Axial Shortening Effects of Repeated Low-level Red-light Therapy in Children With High Myopia: A Multicenter Randomized Controlled Trial

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• PURPOSE: To evaluate the effectiveness and safety of repeated low-level red-light (RLRL) in delaying the progression of high myopes with –6.00 diopters (D) or worse.

• DESIGN: Multicenter, randomized, parallel-group, single-blind clinical trial. A total of 202 high myopic children aged 7 to 12 years with cycloplegia spherical equivalent (SE) refraction ≤–6.00 D, astigmatism less than 2.50 D, and anisometropia of 1.50 D or less were enrolled from March 2022 to December 2022. Follow-up was completed in December 2023.

• METHODS: Eligible participants were randomly allocated to the intervention (RLRL + single vision spectacle) or the control group (single vision spectacle). The RLRL treatment was administered every day for 3 minutes, twice a day, with an interval of at least 4 hours. The primary outcome was the change in axial length (AL) at 12 months compared with baseline. Secondary outcomes included changes in SE, changes in choroidal thickness (ChT), and changes in retinal thickness (RT) in different circle sectors. Outcomes were analyzed by means of intention-to-treat and per-protocol methods.

• RESULTS: After 12 months of treatment, AL and SE changes were –0.11 ± 0.25 mm and 0.18 ± 0.63 D for the RLRL group and 0.32 ± 0.09 mm and –0.80 ± 0.42 D for the control group, respectively. Axial shortening >0.05 mm was 59% in the RLRL and 0% in the control group at 12 months. ChT and RT from a single center were analyzed. In the RLRL group, ChT was thickened in all sectors at 12 months. RT was increased in parafoveal and perifoveal circles. In the control group, all sectors of ChT and only perifoveal RT were significantly thinner at 12 months. The multivariate linear regression model revealed significant correlations between changes in the ChT central foveal circle and RT perifoveal circle at 1 month and AL changes at 12 months. No fundus structure changes, afterimage exceeding 6 minutes, or best-corrected visual acuity decrease were reported.

• CONCLUSIONS: RLRL could effectively shorten the AL and inhibit the progression of myopia in high myopic patients with –6.00 D or worse. AL shortening is sustained over 12 months of treatment. These observed changes appeared to be associated with increases in ChT and RT. (Am J Ophthalmol 2025;270: 203–215. © 2024 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/))

MYOPIA IS A GLOBAL PUBLIC HEALTH PROBLEM, and its prevalence has increased dramatically in recent decades, especially in East Asian countries.[1,2] High myopia is defined as myopic refractive error worse than –6.00 diopters (D)[3] and is associated with a severely elongated eye along with changes in other ocular components that may increase the likelihood of complications such as retinal detachment, glaucoma, scleral thinning, and localized posterior ectasia of the sclera.[4,5]

According to the International Myopia Institute, 50% to 70% of pathologic myopia cases can develop due to high myopia.[6] Additionally, the progression of myopia could increase the risk of myopic maculopathy, in particular, the rate of pathologic myopia was found to be positively associated with myopia more than –7.00 D.[7,8] Therefore, it was crucial and urgent to prioritize myopia control management for children who have progressed to high myopia.

Repeated low-level red-light (RLRL) therapy by emitting 650 nm visible red light emerges as an alternative treatment for myopia control and prevention interven-

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tion.[9,10] Meta-analysis has shown that RLRL produced a significant effect in slowing axial length (AL) elongation (–0.28 mm/year) and spherical equivalent (SE) refraction increases (0.57 D/year).[11] A study on the premyopic children suggested that RLRL could effectively delay AL by –0.17 mm and SE by 0.41 D after 12 months of treatment.[9] Our recent research found that RLRL had a better treatment effect on AL and SE in myopic patients than premyopic participants.[12] This suggested that the effects of RLRL might vary among different populations; therefore, it was imperative to investigate this phenomenon in children with high myopia. Recent research demonstrated RLRL was effective among high myopic children, and the cutoff for SE was ≤–4.00 D.[13] Based on our literature review thus far, there has been no published reports regarding the efficacy of RLRL in individuals with high myopia of –6.00 D or worse.

Therefore, we reported this prospective, multicenter, randomized clinical trial to evaluate the efficacy and safety of RLRL in children with high myopia. In addition, we conducted an analysis of the alterations in the retina and choroid after treatment in both the central and peripheral regions to investigate the factors that influence the outcomes.

METHODS

This 12-month, multicenter, randomized, parallel-group, single-blind clinical trial consisted of 5 study groups. Participants were recruited from 5 tertiary hospitals in China and were enrolled from March 2022 to December 2022. Uniform protocol and equipment were consistently used by the same examiners for all examinations conducted at the 5 clinical sites throughout the duration of the study. All parents provided signed consent for their children to participate. The Ethics Committee of Tianjin Medical University Eye Hospital, Beijing Children's Hospital, Beijing Tsinghua Chang Gung Hospital, Hebei Provincial People's Hospital, and Shijiazhuang People's Hospital approved the study protocol, which adhered to the tenets of the Declaration of Helsinki. The trial was registered with the Chinese Clinical Trial Registry (ChiCTR2200062028).

• **ELIGIBILITY CRITERIA:** The inclusion criteria were as follows: age 7 to 12 years at baseline, SE of ≤–6.00 D, astigmatism less than 2.50 D, anisometropia of 1.50 D or less, and best-corrected visual acuity (BCVA) of 20/20 or more in either eye. The exclusion criteria were any systemic or ocular disease including acute and subacute inflammations or infection of the anterior chamber of the eye, strabismus, binocular vision abnormalities, histories of surgery or any myopia intervention, severe insufficiency of tears, allergic eye diseases, retinal diseases, and any significant systemic illness.

• **RANDOMIZATION AND MASKING:** Eligible participants were randomly allocated to the intervention group and control group in a ratio of 2:1, according to a randomization list pregenerated by a computer program (R software, version 3.2.2). Because of the nature of the intervention, children and their guardians were aware of the study allocation and therefore not blinded. However, all outcome assessors were masked to the participant's treatment allocation.

