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Nasal-temporal asymmetric changes in retinal peripheral refractive error in myopic adolescents induced by overnight orthokeratology lenses

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Objective: To observe the changes in peripheral refraction in myopic adolescents after overnight orthokeratology and its influencing factors.

Methods: This was a prospective study among young myopic adolescents aged 8–14 years ($n = 21$). The peripheral refraction of the subjects was measured at 5, 10, 15, 20, 25, and 30° from the nasal and temporal side to the central fixation by WAM-5500 Open-field refractometer. The axial length, baseline spherical equivalent refraction, and other parameters were measured. The data were measured at baseline and 1, 3, and 12 months after wearing orthokeratology lenses.

Results: The relative peripheral refraction at the nasal and temporal side from central to 30° eccentricity revealed relative hyperopic defocus in all subjects at baseline measurement. One month after wearing the orthokeratology lenses, the relative peripheral refraction changed to myopic defocus, the nasal-temporal relative peripheral refraction was asymmetric, and the observed difference was statistically significant. Positive correlations were found between the change amount of nasal relative peripheral refraction and baseline spherical equivalent refraction, the baseline nasal relative peripheral refraction was higher than that on the temporal side, and after orthokeratology, the value of nasal relative peripheral refraction was lower than that on the temporal side. The changes at 30° on both sides were correlated to the axial elongation ($r_{\text{Nasal}} = 0.565$, $r_{\text{Temporal}} = 0.526$, $p < 0.05$).

Conclusion: This study demonstrated that after orthokeratology, relative peripheral hyperopia in the myopic patients turned into relative peripheral myopia, and the nasal-temporal asymmetry changed significantly after orthokeratology, which was correlated with the baseline refractive state.

KEYWORDS

orthokeratology, myopia, peripheral refraction, relative peripheral refraction, axial length

Introduction

Over the recent years, the prevalence of myopia has been steadily increasing worldwide (1, 2). Among all the available methods used to control myopia, orthokeratology has been receiving increasing attention as a safe and effective method (3–9).

While there are no definite conclusions regarding the principles and mechanisms of orthokeratology lens controlling myopia, according to previous studies, the comparative systematic and perfect possible mechanism might be explained by the theory of the peripheral refraction (10).

Peripheral Refraction (PR) is the retinal, refractive state of different eccentricities from the central fixation, and the relative peripheral refraction (RPR) is the refractive state of the peripheral retina relative to the central fixation (10). The PR can vary between myopia patients (11). The concept of peripheral refraction was first proposed by Hoogerheide and Rempt et al. (12, 13) in 1971. According to the classification of RPR, it can generally be divided into three types: relative peripheral hyperopia (RPH), relative peripheral myopia (RPM), and relative peripheral emmetropia (RPEm). Previous animal experiments have demonstrated that different peripheral defocus areas around the retina induce different refractive states (14–17).

The design of the orthokeratology lens is exactly in line with the optical principle of peripheral defocus (18). Previous studies have found that after wearing the orthokeratology lens, the peripheral refractive state of myopia patients goes through “myopic shift” (10, 19). It also shows the asymmetric change in the nasal and temporal side (20), where the asymmetry refraction might have more effect on the myopia progression.

The principle and mechanism of orthokeratology lens to control myopia have not been accurately determined. It is currently accepted that the reverse geometric design of the orthokeratology lens causes the RPM of the wearers. In the present study, we examined the influence of the orthokeratology lens on peripheral refraction and explored the nasal-temporal asymmetry changes of peripheral refraction after the orthokeratology.

Materials and methods

Study design

This prospectively designed, self-controlled observational study was conducted in accordance with the tenets of the Declaration of Helsinki and approval from the Ethics Committee of West China Hospital, Sichuan University (2017.43). This study was a part of our published study (21). All the subjects or their guardians signed written informed consent before being recruited into the study.

