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Effect of Myopic Defocus on the Retina and Choroid and Its Interaction with Defocus Regions, Diurnal Rhythm, and Accommodation

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Purpose: To explore the effect of defocus region and amount, diurnal rhythm, and accommodation on myopic defocus-induced changes in the retina and choroid.

Design: Four test lenses were used: single-vision soft contact lens (SVCL), bifocal spectacle lens (BSL) with +3.50 diopters (D) addition in the inferior visual field, defocus incorporated multiple segments lens (DIMS), and dual-focus contact lens (DFCL) with +2.00 D addition.

Participants: Twenty-one adults aged between 18 and 30 years, myopia between −1.00 D and −6.00 D, were included.

Methods: Four lenses were used in random order at 4 separate days for each participant. Participants underwent OCT and OCT angiography examinations after distance-viewing (4 m) and near-viewing (20 cm) for 20 minutes with 4 test lenses at both 10 AM and 5 PM.

Main Outcome Measures: Retinal and choroidal thicknesses (RT and ChT) and vessel density were assessed.

Results: The changes in RT, retinal and choroidal vessel density were not significantly different between lenses or times (all $P > 0.05$). Choroidal thickness changes differed between lenses after near-viewing in both the morning and evening and after distance-viewing in the morning (all $P < 0.05$). Compared with SVCL, BSL, DIMS, and DFCL achieved lower ChT reductions (all $P < 0.05$), and BSL showed least reduction. No lenses completely inhibited ChT thinning after near-viewing.

Conclusions: Myopic defocus inhibited choroid thinning more effectively in the morning, and provided sufficient defocus in the superior retina was more effective. The amount of lens defocus in this study (+3.50 D) was insufficient to inhibit choroidal thinning with 5 D accommodation completely.

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Supplemental material available at www.ophthalmologyscience.org.

The choroid is a layer of vasculature between the retina and sclera that provides blood supply to the outer retina and sclera.[1] As myopia progresses, the choroidal vessel layers thin, and choroidal blood perfusion decreases.[2−4] Previous studies have shown that a series of optical interventions imposing peripheral myopic defocus, such as orthokeratology, multifocal contact lenses, and spectacle lenses with lenslets, effectively slow myopia progression and increase the choroidal thickness (ChT).[5−7] In contrast to refractive error or axial length (AL), the choroidal response to defocus is rapid and reversible.[8]

The effect of myopic defocus on the choroid is influenced by many factors. Studies have found a positive dose−response relationship between the amount of defocus and choroid change, with larger defocus amounts having a stronger effect on the ChT.[7] A greater increase in mean macular ChT was observed when myopic defocus was imposed on the superior retina than on the full-field retina, that is the area of defocus distribution also had an impact on effect.[9] In addition, a significant diurnal variation has been observed in the choroid, thickening at night and thinning during the day.[10,11] Moderiano et al[12] found that imposing myopic defocus in the evening led to a greater increase in the ChT than in the morning. Chakraborty et al[13] also found that imposing myopic defocus for 12 hours changed the diurnal rhythm. Therefore, there may be an interaction effect between diurnal rhythm and myopic defocus on the choroid. Accommodation is one of the risk factors for myopia progression and can lead to ChT thinning.[14] Children spend a lot of time at near work when wearing lenses that introduce myopic defocus, the impact of defocus lenses on the choroid during accommodation is also worth exploring. Compared with the choroid, the retina, as a tissue that receives and encodes visual signals,

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has a relatively stable retinal thickness (RT) under the effect of myopic defocus.[15] However, few studies have focused on changes in retinal blood flow with defocus. This study aimed to explore the impact of the lens design, diurnal rhythm, and accommodation on myopic defocus-induced changes in retina and choroid.

Methods

Participants

Myopic adults were recruited from a population of university students. The inclusion criteria included age between 18 and 30 years, spherical equivalent refraction ranging between −1.00 diopters (D) and −6.00 D, astigmatism no more than 1.00 D, and best-corrected visual acuity of 0.1 logarithm of the minimum angle of resolution or better with a single-vision soft contact lens. The exclusion criteria included unable to tolerate wearing contact lenses, having used myopia control interventions within 1 year, and having eye diseases that could influence the results. This study was approved by the Ethics Committee of the Eye Hospital of Wenzhou Medical University, and all work was carried out following the tenets of the Declaration of Helsinki. Written informed consent was obtained from all study participants.

Test Lenses

Four test lenses were used in this study (Fig. S1, available at www.ophthalmologyscience.org): (1) single-vision soft contact lens (SVCL, Biotrue, Bausch & Lomb Inc); (2) bifocal spectacle lens (BSL, Essilor Inc): the lens was divided evenly into upper and lower parts, the upper part is for correcting distance refractive errors, and the lower part is the +3.50 D near addition; (3) defocus incorporated multiple segments spectacle lens (DIMS, Hoya Lens Thailand Ltd): the lens comprises a central zone with 9 mm in diameter for correcting distance refractive errors, and the peripheral part has multiple lenslets with +3.50 D positive power; and (4) dual-focus soft contact lens (DFCL, Misight, CooperVision Inc): the lens contains a central correction area of 3.36 mm surrounded by concentric zones of alternating distance and +2.00-D near powers.