• **INTERVENTION AND COMPLIANCE MONITORING:** All children were dispensed single-vision spectacles throughout the study. The updated spectacles were provided if SE changed by –0.50 D or more. Participants in the intervention group used the RLRL device (Eyerising; Suzhou Xuanjia Optoelectronics Technology) at home. Participants were administered treatment every day for 3 minutes twice a day with an interval of at least 4 hours between the 2 sessions. The RLRL device consists of semiconductor laser diodes, which delivers low-level red light with a wavelength of 650 ± 10 nm at an illuminance level of approximately 1600 lux through the pupil to the fundus. At the first visit, the supervisors adjusted the best positions and spectacles for participants before use to ensure the light enters the eyes properly. The device automatically recorded the date and time of therapy sessions and sent these via the Internet to the server to provide an accurate measure of compliance. A reminder message was issued to the subject and supervisor to ensure a 75% treatment rate, as long as the subject had not logged into the system for 2 days consecutively. Additionally, the power of the device was also detected by the server. In the event of an unforeseen fluctuation, such as the power fluctuation was greater than 0.5 mW, the device was remotely shut down. Participants were required to complete the RLRL treatment at least 5 days per week following the guidelines of the treatment. If the total treatment session was less than 5 days per week or suspension of more than 2 consecutive days, the supervisor would contact parent or guardian of the participants to comply with the study and treatment guidelines. After 12 months of treatment, participants who had a treatment compliance rate of at least 75% were included for further analysis.

• **STUDY OUTCOMES:** At the first visit, subjects underwent a serial of comprehensive ocular examinations, including visual acuity, intraocular pressure, slit-lamp ophthalmic examination, and fundus examination. AL, cycloplegic refraction, retinal thickness (RT), and choroidal thickness (ChT) were measured before and 1, 3, 6, 9, and 12 months after the treatment. To avoid diurnal variation, all evaluations were performed from 9 to 11 AM. The primary outcome was the change in AL at 12 months compared with baseline. AL was measured before cycloplegia with a noncontact Biometer (Lenstar LS-900; Haag-Streit AG). The parameter was determined by a mean value of 3 successive measurements with intra-session differences of 3 repeated

measures ≤0.02 mm. The average was used as a representative value for further analysis.

A key secondary outcome was the change in SE. Cycloplegia was conducted with 1% cyclopentolate (Alcon) 5 minutes apart, 3 times. When the pupil had no reflex to light and pupil size was more than 6.0 mm, complete cycloplegia was achieved. After full cycloplegia, cycloplegic refraction data were obtained using an autorefractor (KR-800, Topcon) with an average of 3 measurements within a minimum deviation of 0.25 D for spherical and cylinder power and 5° for axis. The SE was calculated using the sum of the spherical power and half of the cylindrical power.

Other secondary outcomes included changes of ChT and RT in different circle sectors. All participants enrolled from Tianjin Medical University Eye Hospital had their RT and ChT assessed using swept-source optical coherence tomography (SS-OCT) (VG200, Svision Imaging, Ltd.), which contained a swept-source laser with a central wavelength of 1050 nm and scan rate of 200,000 A-scans per second. The device had a full-width at half maximum axial resolution of approximately 5 µm in tissue and an estimated lateral resolution at the retinal surface of approximately 15 µm.[14] All SS-OCT image acquisition was performed under full cycloplegia to minimize the accommodation effect on measurement parameters.[15] RT was defined as the distance between the inner limiting membrane and the apical boundary of the retinal pigment epithelium. The vertical distance between Bruch's membrane and the choroid—sclera interface was defined as the ChT. SS-OCT software automatically obtained RT and ChT. The Early Treatment Diabetic Retinopathy Study (ETDRS), known as the "ETDRS grid," was used for further analysis of the retina and choroid. The 6×6-mm grid was focused on the macula, and the concentric circle pattern was as follows: central circle with a 1-mm diameter (central foveal circle), inner circle with a 3-mm diameter (parafoveal circle), and outer circle with a 6-mm diameter (perifoveal circle).[16] Through the use of built-in software, the average thickness in each sector of the circle was automatically determined. All sectors were assessed to analyze the average thickness in the macular area. Every scanning operation was performed by a well-trained operator, and all the pictures were reviewed to have a signal strength greater than 7.

In addition, anterior segment parameters including central corneal thickness, flat meridian (K_1), steep meridian (K_2), lens thickness, and anterior chamber depth were measured at baseline and each follow-up. They were obtained while measuring the AL with the noncontact Biometer.

• **SAMPLE SIZE:** The sample size estimation was conducted based on the assumption of an α level of 0.05, 80% power, annual axial elongation of 0.34 mm (SD, 0.22 mm) over 12 months,[17] and a 50% treatment effect (reducing axial elongation by 0.17 mm). The intervention group and control group were allocated in a 2:1 ratio, and the sample size required was 83 participants in total. Adjusting for 20% loss to follow-up yielded a total sample size of 105 participants.

• **ADVERSE EVENTS:** At baseline, all intervention group participants underwent a 3-minute RLRL treatment for safety analysis. If the afterimage lasted more than 6 minutes,[9,18] the participants were deemed overly sensitive to the intervention and were excluded (n = 2). At each follow-up visit, participants and their parents were asked to report any negative effect, including but not limited to discomfort, itching, dryness, dazzling, short-term glare, flash blindness, and afterimage duration. The treatment was promptly discontinued if the participant in the intervention group had any severe adverse event, including sudden visual loss of 2 or more lines or a scotoma observed in the center of the participant's viewing field.

• **STATISTICAL ANALYSIS:** Data collected from right eye from subjects were included in this analysis. RT and ChT data only from a single center (Tianjin Medical University Eye Hospital) were included in statistical analysis. Continuous data and categorical data were represented by mean ± SD and N (%), respectively. The data normality was confirmed using a Kolmogorov–Smirnov test. For quantitative variables, based on the applicable conditions, the *t* test and Wilcoxon test were used to compare the differences between the RLRL group and the control group. For categorical variables, the chi-square test was used to compare the distributional differences between the RLRL group and the control group.

Outcomes were analyzed by means of intention-to-treat (ITT) and per-protocol (PP) methods. Participants who attended at least 1 subsequent follow-up visit were included in the ITT, and the missing data were not imputed. For some participants who interrupted treatment, only the data before the interruption were calculated for ITT statistical analysis. The ITT analysis was used to analyze the effectiveness of RLRL treatment. In addition, participants finished all the treatment, and follow-up visits were analyzed in PP analysis. The factors affecting the RLRL treatment effect was analyzed by the PP. Changes in AL and SE were defined as the differences between follow-ups and the baseline measurement value. Treatment efficacy in respect of the primary outcome (changes in AL) and secondary outcomes (changes in SE), as well as changes of anterior segment parameters on multiple follow-up visit time points were demonstrated by the longitudinal mixed model.

Similar to the definitions of changes in AL and SE, the changes of OCT value (ChT and RT) were defined as the difference between the measurement value at each follow-up and baseline. The independent-sample *t* test was used to compare baseline parameters (including age, gender, AL, and SE) between participants who completed OCT measurement (OCT group) and did not complete OCT measurement (non-OCT group). Sensitivity analyses were

conducted to assess the treatment effects of therapy in controlling myopia progression, specifically AL elongation. The RLRL group was divided into 2 subgroups by AL shortening ≤0.05 mm and >0.05 mm after RLRL treatment, and baseline parameters (including age, gender, AL, SE, ChT and RT) were compared by an independent-sample *t* test. The RLRL group and the control group were divided into 2 subgroups based on baseline SE (–6.00~–8.00 D vs <–8.00 D) and age (7-9 years vs 10-12 years), respectively. The AL elongation difference between the RLRL group and the control group at 12 months was compared across different baseline SE and age subgroups.