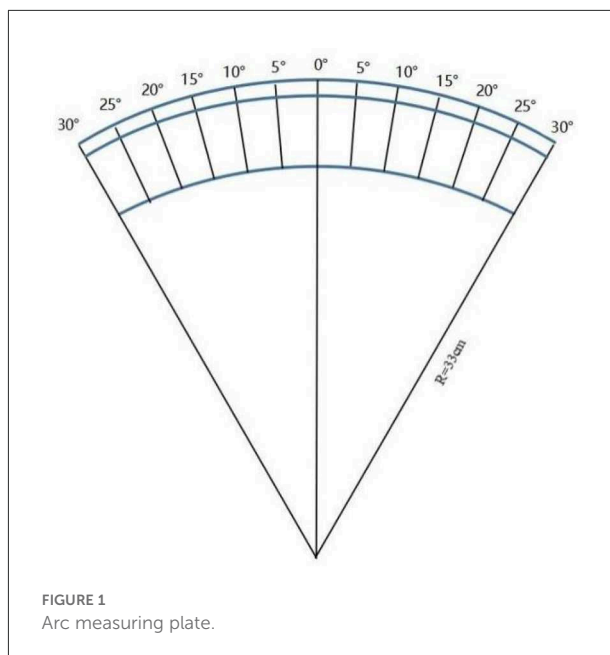


FIGURE 1
Arc measuring plate.

Inclusion and exclusion criteria

This study included myopic patients aged 8~14 years, with the degree of myopia between -1.00D and -5.00D and the degree of astigmatism $\leq 1.50\text{D}$. Good compliance and regular visits were also vital. Patients with contact lens contraindications (such as dry eye, eyelid gland dysfunction, eyelid insufficiency, allergic rhinitis, etc.), eye trauma surgery, severe allergies to cycloplegia drugs (compound toppicamine eye drops) or contact lens care solution, strabismus, amblyopia, or other eye diseases, and general diseases (such as diabetes, Down's syndrome, rheumatoid arthritis, etc.) were excluded.

Orthokeratology lens fitting process

Referring to the orthokeratology lens fitting standard (22), all subjects in this study were fitted with the same brand of orthokeratology lens so as to reduce the differences and effects between different brands and minimize such variations in different measurements due to various lens designs. The lenses were Euclid VST designs (Euclid Systems Corporation, USA). The lenses were manufactured with the oprifocon A (Boston Equalens II) which the oxygen permeability (DK) was $85 \times 10^{-11} (\text{cm}^2/\text{s}) [\text{mLO}_2/(\text{mL} \times \text{mmHg})]$. During the fitting process, the lens were ensured to maintain the contral position of the lens on the cornea, and the central position of the overnight orthokeratology lens was checked by the corneal topography after the lens were removed by the wearers during the follow-up period.

TABLE 1 Clinical baseline data of the subjects.

	Right eye (n = 19)	Left eye (n = 19)
Age(yr)	9.84 ± 1.64	
Sexuality		
Male	10 (52.63%)	
Female	9 (47.37%)	
SE ₀ (D)	- 2.73 ± 1.09	- 2.76 ± 1.19
IOP(mmHg)	15.82 ± 2.05	15.56 ± 2.52
AL(mm)	24.78 ± 0.93	24.80 ± 0.96

SE₀, initial spherical equivalent; IOP, intraocular pressure; PD, pupil diameter; AL, axial length.

Peripheral refraction

The data from both eyes were highly correlated and only the data of the right eye were included in further analysis.

The PR of the right eye was measured by WAM-5500 open-field auto-refractor. To exclude the influence of accommodation in dynamic measurement, the patients were required to accept the cycloplegia (compound tropicamide eye drops) every 5 minutes for a total of 4 times. After the last time, they were required to close eyes and rest for 20 minutes, a penlight was used to evaluate the dilation of the pupil before the measurement, and the accommodative amplitude was measured to ensure the influence of accommodation have been eliminated.

The subject, whose head was fixed by the frontal support and chin rest, were asked to stare at the measuring plate at 33 cm (Figure 1), the measuring plate was fixed to the rod, which is using to fix the visual target, after which the optometrist

would move the Maltese cross along the scale (central fixation to nasal 30°, temporal 30°, 5° as dividing points), measuring each eccentricity for nine times and recording it with spherical equivalent (SE).

