumura S, Kuo AN, Saw SM. An update of eye shape and myopia. *Eye Contact Lens*. 2019;45(5):279–285.
5. Chen X, Sankaridurg P, Donovan L, et al. Characteristics of peripheral refractive errors of myopic and non-myopic Chinese eyes. *Vision Res*. 2010;50(1):31–35.
6. Atchison DA. The Glenn A. Fry Award Lecture 2011: peripheral optics of the human eye. *Optom Vis Sci*. 2012;89(7):E954–E966.
7. Atchison DA, Pritchard N, Schmid KL. Peripheral refraction along the horizontal and vertical visual fields in myopia. *Vision Res*. 2006;46(8–9):1450–1458.
8. Calver R, Radhakrishnan H, Osuobeni E, O'Leary D. Peripheral refraction for distance and near vision in emmetropes and myopes. *Ophthalmic Physiol Opt*. 2007;27(6):584–593.
9. Mutti DO, Hayes JR, Mitchell GL, et al. Refractive error, axial length, and relative peripheral refractive error before and after the onset of myopia. *Invest Ophthalmol Vis Sci*. 2007;48(6):2510–2519.
10. Benavente-Perez A, Nour A, Troilo D. The effect of simultaneous negative and positive defocus on eye growth and development of refractive state in marmosets. *Invest Ophthalmol Vis Sci*. 2012;53(10):6479–6487.
11. Benavente-Perez A, Nour A, Troilo D. Axial eye growth and refractive error development can be modified by exposing the peripheral retina to relative myopic or hyperopic defocus. *Invest Ophthalmol Vis Sci*. 2014;55(10):6765–6773.
12. Smith EL, 3rd, Hung LF, Huang J. Relative peripheral hyperopic defocus alters central refractive development in infant monkeys. *Vision Res*. 2009;49(19):2386–2392.
13. Norton TT, Siegwart JT, Jr., Amedo AO. Effectiveness of hyperopic defocus, minimal defocus, or myopic defocus in competition with a myopiagenic stimulus in tree shrew eyes. *Invest Ophthalmol Vis Sci*. 2006;47(11):4687–4699.
14. Liu Y, Wildsoet C. The effect of two-zone concentric bifocal spectacle lenses on refractive error development and eye growth in young chicks. *Invest Ophthalmol Vis Sci*. 2011;52(2):1078–1086.
15. Gonzalez-Meijome JM, Faria-Ribeiro MA, Lopes-Ferreira DP, Fernandes P, Carracedo G, Queiros A. Changes in peripheral refractive profile after orthokeratology for different degrees of myopia. *Curr Eye Res*. 2016;41(2):199–207.
16. Lam CS, Tang WC, Tse DY, Tang YY, To CH. Defocus Incorporated Soft Contact (DISC) lens slows myopia progression in Hong Kong Chinese schoolchildren: a 2-year randomised clinical trial. *Br J Ophthalmol*. 2014;98(1):40–45.
17. Lam CSY, Tang WC, Tse DY, et al. Defocus Incorporated Multiple Segments (DIMS) spectacle lenses slow myopia progression: a 2-year randomised clinical trial. *Br J Ophthalmol*. 2020;104(3):363–368.
18. Bao J, Yang A, Huang Y, et al. One-year myopia control efficacy of spectacle lenses with aspherical lenslets. *Br J Ophthalmol*. 2022;106(8):1171–1176.
19. Li SM, Kang MT, Wu SS, et al. Efficacy, safety and acceptability of orthokeratology on slowing axial elongation in myopic children by meta-analysis. *Curr Eye Res*. 2016;41(5):600–608.
20. Chamberlain P, Peixoto-de-Matos SC, Logan NS, Ngo C, Jones D, Young G. A 3-year randomized clinical trial of MiSight lenses for myopia control. *Optom Vis Sci*. 2019;96(8):556–567.
21. Bao J, Huang Y, Li X, et al. Spectacle lenses with aspherical lenslets for myopia control vs single-vision spectacle lenses: a randomized clinical trial. *JAMA Ophthalmol*. 2022;140(5):472–478.
22. Mallen EA, Kashyap P. Technical note: measurement of retinal contour and supine axial length using the Zeiss IOLMaster. *Ophthalmic Physiol Opt*. 2007;27(4):404–411.
23. Huang Y, Li X, Ding C, Chen Y, Chen H, Bao J. Orthokeratology reshapes eyes to be less prolate and more symmetric. *Cont Lens Anterior Eye*. 2022:45(4):101532.
24. Ding X, Wang D, Huang Q, Zhang J, Chang J, He M. Distribution and heritability of peripheral eye length in Chinese children and adolescents: the Guangzhou Twin Eye Study. *Invest Ophthalmol Vis Sci*. 2013;54(2):1048–1053.
25. Zhang HY, Lam CSY, Tang WC, Leung M, To CH. Defocus Incorporated Multiple Segments spectacle lenses changed the relative peripheral refraction: a 2-year randomized clinical trial. *Invest Ophthalmol Vis Sci*. 2020;61(5):53.

26. Fung MMY, Choi KY, Chan HHL. The effect of simultaneous dual-focus integration on the global flash multifocal electroretinogram in the human eye. *Ophthalmic Physiol Opt*. 2021;41(1):171–178.
27. Zhang HY, Lam CSY, Tang WC, Lee PH, Tse DY, To CH. Changes in relative peripheral refraction in children who switched from single-vision lenses to Defocus Incorporated Multiple Segments lenses. *Ophthalmic Physiol Opt*. 2023;43(3):319–326.
28. Mutti DO, Sinnott LT, Berntsen DA, et al. The effect of multifocal soft contact lens wear on axial and peripheral eye elongation in the BLINK study. *Invest Ophthalmol Vis Sci*. 2022;63(10):17.
29. Diether S, Schaeffel F. Local changes in eye growth induced by imposed local refractive error despite active accommodation. *Vision Res*. 1997;37(6):659–668.
30. Smith EL, 3rd, Hung LF, Huang J, Blasdel TL, Humbird TL, Bockhorst KH. Effects of optical defocus on refractive development in monkeys: evidence for local, regionally selective mechanisms. *Invest Ophthalmol Vis Sci*. 2010;51(8):3864–3873.
31. Zhang H, Lam CSY, Tang W-C, et al. Myopia control effect is influenced by baseline relative peripheral refraction in children wearing Defocus Incorporated Multiple Segments (DIMS) spectacle lenses. *J Clin Med*. 2022;11(9):2294.