The repeated-measures analysis of variance was used to describe the trend of OCT values changes. A paired *t* test was also performed with Bonferroni correction of the *P* value. This study used the generalized linear model to explore the relationship between OCT value and AL changes at 1-year follow-up. First, age, gender, baseline AL, and baseline OCT values were included in the model. Then the Backward method was used to select the best model. Afterward, according to the above best model, we continued to include OCT value changes of each sector at 1-month follow-up and then used the Backward method with Akaike Information Criterion evaluation to select the best model until the 6-month follow-up. Linear regression models assessed baseline factors associated with changes in ChT and RT (central foveal circle, parafoveal circle, and perifoveal circle) over 12 months in the RLRL group. Potential covariates included baseline age, AL, ChT, and RT. In this study, all statistical tests were 2-sided and a *P* value < .05 was considered statistically significant. All analyses were performed using R 4.2.0.

RESULTS

Children with myopia (n = 252) were recruited and assessed for eligibility. A total of 202 subjects (80%) were enrolled in this study, including 132 in the RLRL group (130 of 132 had at least 1 follow-up and were included in the primary analysis [98%]) and 70 in the control group (68 of 70 had at least 1 follow-up and were included in the primary analysis [97%]). Of 202 included children, 169 (84%) completed all follow-up visits, including 113 in the RLRL group and 56 in the control group. Five subjects dropped out because RLRL compliance was below 75%, 20 subjects dropped out because they chose other myopia control methods, and 8 subjects were lost to follow-up, as detailed in Figure 1. A total of 74 patients (RLRL: n = 50; control: n = 24) completed comprehensive follow-up visits of OCT examination.

• **BASELINE CHARACTERISTICS:** The mean age at baseline was 10.2 ± 1.7 years, and 46% of subjects were male. The baseline demographic and ocular characteristics of the subjects in the 2 groups are presented in Table 1. There were no statistically significant differences in age, gender, baseline SE, baseline AL, baseline BCVA, baseline ChT, and RT between the 2 groups (all $P > .05$). Baseline age, gender, AL, and SE between the OCT group and non-OCT group are summarized in Table 2. There were no statistically significant differences between the 2 groups (all $P > .05$).

TABLE 1. Demographics and Baseline Data Between Groups (Mean ± SD)

Parameters	RLRL (N = 130)	Control (N = 68)	*P*
Gender (M/F)	61/69	30/38	.707
Age (y)	10.1 ± 1.7	10.5 ± 1.6	.081
SE (D)	–7.75 ± 1.91	–7.65 ± 1.70	.671
AL (mm)	26.50 ± 1.03	26.38 ± 0.99	.458
BCVA (logMAR)	–0.004 ± 0.017	–0.006 ± 0.020	.427
OCT parameters	**(N = 50)**	**(N = 24)**	
ChT_ cen (μm)	249 ± 69	261 ± 64	.478
ChT_ para (μm)	252 ± 64	262 ± 61	.553
ChT_ peri (μm)	246 ± 56	256 ± 55	.472
RT_ cen (μm)	263 ± 23	257 ± 20	.282
RT_ para (μm)	320 ± 14	322 ± 13	.532
RT_ peri (μm)	274 ± 12	278 ± 12	.220

AL = axial length; cen = central foveal circle; ChT = choroidal thickness; F = female; M = male; OCT = optical coherence tomography; para = parafoveal circle; peri = perifoveal circle; RLRL = repeated low-level red-light; RT = retinal thickness; SE = spherical equivalent.

TABLE 2. Demographics and Baseline Data: OCT Group Versus Non-OCT Group (Mean ± SD)

Parameters	OCT (N = 74)	Non-OCT (N = 124)	*P*
Gender (M/F)	35/39	56/68	.770
Age (y)	10.2 ± 1.8	10.2 ± 1.5	.996
SE (D)	–7.73 ± 2.21	–7.72 ± 1.55	.952
AL (mm)	26.53 ± 0.99	26.44 ± 1.04	.568

AL = axial length; F = female; M = male; OCT = optical coherence tomography; SE = spherical equivalent.

Baseline BCVA (logarithm of the minimum angle of resolution) is shown in Table 1. After 12 months of treatment, BCVA (logarithm of the minimum angle of resolution) was –0.003 ± 0.015 in the RLRL group and –0.004 ± 0.018 in the control group. Longitudinal mixed model indicated that there was no statistical difference in BCVA before and after the treatment ($P = .994$).

• **CHANGE IN AL AND SE:** After 12 months, the average AL change in the RLRL group was –0.11 ± 0.25 mm, and