Relative Peripheral Refraction (RPR) is defined as the difference of refractive state between each eccentricity and the central retina. The RPR equation was as follows:

$$RPR = SE_X - SE_c \tag{1}$$

where SE_X represents the SE of the X eccentricity from the center and SE_c represents the SE of the central fixation.

The initial spherical equivalent (SE₀) (NIDEK RT-600, <https://www.nidek-intl.com/>), the intraocular pressure (IOP) (Canon TX-20, <https://global.canon/en/>) and axial length (AL) (ZEISSIOL Master 500, <https://www.zeiss.com/meditec/int/home.html>) were measured at BL, 1, 3, and 12 months.

Statistical analysis

SPSS 22.0 and STATA16.0 software were used for the statistical analyses. Normality was tested with the Shapiro–Wilk normality test. Continuous variables were expressed as means with standard deviation (SD), or medians with the interquartile range (IQR), as appropriate. Single-factor repeated-measures analysis of variance (ANOVA) was used to compare the measured data at each time point. Paired *t*-test and Wilcoxon signed-rank test were used to observe the difference of RPR at each eccentricity. Non-parametric data were analyzed by Friedman test followed by Dunn’s multiple comparisons test. Correlations were analyzed by using

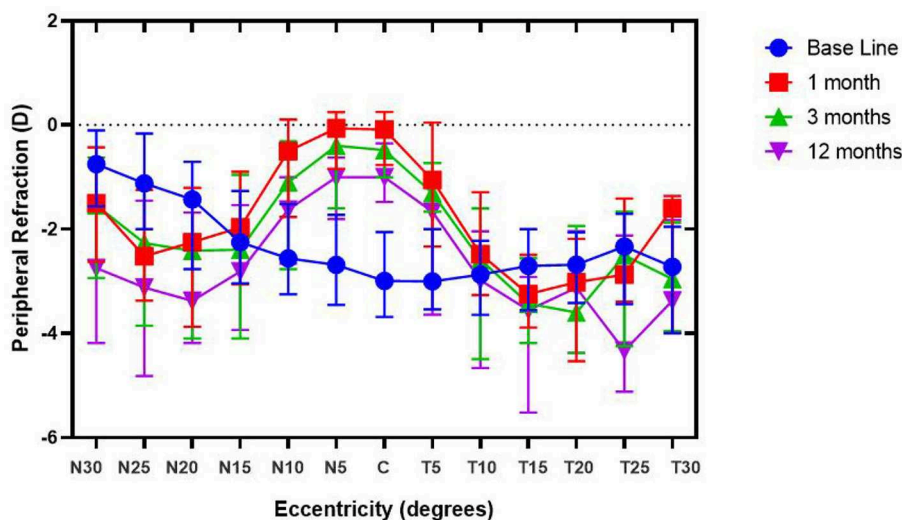


FIGURE 2 Peripheral refraction of subjects during the follow-up period. Relative peripheral refraction before (RPR_{Baseline}) and after orthokeratology treatment (RPR_{1/3/12month(s)}) for spherical equivalent (SE), with different degrees of eccentricity [30 nasal (N) to 30 temporal (T) across the retina].