Experimental Procedures

Each participant underwent 8 experimental sessions over 4 separate days, randomly using the 4 test lenses at both 10 AM and 5 PM. A test lens was added to the right eye while the left eye was closed and occluded.

Each session consisted of 5 experimental procedures (Fig. S2, available at www.ophthalmologyscience.org): (1) At the beginning of each session, participants were asked to undergo a 20-minute washout period to eliminate the impact of near work before the experiment, in which participant wore an SVCL and watched visual tasks on a television screen (97.5 × 64 cm) at a distance of 4 m. (2) Next, participants wore 1 of the test lenses and watched the 20-minute visual tasks on the television screen at 4 meters (distance-viewing) or on a phone screen (12 meters × 6.8 cm) at 20 cm (near-viewing) randomly. (3) After this procedure, participants underwent another 20-minute washout period with the SVCL. (4) After that, participants wore the same test lens to watch the visual tasks for 20 minutes at the other distance (20 cm or 4 m). (5) Finally, a last washout period was undertaken with the SVCL. The TV series "My Own Swordsman" was chosen as the visual task, with the screens placed at the primary gaze (i.e., straight ahead) for both distance- and near-viewing. Ocular measurements for the right eye were performed immediately after each visual task, measurements after step 1 were defined as the baseline. All measurements and viewings were performed in a dark environment, with the display as the only light source. Measurements of the choroid and AL were taken with the device positioned close to the participants, so the participant did not need to move. Two examinations lasted about 3 minutes, with a fixed sequence starting with choroid measurement followed by AL measurement.

Measurements

AL measurements were obtained by a Lenstar LS900 (Haag Streit AG). The average of 3 individual measurements that differed no more than 0.02 mm was taken as the final value.

Measurements of ChT and RT were obtained using swept-source OCT (Topcon Corporation). The swept-source OCT device contained a solid state laser with a scanning speed of 100 000 A-scans per second and a central wavelength of 1050 nm. Optical coherence tomography images were captured 3 times using the 12-line radial scan pattern centered on the fovea, with a length of 6 mm. The 2 masked and trained study staff manually corrected the choroid boundaries (choroidal−scleral and retinal−choroidal interfaces) in all OCT images and averaged them. The central 6 × 6 mm circular region was partitioned into 9 regions according to the ETDRS.[16] The 9 regions were classified as the 1-mm central foveal (C), nasal region between 1 mm and 3 mm (N3), superior region between 1 mm and 3 mm (S3), temporal region between 1 mm and 3 mm (T3), inferior region between 1 mm and 3 mm (I3), nasal region between 3 mm and 6-mm (N6), superior region between 3 mm and 6 mm (S6), temporal region between 3 mm and 6 mm (T6), and inferior region between 3 mm and 6 mm (I6).

The retinal and choroidal vessel densities were obtained with OCT angiography (OCTA) for 3 measurements according to the following parameters: fovea as the center, scanning range of 3 × 3 mm, scanning density of 512 × 512, and superimposition of each image by 4 B-scans. IMAGEnet 6 software, built in to the OCTA device, was used to analyze the OCTA images and automatically calculate the vessel density. The retinal superficial vessel density (RSVD), retinal deep vessel density (RDVD), choroidal vessel density (CVD) and choriocapillary vessel density (CcVD) at the C, N3, T3, S3 and I3 regions were obtained. Retinal superficial vessel density was defined from 2.6 μm below the internal limiting membrane to 15.6 μm below the inner plexiform layer-inner nuclear layer (IPL/INL) interface; RDVD was defined from 15.6 μm below the IPL/INL interface to 70.2 μm below the IPL/INL interface; CcVD was defined from 20.8 μm below the retinal pigment epithelium/Bruch's membrane interface; and CVD was defined from the retinal pigment epithelium/Bruch's membrane interface to the choroid/sclera interface (Fig. S3, available at www.ophthalmologyscience.org).

Statistical Analysis

SPSS 25.0 (SPSS Inc) was used for analysis. The measurement after the first washout in each session was defined as the baseline and was compared between lenses and times by repeated measures analysis of variance. Analysis of variance was performed to examine the changes after distance- or near-viewing from baseline for different lenses. For any variable with statistically significant main or interaction effects ($P < 0.05$), least significant difference post hoc tests were conducted. All data are expressed as the mean ± standard deviation.

Results

A total of 21 healthy adults (12 females) aged 23.7 ± 2.1 years with myopia of −3.60 ± 1.42 D and AL of 25.36 ±

1.06 mm participated in this study. The baseline AL, RT, ChT, and vessel density were not significantly different between lenses and times (both $P > 0.05$), except for differences between times for the RSVD at S3 ($P = 0.01$) and the RDVD at N3 ($P = 0.04$) and between lenses for the CVD at C ($P = 0.01$). Table 1 shows the baseline RT, ChT, and vessel density values obtained in the morning on the day of the test with SVCL.