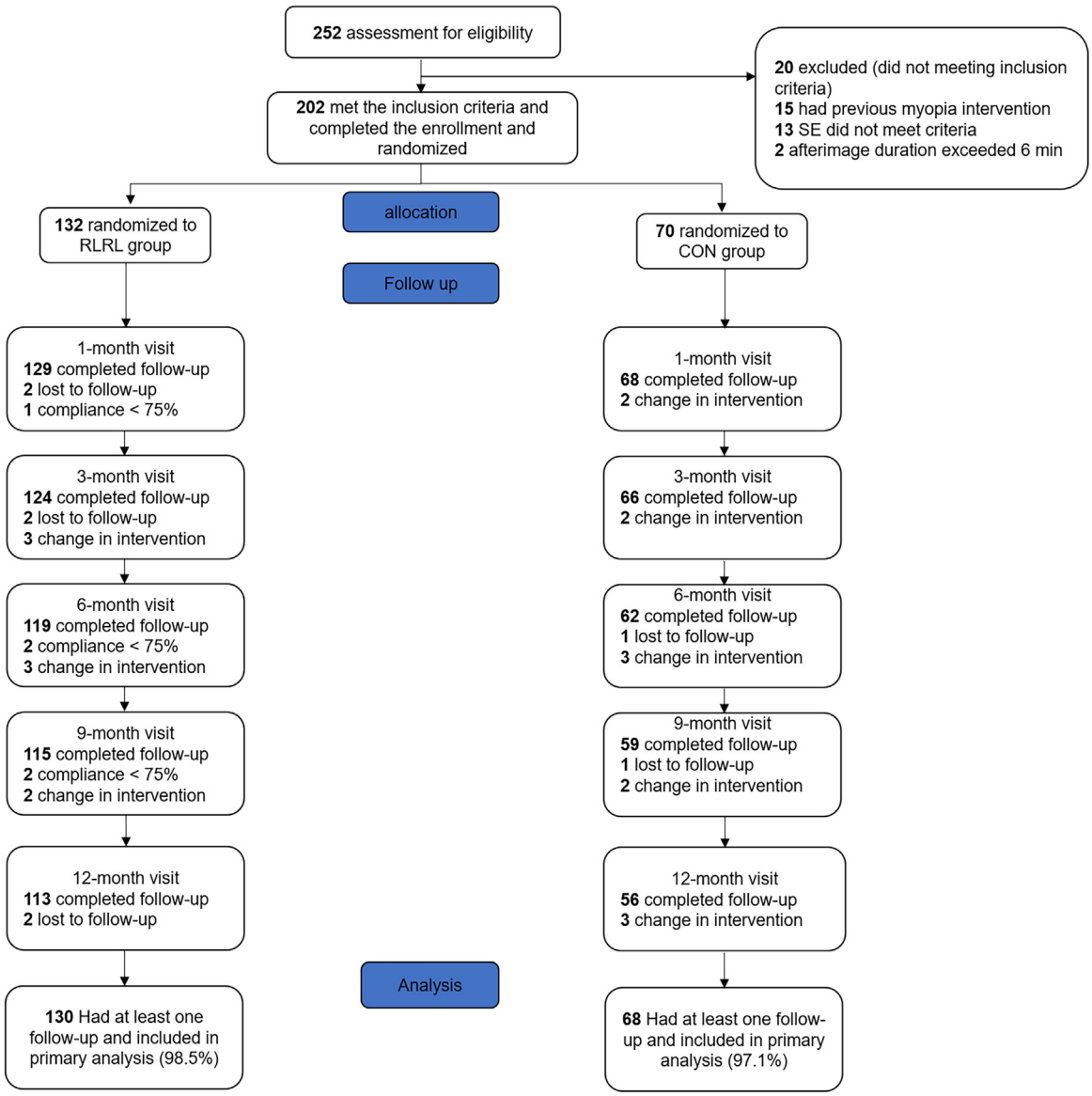

FIGURE 1. Flow diagram of the study. SE = spherical equivalent.

the change in the control group was 0.32 ± 0.09 mm ($P < .001$). The detailed changes of AL in the 2 groups at each follow-up time point are shown in Figure 2A. An AL shortening greater than 0.05 mm was defined as significant shortening. In the RLRL group, the time point with the maximum AL shortening was at 9 months after treatment, which was –0.13 ± 0.20 mm, and there was a 63% ratio of AL shortening >0.05 mm. There were still 59% of subjects with significant AL reduction at 12-month follow-up.

After 12 months, the SE change in the RLRL group was 0.18 ± 0.63 D, and the change in the control group was –0.80 ± 0.42 D ($P < .001$). The detailed changes of SE in the 2 groups at each follow-up time point are shown in Figure 2B.

• **CHANGE IN ChT AND RT:** Figure 3A illustrates the changes in ChT within the central foveal, parafoveal, and perifoveal circle sectors of the ETDRS grid at each follow-up. Overall, in the RLRL group, 3 sectors of the choroid were significantly thicker at 1 month of treatment. In the central foveal circle, the ChT thickened by 17.40 ± 25.61 μm; in the parafoveal circle, the ChT thickened by 18.52 ± 25.14 μm, and in the perifoveal circle, the ChT thickened by 18.10 ± 25.56 μm (all $P < .001$), which stabilized at 1-month follow-up. At 12 months of treatment, ChT in the central foveal circle thickened by 21.02 ± 33.59 μm, ChT in the parafoveal circle thickened by 21.40 ± 32.01 μm, and in the perifoveal circle ChT thickened by 19.66 ± 29.99 μm (all $P < .001$). There was no significant difference in changes among the 3 sectors ($P > .999$). In the control

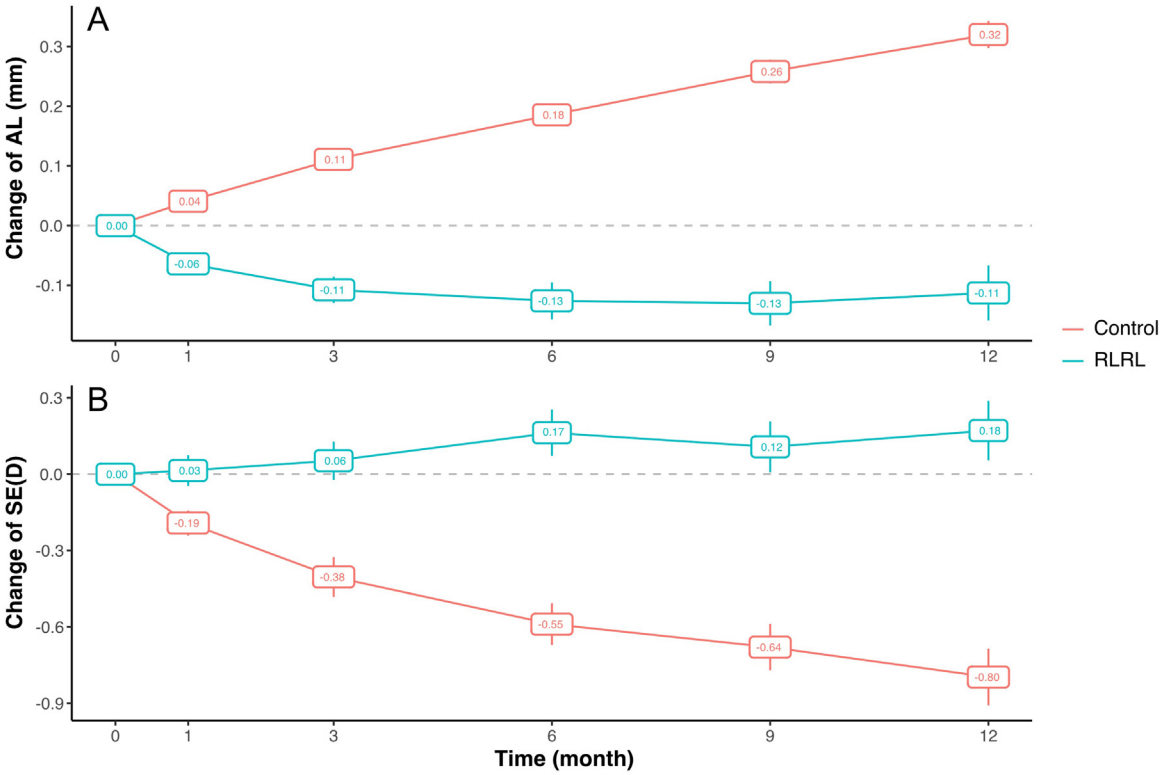

FIGURE 2. Time courses of changes in AL (A) and SE (B) in the 2 groups. Data shown by mean ± 95% CI. AL = axial length; SE = spherical equivalent.