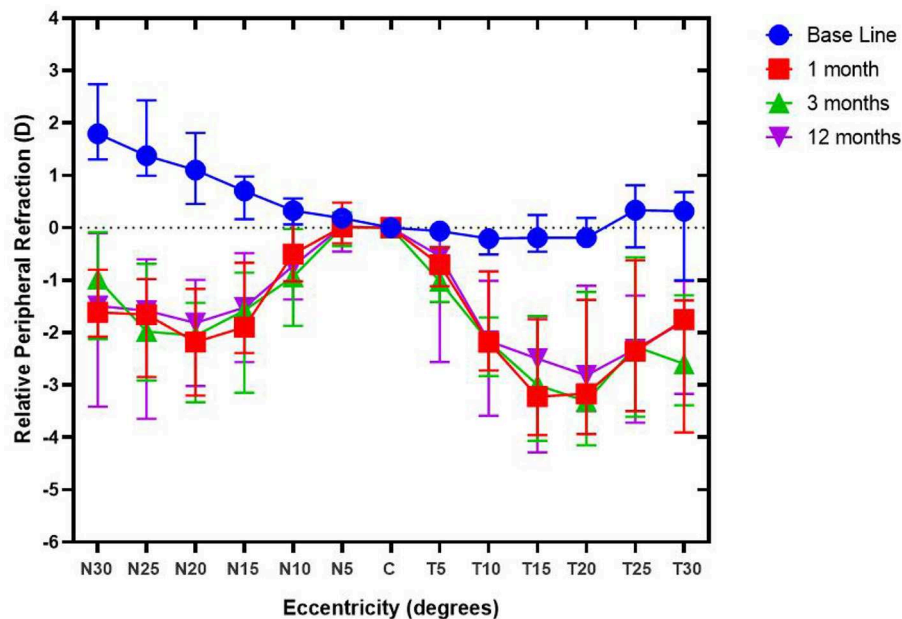


FIGURE 3

Relative peripheral refraction of subjects during the follow-up period. Relative peripheral refraction before ($RPR_{Baseline}$) and after orthokeratology treatment ($RPR_{1/3/12month(s)}$) for spherical equivalent (SE), with different degrees of eccentricity [30 nasal (N) to 30 temporal (T) across the retina].

Spearman's (non-normality) or Pearson (normality) correlation. All values were rounded to three decimal digits. $P < 0.05$ represented a statistically significant difference.

Results

Demographics

A total of 21 subjects who accepted the peripheral refraction measurement were enrolled in the present study. They were measured at baseline (BL), 1, 3, and 12 months after wearing the lenses. The data from right eye were enrolled to RPR analysis to avoid bias. Among them, two subjects missed the last peripheral refraction measurement due to studying abroad and thus were excluded from the data processing. The demographics of the subjects are shown in Table 1.

Peripheral refraction

The PR of these subjects was measured before and after the orthokeratology lens (Figure 2). Also, the RPR of subjects is shown in Figure 3. During the follow-up period, the defocus area around the nasal and temporal periphery changed. Figure 3 shows the RPR changes from relative hyperopic to relative myopic defocus. The significant differences of RPR at each eccentricity

in the different follow-up periods were calculated (Table 2).

During the follow-up period, the mean value of the axial length in right eyes of the participants was 24.78 ± 0.93 mm, the mean value of the axial length of subjects after 12 months follow-up period was 24.95 ± 0.88 mm. The mean value of axial length elongation was 0.01 ± 0.04 mm at the 1st month follow-up, 0.04 ± 0.07 mm at the 3rd month follow-up and 0.17 ± 0.14 mm at the 12th month follow-up (Figure 4), it suggested that the value at the end of the follow-up (12th month follow-up) was significantly different from the baseline value ($p = 0.0004$).

Table 2 demonstrated that the nasal-temporal asymmetry still existed before and after the orthokeratology lens, however, it should be noted that the difference changed after the orthokeratology lens. The value of nasal RPR at each eccentricity was larger than that in the temporal RPR before orthokeratology. In contrast, after the orthokeratology lens, the value of the temporal RPR at different eccentricities was larger than that of the nasal RPR. However, the asymmetry of RPR in the nasal and temporal side existed until 20° eccentricity after orthokeratology, while beyond the $20\text{--}30^\circ$ of each eccentricity, it showed fewer asymmetric changes.

After 3 months, the change amount of axial length (ΔAL) was associated with the change amount of relative peripheral refraction (ΔRPR) at the N30 ($p = 0.012$), T5 ($p = 0.042$), T10

TABLE 2 Relative peripheral refraction (Mean \pm SD) after treatment for each eccentric nasal (N) and temporal (T) side; statistical significance for comparison between pre- and post-treatment (p^a), and significance for the comparison of relative peripheral refraction at corresponding nasal-temporal side among each follow-up record (p^b).