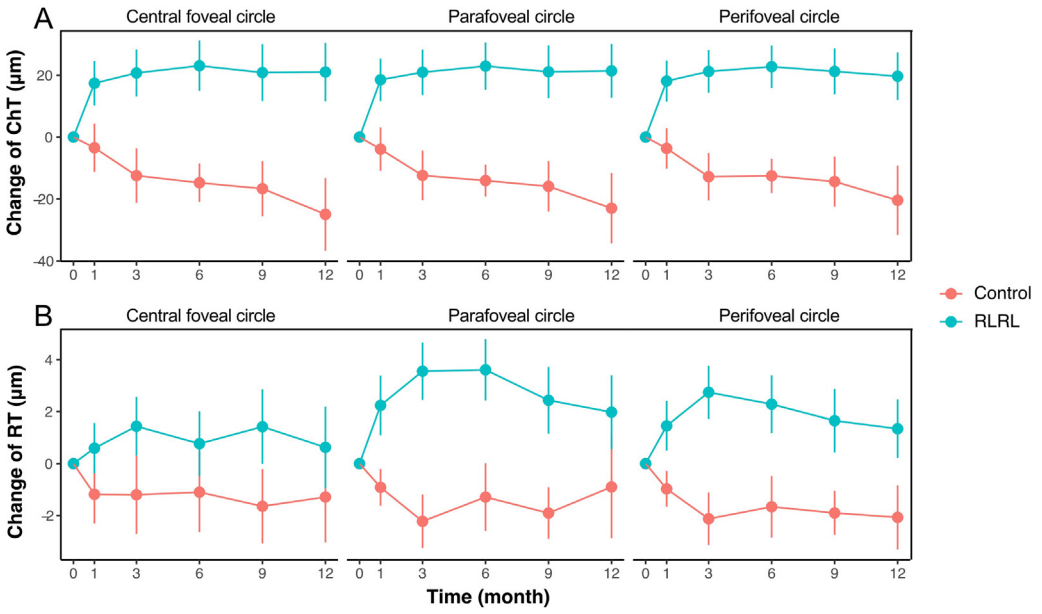

FIGURE 3. Time courses of changes in ChT (A) and RT (B) in central foveal, parafoveal, and perifoveal circle sectors between control group and repeated low-level red-light (RLRL) group. Data shown by mean ± 95% CI. ChT = choroidal thickness; RT = retinal thickness.

group, all sectors of the ChT were significantly thinner at 12 months. In the central foveal circle, ChT thinned by –24.77 ± 27.50 μm; in the parafoveal circle, ChT thinned by –22.84 ± 27.67 μm; and in the perifoveal circle, ChT thinned by –20.56 ± 27.99 μm (all $P < .001$).

The detailed changes of RT in central foveal, parafoveal, and perifoveal circle sectors of the ETDRS grid at each follow-up are shown in Figure 3B. In the RLRL group, the retina thickened significantly from 0 to 3 months of treatment. In the central foveal circle, RT thickened by 1.44 ± 4.02 μm ($P = .015$); in the parafoveal circle, RT thickened by 3.56 ± 4.24 μm ($P < .001$); and in the perifoveal circle, RT thickened by 2.75 ± 4.74 μm ($P <= .001$). There was a trend of thinning in RT from 3 months to 12 months of treatment. At 12 months of treatment, RT in the central foveal circle was 0.63 ± 5.58 μm thicker than at baseline ($P = .435$), RT in the parafoveal circle thickened by 1.98 ± 5.96 μm ($P = .009$), and RT in the perifoveal circle thickened by 1.34 ± 6.05 μm ($P = .023$). In the control group, at 12-month follow-up visit, there were no significant RT changes in the central foveal circle ($P = .109$) and parafoveal circle ($P = .339$); RT in the perifoveal circle thinned, which thinned by –2.16 ± 5.67 μm on average ($P = .002$). The details of ChT and RT changes were summarized in table S1.

• **CHANGES IN ANTERIOR SEGMENT PARAMETERS:** Data of anterior segment parameters (central corneal thickness, K_1, K_2, lens thickness, anterior chamber depth) are summarized in Table 3. There were no statistically significant differences in anterior segment parameters before and after treatment (all $P > .05$).

• **MULTIVARIATE LINEAR REGRESSION MODEL:** A linear regression model was used to identify the risk factors or determinants for AL changes where the baseline parameters (including age, gender, AL, ChT, and RT) and the changes in ChT and RT at 1, 3, and 6 months were included. The results indicated that only ChT changes in the foveal sector at 1 month and RT changes in the perifoveal sector at 1 month were significantly related to AL changes at 12 months (Table 4). After 1 month of treatment, a greater magnitude of foveal ChT and peripheral RT thickening were observed, suggesting a more effective AL control effect.

• **FACTORS ASSOCIATED WITH ChT AND RT THICKENING:** Multiple regression results showed that the change of ChT at 12 months was only negatively correlated with the baseline ChT (central foveal circle: $\beta = –0.203$, $P = .010$, parafoveal circle: $\beta = 0.186$, $P = .023$, perifoveal circle: $\beta = 0.257$, $P = .002$). The change of RT at 12 months was not correlated with any factors of the included covariates.

• **SENSITIVITY AND SUBGROUP ANALYSES:** The results of age, gender, AL, SE, ChT, and RT in different RLRL subgroups divided by AL changes are summarized in Table 5. The results demonstrated that participants who achieved greater than 0.05 mm AL shortening had thinner baseline ChT (all $P < .001$), whereas there were no statistically significant differences in other parameters (all $P > .05$). Baseline subgroup analyses were conducted to compare the myopia control effect (AL changes) in participants with varying baseline SE values and in different age groups. The AL changes in participants with varying baseline SE values (–6.00∼–8.00 D vs <–8.00 D) and in different age groups (7-9 years vs 10-12 years) did not show significant differences (Table 6).

• **SAFETY:** Two senior specialists in fundus diseases diagnosed the follow-up OCT results. A third specialist was hired for diagnosis when there were conflicting diagnoses between the 2 senior specialists. There were no significant changes in the fundus structure during the entire study, and no participants reported an afterimage exceeding 6 minutes or a decrease in best-corrected visual acuity.

DISCUSSION

This study provided evidence supporting that RLRL can effectively delay the progression of myopia in high myopic children. After 12 months of RLRL treatment, it showed AL shortening and SE regression, which may be related to thickening of the retina and choroid.