Eccentricity	RPR(p^a)	Eccentricity	RPR(p^a)	[p^b]
N30		T30		
Base Line	2.197 \pm 1.128	Base Line	- 0.033 \pm 1.177	<0.0001*
1 month	- 1.366 \pm 1.267(<0.0001*)	1 month	- 2.048 \pm 1.789(<0.0001*)	0.057*
3 months	- 0.949 \pm 2.001(<0.0001+)	3 months	- 2.571 \pm 1.568(<0.0001*)	0.024+
12 months	- 1.722 \pm 1.758(<0.0001+)	12 months	- 2.081 \pm 1.748(<0.0001*)	0.260+
N25		T25		
Base Line	1.673 \pm 0.898	Base Line	0.278 \pm 0.800	<0.0001*
1 month	- 1.796 \pm 1.372(<0.0001*)	1 month	- 1.959 \pm 1.763(<0.0001*)	0.646*
3 months	- 1.873 \pm 1.411(<0.0001*)	3 months	- 2.135 \pm 2.094(<0.0001*)	0.534*
12 months	- 2.101 \pm 1.781(<0.0001*)	12 months	- 2.621 \pm 1.651(<0.0001*)	0.276*
N20		T20		
Base Line	1.121 \pm 0.732	Base Line	- 0.054 \pm 0.701	<0.0001*
1 month	- 2.054 \pm 1.493(<0.0001*)	1 month	- 2.984 \pm 1.788(<0.0001*)	0.001*
3 months	- 2.214 \pm 1.194(<0.0001*)	3 months	- 2.894 \pm 1.875(<0.0001*)	0.071*
12 months	- 2.101 \pm 1.725(<0.0001*)	12 months	- 2.407 \pm 1.833(<0.0001*)	0.442*
N15		T15		
Base Line	0.652 \pm 0.484	Base Line	- 0.130 \pm 0.600	<0.0001*
1 month	- 1.466 \pm 1.283(<0.0001*)	1 month	- 2.857 \pm 1.560(<0.0001*)	0.001*
3 months	- 1.877 \pm 1.321(<0.0001*)	3 months	- 3.011 \pm 1.489(<0.0001*)	0.009*
12 months	- 1.646 \pm 1.501(<0.0001*)	12 months	- 2.999 \pm 1.853(<0.0001*)	0.006*
N10		T10		
Base Line	0.327 \pm 0.369	Base Line	- 0.205 \pm 0.433	<0.0001*
1 month	- 0.586 \pm 1.037(0.001*)	1 month	- 2.268 \pm 1.534(0.0001*)	0.001*
3 months	- 0.896 \pm 1.289(0.002*)	3 months	- 2.356 \pm 1.475(<0.0001*)	0.002*
12 months	- 0.777 \pm 1.099(0.001*)	12 months	- 2.382 \pm 1.615(<0.0001*)	<0.0001*
N5		T5		
Base Line	0.207 \pm 0.282	Base Line	- 0.027 \pm 0.391	0.009+
1 month	- 0.053 \pm 0.842(0.409+)	1 month	- 0.871 \pm 0.817(0.002*)	0.009*
3 months	- 0.137 \pm 0.687(0.091+)	3 months	- 0.958 \pm 0.634(0.0002*)	0.001*
12 months	- 0.169 \pm 0.648(0.027+)	12 months	- 1.147 \pm 1.305(<0.0001+)	0.018+

(^a) parametric tests; (+) Non-parametric tests; boldface: $p < 0.05$.

($p = 0.014$), and T30 ($p = 0.021$), and there were no significant changes in other positions (Figure 5).

$$\Delta RPR = RPR_3 - RPR_0 \quad (2)$$

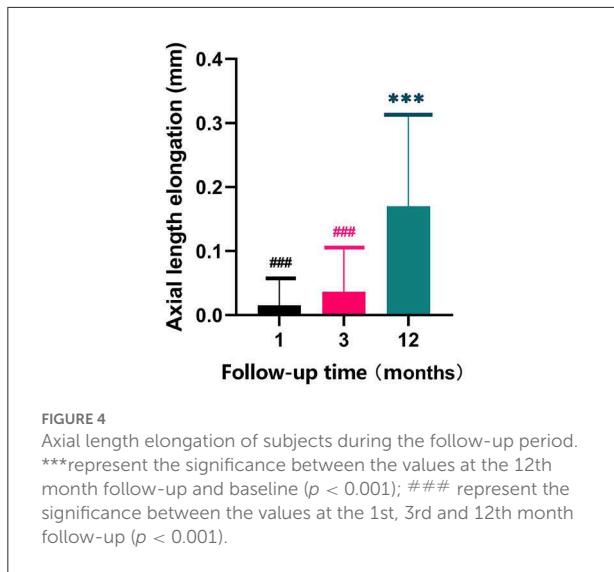
$$\Delta AL = AL_3 - AL_0 \quad (3)$$

After 1 month of orthokeratology, the change amount of ΔRPR was not related to the SE_0 (Table 3). After 3 months of wearing the lens, a positive correlation was found between the ΔRPR and the SE_0 , and the

asymmetric effect on the nasal and temporal side was observed. Also, a stronger correlation was found on the nasal side. One year after wearing the lens, the number of ΔRPR changes associated with the SE_0 decreased at different eccentricities but still showed nasal and temporal asymmetry and a stronger correlation with the number of nasal RPR changes.

Discussion

Due to the unique design of the orthokeratology lens, when the lens covers the wearer's cornea, the reverse geometric design of the lens can come in direct contact with the cornea's front



surface, thus changing the corneal curvature (19, 23) and RPR through some mechanisms (10). In addition to reshaping the corneal form, the orthokeratology lens may function under the principle of peripheral refraction to control myopia. This study measured the orthokeratology lens wearer in the nasal, temporal gaze range of the refractive state. Our results revealed that the RPR of myopia patients changed after orthokeratology. We also highlighted the asymmetric changes of RPR at the nasal and temporal side before and after the orthokeratology lens and explored the reasons that might cause the asymmetric RPR.

Since horizontal PR has been more significantly related to myopia than vertical PR (24, 25), only horizontal PR was measured in this study. Most subjects were RPH before the

orthokeratology. Preclinical studies showed that peripheral retinal focus could promote myopia progression (26, 27). In their clinical studies, Hoogerheide and Rempt et al. (12, 13) firstly suggested that the myopia progression in patients with RPH was faster than in those with RPM in the same age group, while the young adults with positive parental myopia had increasing AL and RPH compared to the control group with negative parental myopia (28).

This study found that after the orthokeratology, the RPR of wearers changed from PRH to PRM, and the difference was statistically significant. These results prove that the design principle of the orthokeratology lens does affect the RPR of the lens wearers (29). The previous study compared the RPR of myopic patients with a single vision frame lens, revealing that the subjects with a single vision frame lens did not change with PRH, and the orthokeratology group patients changed from PRH to PRM, which was consistent with our study results (30, 31). According to the results of this study, the initial nasal RPR was larger than that on the temporal side. After wearing the orthokeratology lens, the value of nasal RPR was smaller than that in the temporal side and changed into PRM. Moreover, it seems that orthokeratology promoted the symmetric RPR changes in the nasal and temporal side of lens wearers (19). The specific cause of the RPR changes might be related to the mechanism of the myopia control effect exerted by the orthokeratology lens.

This study also found that the RPR amount of N30 and T30 after 3 months of lens wearing was positively correlated to the AL. This conclusion is similar to the results of Gifford et al. (30, 31), who confirmed that the peripheral defocus could directly affect the number of changes in the AL, i.e., the progression of myopia (32, 33) suggested that the change of the AL could be preliminarily predicted according to the change of RPR.