• **RLRL EFFECT IN HIGH MYOPIA:** In recent years, the phenomenon of AL shortening has been reported in myopia intervention methods, such as orthokeratology lenses and low-dose atropine.[19,20] Considering the physical growth in the AL and the difference among the myopic intervention methods, this phenomenon was weak and had a less proportion.[19,21,22] RLRL showed a greater magnitude of AL shortening, suggesting it was an effective myopia control intervention.[9,10,23] In the premyopia and mild myopia groups, AL usually reached the maximum shortening at 1 to 3 months of treatment. The average AL shortening was 0.02 to 0.06 mm, and 23% to 40% of individuals had AL shortening over 0.05 mm and then changed to an elongation trend. At 12 months, 13% to 22% of participants still had axial shortening exceeding 0.05 mm.[9,10,21,23] In high myopia (the cutoff SE ≤ –4.00 D), the change in AL was –0.06 mm in the RLRL group and 0.34 mm in the control group at 12-month follow-up. Additionally, 50.3% of the intervention group were experiencing AL more than 0.05 mm after 12 months.[13] In our study with SE ≤ –6.00 D, we found that children with high myopia showed a maximum of 0.13 mm AL shortening at 9 months of treatment, and 63% of the subjects had AL shortening >0.05 mm. At 12

TABLE 3. Time Courses of the Change of Anterior Segment Parameters Between Repeated Low-Level Red-Light Group and Control Group

Time/Visit	Mean (95% CI)		Mean Difference (95% CI)	*P*
	RLRL	Control		
Change of ACD, mm	**(N = 130)**	**(N = 68)**		
1 mo	–0.003 (–0.007 to 0.001)	–0.003 (–0.011 to 0.005)	0.000 (–0.008 to 0.008)	.222
3 mo	–0.009 (–0.013 to –0.005)	–0.011 (–0.021 to –0.001)	0.002 (–0.008 to 0.012)	
6 mo	–0.016 (–0.020 to –0.012)	–0.016 (–0.028 to –0.004)	0.001 (–0.011 to 0.013)	
9 mo	–0.013 (–0.019 to –0.007)	–0.016 (–0.029 to –0.003)	0.003 (–0.011 to 0.017)	
12 mo	–0.011 (–0.017 to –0.005)	–0.013 (–0.026 to 0.000)	0.002 (–0.012 to 0.016)	
Change of LT, mm	**(N = 130)**	**(N = 68)**		
1 mo	–0.006 (–0.014 to 0.002)	0.002 (–0.024 to 0.029)	–0.008 (–0.035 to 0.019)	
3 mo	0.001 (–0.012 to 0.014)	0.002 (–0.030 to 0.034)	–0.001 (–0.032 to 0.030)	
6 mo	0.003 (–0.008 to 0.013)	0.007 (–0.045 to 0.059)	–0.004 (–0.053 to 0.045)	.807
9 mo	–0.005 (–0.018 to 0.007)	0.010 (–0.028 to 0.049)	–0.015 (–0.054 to 0.024)	
12 mo	–0.003 (–0.018 to 0.013)	–0.001 (–0.037 to 0.034)	–0.002 (–0.039 to 0.035)	
Change of CCT, μm	**(N = 130)**	**(N = 68)**		
1 mo	0.685 (0.311-1.059)	0.368 (–0.004 to 0.740)	0.317 (–0.210 to 0.844)	.631
3 mo	0.546 (0.111-0.981)	0.309 (–0.096 to 0.714)	0.237 (–0.359 to 0.833)	
6 mo	0.608 (0.077-1.139)	0.471 (–0.139 to 1.081)	0.137 (–0.672 to 0.946)	
9 mo	0.738 (0.175-1.301)	0.603 (–0.052 to 1.258)	0.136 (–0.726 to 0.998)	
12 mo	1.031 (0.453-1.609)	1.015 (0.290-1.740)	0.016 (–0.911 to 0.943)	
Change of K_1, D	**(N = 130)**	**(N = 68)**		
1 mo	0.003 (–0.009 to 0.015)	–0.009 (–0.025 to 0.007)	0.012 (–0.008 to 0.032)	.801
3 mo	–0.002 (–0.014 to 0.010)	–0.024 (–0.042 to –0.006)	0.022 (0.000-0.044)	
6 mo	–0.018 (–0.032 to –0.004)	–0.022 (–0.040 to –0.004)	0.005 (–0.017 to 0.027)	
9 mo	–0.024 (–0.040 to –0.008)	–0.041 (–0.063 to –0.019)	0.017 (–0.010 to 0.044)	
12 mo	–0.029 (–0.045 to –0.013)	–0.042 (–0.064 to –0.020)	0.013 (–0.014 to 0.040)	
Change of K_2, D	**(N = 130)**	**(N = 68)**		
1 mo	0.004 (–0.014 to 0.022)	–0.006 (–0.016 to 0.004)	0.010 (–0.010 to 0.030)	.839
3 mo	0.014 (–0.006 to 0.034)	0.002 (–0.012 to 0.016)	0.012 (–0.012 to 0.036)	
6 mo	0.010 (–0.012 to 0.032)	0.004 (–0.012 to 0.020)	0.006 (–0.021 to 0.033)	
9 mo	0.009 (–0.013 to 0.031)	0.002 (–0.012 to 0.016)	0.007 (–0.018 to 0.032)	
12 mo	0.016 (–0.008 to 0.040)	0.004 (–0.012 to 0.020)	0.012 (–0.015 to 0.039)	

ACD = anterior chamber depth; CCT = central corneal thickness; K_1 = flat meridian; K_2 = steep meridian; LT = lens thickness; RLRL = repeated low-level red-light.

months, 59% of the children still had a shortened AL of more than 0.05 mm, and the average AL change was still 0.11 mm shorter than before treatment. We also speculated that RLRL may have varying treatment effects in the different myopia groups. Our recent research showed that after RLRL treatment, children with mild to moderate myopia had better control effects on AL and SE compared with premyopic children.[12] The differences of RLRL treatment effect among individuals with high and mild myopia should be confirmed in future studies. To our knowledge, this is the first research to investigate the average AL shortening and SE decrease after 1 year of intervention for high myopia – 6.00 D or worse. In previous studies, other interventions showed a myopia control effect from 58% to 71%.[24,25] The results of this study indicate that compared with the control group with single-vision spectacles, the control effects of AL and SE were 134% and 123%, respectively. This suggested that RLRL may hold a higher potential as an intervention to control high myopia.

• **THICKENED CHOROID AND RETINA:** Choroidal thickening was considered one of the reasons for AL shortening caused by RLRL.[15] Previous studies showed that choroidal blood perfusion could be enhanced after RLRL treatment.[26,27] This was also one of the hypotheses for myopia control via RLRL to delay the progression of myopia. It has been indicated that the AL-associated reduction in ChT was most marked in the subfoveal sector and decreased toward the periphery.[16] In our study, there were no statistically significant differences in changes of choroidal thickening from central to peripheral sectors after RLRL. After 1 month of treatment, the change peaked and then stabilized. This condition was different from the changes in mild myopia, which in those myopia groups, changes in choroidal

TABLE 4. Details of Multivariate Linear Regression Model for Association Between Potential Factors and Changes in Axial Length Over 12 Months in RLRL Group

Variables Included	β (95% CI)	P
AL baseline	−0.091 (−0.269 to 0.087)	.207
Gender	−0.140 (−0.363 to 0.082)	.468
Age	0.049 (−0.007 to 0.105)	.109
ChT-cen-0m	0.001 (−0.007 to 0.009)	.706
△ChT-cen-1m	**−0.019 (−0.032 to −0.007)**	**.012[a]**
△ChT-cen-3m	0.015 (−0.008 to 0.038)	.249
△ChT-cen-6m	−0.005 (−0.024 to 0.014)	.788
ChT-para-0m	−0.006 (−0.018 to 0.006)	.527
△ChT-para-1m	0.018 (−0.009 to 0.044)	.303
△ChT-para-3m	−0.011 (−0.055 to 0.032)	.596
△ChT-para-6m	0.000 (−0.032 to 0.031)	.995
ChT-peri-0m	0.006 (−0.003 to 0.014)	.473
△ChT-peri-1m	0.000 (−0.019 to 0.019)	.784
△ChT-peri-3m	−0.008 (−0.038 to 0.021)	.712
△ChT-peri-6m	0.006 (−0.011 to 0.024)	.618
RT-cen-0m	0.000 (−0.007 to 0.006)	.898
△RT-cen-1m	0.009 (−0.016 to 0.034)	.403
△RT-cen-3m	0.000 (−0.024 to 0.023)	.912
△RT-cen-6m	−0.002 (−0.027 to 0.022)	.919
RT-para-0m	−0.005 (−0.021 to 0.011)	.513
△RT-para-1m	0.019 (−0.014 to 0.052)	.278
△RT-para-3m	0.000 (−0.046 to 0.045)	.991
△RT-para-6m	−0.005 (−0.057 to 0.047)	.611
RT-peri-0m	0.003 (−0.010 to 0.016)	.851
△RT-peri-1m	**−0.036 (−0.067 to −0.005)**	**.007[a]**
△RT-peri-3m	0.016 (−0.031 to 0.062)	.642
△RT-peri-6m	−0.003 (−0.056 to 0.051)	.812

AL = axial length; cen = central foveal circle sector; △ChT = choroidal thickness changes; para = parafoveal circle sector; peri = perifoveal circle sector; △RT = retinal thickness changes; 0m = visit before treatment; 1m,3m,6m = visit at 1, 3, 6 months.

[a]$P < .05$ was considered statistically significant.

TABLE 5. Baseline Data: Patients With Axial Length Shortening ≤0.05 mm Versus >0.05 mm at 12 Months (Mean ± SD)

Parameters	≤0.05	>0.05	P
	(N = 46)	**(N = 67)**	
Gender (M/F)	29/17	39/28	.697
Age (y)	10.1 ± 1.3	10.18 ± 2.0	.835
SE (D)	−7.64 ± 1.71	−7.94 ± 2.06	.416
AL (mm)	26.40 ± 0.85	26.65 ± 1.06	.183
OCT parameters	**(N = 27)**	**(N = 23)**	
ChT_ cen (μm)	279 ± 63	214 ± 60	<.001[a]
ChT_ para (μm)	280 ± 59	219 ± 54	<.001[a]
ChT_ peri (μm)	270 ± 49	218 ± 50	<.001[a]
RT_ cen (μm)	262 ± 17	265 ± 29	.734
RT_ para (μm)	322 ± 13	317 ± 15	.250
RT_ peri (μm)	277 ± 12	272 ± 12	.161

AL = axial length; cen = central foveal circle; ChT = choroidal thickness; F = female; M = male; OCT = optical coherence tomography; para = parafoveal circle; peri = perifoveal circle; RT = retinal thickness; SE = spherical equivalent.

[a]$P < .05$ was considered statistically significant.

thickening reached the maximum after RLRL at 1 month of treatment and then gradually retreated.[10,28] Several reasons may account for the variance in ChT response to RLRL between individuals with mild and high myopia. Children with high myopia had thinner ChT at baseline than children with low myopia.[16] Of note, the thinner the baseline ChT, the greater the degree of thickening after 12 months of RLRL treatment in this study. Thus, we speculated that greater improvements can be observed in ChT in participants with high myopia than in participants with mild myopia. On the other hand, there were significant relationships between ChT changes and treatment rates.[15] The treatment compliance of partial participants was <50% in Xiong and colleagues' study,[15] whereas in our study all participants had a compliance rate >75%. In addition, Xiong and associates speculated that the decrease in ChT after 3 to 6 months of treatment was due to a large dropout rate caused by Coronavirus Disease 2019, whereas ChT increase at 12 months of treatment was due to the increase in the follow-up rate.[15] Further research is needed to clarify the differences and causes of ChT changes in different myopic populations after RLRL treatment.

It is worth noting that the mechanism for AL shortening has not been confirmed. Numerous studies have indicated that ChT thickening cannot fully explain AL shortening.[9,10,12,15,27] Considering that the parameters in the anterior segment did not change (Table 3), a hypothesis was proposed that RLRL treatment might increase blood flow and metabolism of the fundus, thus ameliorating scleral hypoxia and restoring scleral collagen levels.[10,29,30]

Because of the relationship between AL and RT,[31] we also analyzed the changes in RT. After RLRL treatment, the retina was significantly thickened, and the changes in parafoveal and peripheral sectors were greater than in the center foveal sector. A previous study indicated that changes in retinal capillary blood density affected RT.[32] Compared with mild and moderate myopia, the density of retinal microvessels in high myopia further decreased, which was considered to be related to the increase in AL, whereas there were no significant differences in the foveal area.[32,33] In addition, there was a higher loss rate of capillary density in the deep capillary plexus (DCP) in high myopia. DCP contributes to photoreceptor inner segment oxygen requirements.[34-36] Thus, hypoperfusion of the DCP may result in poor nutrition and hypoxia in the outer retina and photoreceptors, which may cause chorioretinal atrophy.[35-37] Of note, red light could improve photoreceptor function by changing thresholds for tritan and protan function, which might modulate the metabolism of the fundus.[38] Considering that there were no RT changes reported

TABLE 6. Sensitivity Analysis of Mean Changes in Axial Length From Baseline at 12-Month Follow-up Among Different Age Groups and Severity of Myopia