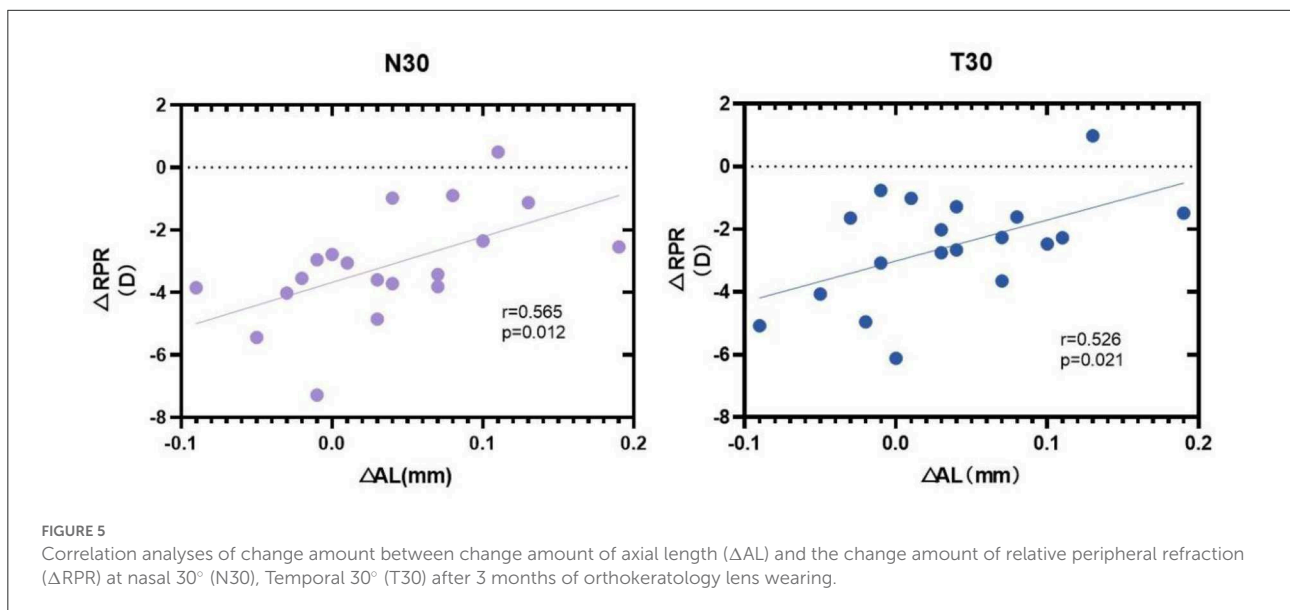


TABLE 3 Correlation analyses between the RPR change amount and SE₀ during the follow-up period (Controlling for age and sex).

Follow-up period (months)	N30	N25	N20	N15	N10	N5	T5	T10	T15	T20	T25	T30
1												
r	0.472	0.485	0.338	0.066	-0.027	-0.044	0.587	0.486	0.142	0.337	0.545	0.603
p	0.056	0.049	0.185	0.803	0.919	0.866	0.013	0.048	0.586	0.186	0.024	0.010
3												
r	0.625	0.643	0.556	0.428	0.626	0.317	0.449	0.511	0.399	0.468	0.407	0.539
p	0.007	0.005	0.020	0.087	0.007	0.215	0.071	0.036	0.112	0.058	0.105	0.026
12												
r	0.286	0.479	0.181	0.414	0.011	-0.439	0.228	0.408	0.235	0.273	0.447	0.208
p	0.266	0.052	0.487	0.099	0.967	0.078	0.378	0.104	0.364	0.288	0.072	0.424

Based on the results of the one-year follow-up, the researchers found that the RPR at the nasal side was positively related to the SE₀, which is similar to the results of Charman et al. (34), and might be one of the reasons explaining the asymmetric changes in the nasal and temporal side. These results can serve as a reference for designing individualized orthokeratology lenses for better myopia control efficacy.

Nevertheless, this study had some shortcomings, the small sample size leading to bias in the results, so further research on the issue should be conducted with a larger sample size. Furthermore, our study was limited in terms of follow-up time, and follow-up duration of this study need to be improved as well.

Conclusion

Taken together, these results suggested that the correlations mentioned below revealed a nasal-temporal asymmetry in RPR, where the SE₀ was more strongly correlated with the nasal RPR changes. The correlation was one of the reasons for the asymmetric changes in the nasal, temporal RPR after orthokeratology, which can serve as a reference for designing individualized orthokeratology lenses for better myopia control efficacy.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of West China Hospital, Sichuan University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

Study design, concept, and data extracting: XC, YX, and LL. Database search: XC and YX. Data analysis: XC and XQ. Manuscript writing: XC. Manuscript revising: XC and LL. All authors approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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