		AL Change, mm, Mean (95% CI)			
		RLRL	Control	Mean Difference1	Mean Difference2
Age (y)	7-9	−0.094 (−0.151 to −0.037)	0.340 (0.305-0.375)	−0.434 (−0.501 to −0.367)	0.001 (−0.103-0.105)
	10-12	−0.138 (−0.214 to −0.062)	0.297 (0.272-0.322)	−0.435 (−0.515 to −0.355)	
SE (D)	−6.00∼−8.00	−0.092 (−0.143 to −0.041)	0.326 (0.295-0.357)	−0.418 (−0.477 to −0.359)	0.046 (−0.070-0.162)
	<−8.00	−0.157 (−0.253 to −0.061)	0.307 (0.280-0.334)	−0.464 (−0.564 to −0.364)	

AL = axial length; Mean Difference1 = (RLRL AL change) – (SV AL change); Mean Difference2 = (first age or SE group difference1) – (second age or SE group difference1); SE = spherical equivalent.

in any area after RLRL treatment in mild to moderate myopia or premyopia, this might be another reason that RLRL treatment may have a more significant effect in children with high myopia. In addition, previous studies have shown that exposure to intense light can cause inflammation and edema in the retina.[39,40] Although whether a long-term low-level laser irradiation could cause hazardous effects has not been confirmed, we cannot rule out that retinal thickening after RLRL treatment was caused by inflammation or edema. However, in a biomedical animal experiment, treatment with red light could increase RT by diminishing retinal inflammation.[41] Furthermore, the anti-inflammatory effect of RLRL may be various after a period of treatment due to the changes of inflammation levels.[42] Thus, further studies should confirm the mechanism of RT changes after RLRL treatment.

• **RELATIONSHIP BETWEEN AL CHANGES AND OTHER PARAMETERS:** The change in SE was affected by multiple factors, such as cornea, crystalline lens, and AL. Previous research proved that compared with SE, AL was a more satisfactory prediction parameter.[15] Therefore, AL was used as the main indicator for effect valuation. Our research indicated that in high myopia, in the central foveal sector, the 1-month ChT change was associated with AL changes in 12 months. This could be due to the stabilization of ChT changes after 1 month. We found there was a higher correlation between choroidal changes in the central foveal area and AL changes in children with high myopia compared with peripheral areas. We believed that this should be an indicator worth placing in a more important position for analyzing changes in AL in the future. In addition, our linear regression analysis highlighted that retinal changes in the perifoveal sector at the 1-month mark were significantly associated with long-term AL changes. This association suggested that modifications in the perifoveal retinal area could play a critical role in AL development. A previous study in myopic children indicated that peripheral RT decreased as AL increased.[43] Similar results were found in premyopic children, but no significant changes were observed in the foveal area.[44] In this study, the peripheral RT thinned more than the foveal area during follow-up was analyzed in the high myopia control group. It indicated that there might a potential influence of the peripheral retinal area on AL changes.

• **ADVERSE EVENTS:** In this study, no participants experienced any severe adverse reactions or issues. However, the safety of RLRL treatment for myopia was of prime importance because it involves the health and well-being of children. A recent study evaluated 2 RLRL devices that they may put the retina at risk of photochemical and thermal damages.[45] It is worth noting that the equipment we used met the latest American National Standards Institute Z80.36-2021 Group 1 device classification.[46] Although neither of the devices was used in our study, clinicians should be vigilant to safety assessments, for example, monitoring and setting the power of the equipment. In addition, a recent case report mentioned retinal damage after RLRL exposure,[47] which led to a decline in BCVA and prolonged afterimage.[45] Therefore, visual acuity and afterimage were important indicators that should be monitored cautiously to assess the safety of RLRL treatment during the follow-up. Although the damage described in the case study was able to be reversed, it was important for us to remain cautious and attentive regarding the potential risks. We should focus on accurately assessing high-contrast visual acuity and children's impression of afterimages, as well as enhancing effective supervision throughout therapy.[47]

• **RLRL AND HIGH MYOPIA CONTROL:** It has always been a clinical challenge to treat children with early-onset high myopia.[48] The possibility of fundus lesions in the future increased with the early onset of high myopia.[48] Research on myopia control for this demographic has been limited, yet available studies indicated that children with high myopia were more susceptible to complications compared with those with mild myopia. For example, orthokeratology lenses exhibited a higher proportion of corneal staining and a greater degree of visual quality decline in patients with high myopia.[49-51] RLRL has shown a better myopia control effect and is proposed as an innovative intervention for high myopia in children. If an intervention could keep AL relatively unchanged or even shortened, the risk of related

complications in high myopic children may be reduced. In addition, our previous research also pointed out that the effect of RLRL on shortening AL was applicable to adults.[27] Subsequent research should focus on whether RLRL can be applied to the treatment of adult myopic maculopathy. It is essential to approach the enthusiasm for RLRL's control effect with caution, because interventions with higher control rates might exhibit a stronger rebound effect upon discontinuation.[52] Further research should focus on the differences in the rebound effect in different individuals after discontinuation.

• **LIMITATIONS:** First, this study analyzed only the data in the 12-month follow-up, and the maintenance of the AL shortening effect in high myopic children was not yet clear. Subsequent research should focus on long-term effects. Second, this study did not analyze the rebound effect after discontinuation. Third, there was no appropriate sham equipment for the control groups. Because this was the assessor blinded study (single-blind), some participants in the control group were lost because of the urgent myopia control request by their parents and guardians.[53] Future studies should take into consideration a double-blind study design, possibly a sham control group, to avoid loss of participants. Fourth, we analyzed only OCT data from a single center, and further study will aim to increase the OCT sample size to confirm the relevant results. In addition, we did not analyze the changes in retinal capillary or microvascular density, and future research should focus on these changes to explore the reasons for retinal thickening. Last, we did not measure the changes in sclera. The sclera undergoes several changes during the development and progression of myopia, which are at first subtle at the gross anatomic level but may give way to more substantial changes when the pathological complications develop, such as maculopathies, retinal schisis, and detachment.[30] Measuring changes in the sclera is crucial for understanding the pathological changes in the fundus of patients with high myopia.

CONCLUSIONS

This study indicated that RLRL was an effective and safe method to delay the progression of myopia in children with high myopia –6.00 D or worse after 12 months of treatment. AL shortening is sustained over 12 months of treatment. This change may be related to choroidal and retinal thickening.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Guihua Liu: Writing – original draft, Methodology, Data curation. **Lin Liu:** Investigation, Data curation. **Hua Rong:** Formal analysis, Data curation. **Li Li:** Investigation, Data curation. **Xuan Liu:** Investigation, Data curation. **Zhiyang Jia:** Investigation, Data curation. **Hua Zhang:** Investigation, Data curation. **Biying Wang:** Writing – review & editing, Investigation. **Desheng Song:** Methodology, Formal analysis. **Jiamei Hu:** Investigation. **Xinrui Shi:** Investigation. **Bei Du:** Writing – review & editing, Project administration. **Ruihua Wei:** Writing – review & editing, Project administration, Funding acquisition.

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