Choroidal Thickness

Significant differences in ChT changes were observed between lenses after both distance- and near-viewing in the morning and only after near-viewing in the evening; there were no difference in changes between lenses after distance-viewing in the evening (Fig 4; Tables S2 and S3, available at www.ophthalmologyscience.org). Significantly greater ChT reductions were obtained with SVCL than with BSL, DIMS, and DFCL. In addition, the reduction in the ChT with BSL was significantly less than that with DIMS after distance-viewing in the morning (all $P < 0.05$).

Significantly greater reductions in the ChT were achieved with SVCL in the morning than in the evening in all regions after both near- and distance- viewing (all $P < 0.05$ by paired t test; Table S4, available at www.ophthalmologyscience.org). The reduction achieved with DIMS was greater in the morning than in the evening in the C and T3 regions after distance-viewing (both $P < 0.05$).

Choriocapillary and Choroidal Vessel Densities

Significant differences were observed in the changes in the CcVD and CVD between different regions both after distance and near-viewing (all $P < 0.05$). There were no significant differences between lenses or between times, or significant interaction between lenses and times, but a significant interaction effect between lens and region was found after distance-viewing (Fig 5, all $P < 0.05$).

Retinal Thickness and Vessel Density

There were no significant differences in the changes in the RT between different lenses, times or regions after distance- or near- viewing (Fig 6A–H). Significant differences in the changes in the RSVD were found between different regions after distance- and near- viewing and in the RDVD after near-viewing (Fig 6I–P, all $P < 0.05$). Differences between lenses were significant only in the RDVD after distance-viewing in the morning ($P = 0.02$), and least significant difference post hoc tests showed the changes with DFCL were greater than those with BSL and DIMS in the N3 region (both $P < 0.05$).

Axial Length

Analysis of the AL revealed no significant difference between lenses or between times, or significant interaction between lenses and times (Fig 7).

Discussion

All 3 lenses designed with myopic defocus, particularly the BSL, significantly inhibited the choroidal thinning caused by morning rhythms and accommodation with respect to the SVCL. However, all 3 lenses with defocus signals used in this study could not completely inhibit the choroidal thinning caused by +5 D accommodation, and the effect was slightly better in the morning than in the evening in some regions. Myopic defocus, diurnal rhythm, and accommodation had little influence on the RT and vessel density of the retina and choroid.

Of the 3 myopic defocus lenses, the BSL had the best efficacy in inhibiting choroidal thinning in all regions. BSL produce the same amount of defocus as DIMS (+3.50 D), but had better effect on the choroid than DIMS in all regions. Hoseini-Yazdi et al[9] reported that greater choroidal thickening was achieved in the vertical regions by exposure to +3 D superior retinal myopic defocus than by exposure to +3 D full-field myopic defocus, they have the same defocus amount in the superior retina, but the total defocus of full-field was twice that of the only superior retina. In addition, they did not make any measurements in the horizontal regions. In this study, the total amount of defocus was similar between BSL and DIMS, but the

Table 1. Baseline RT, ChT and Vessel Density Values Obtained with SVCL in the Morning

	RT (μm)	ChT (μm)	RSVD (%)	RDVD (%)	CcVD (%)	CVD (%)
C	232 ± 16	281 ± 81	20.79 ± 3.97	16.45 ± 3.54	56.17 ± 3.23	53.77 ± 7.52
N3	312 ± 15	255 ± 79	48.19 ± 1.69	49.53 ± 2.37	54.76 ± 3.92	51.07 ± 7.68
T3	301 ± 12	291 ± 75	46.89 ± 2.24	48.43 ± 2.53	55.65 ± 3.25	50.42 ± 4.53
S3	314 ± 12	286 ± 81	50.05 ± 2.43	51.42 ± 2.48	53.87 ± 2.78	47.41 ± 5.27
I3	312 ± 13	285 ± 84	47.39 ± 2.57	50.94 ± 3.40	54.04 ± 3.89	46.58 ± 5.93
N6	294 ± 11	213 ± 72	-	-	-	-
T6	257 ± 10	291 ± 68	-	-	-	-
S6	278 ± 10	286 ± 75	-	-	-	-
I6	262 ± 9	277 ± 80	-	-	-	-

All values are expressed as the mean ± standard deviation. C = 1-mm central foveal; CcVD = choriocapillary vessel density; ChT = choroidal thickness; CVD = choroidal vessel density; I3 = inferior region between 1 mm and 3 mm; I6 = inferior region between 3 mm and 6 mm; N3 = nasal region between 1 mm and 3 mm; N6 = nasal region between 3 mm and 6 mm; RDVD = retinal deep vessel density; RSVD = retinal superficial vessel density; RT = retinal thickness; S3 = superior region between 1 mm and 3 mm; S6, superior region between 3 mm and 6 mm; T3 = temporal region between 1 mm and 3 mm; T6 = temporal region between 3 mm and 6 mm.

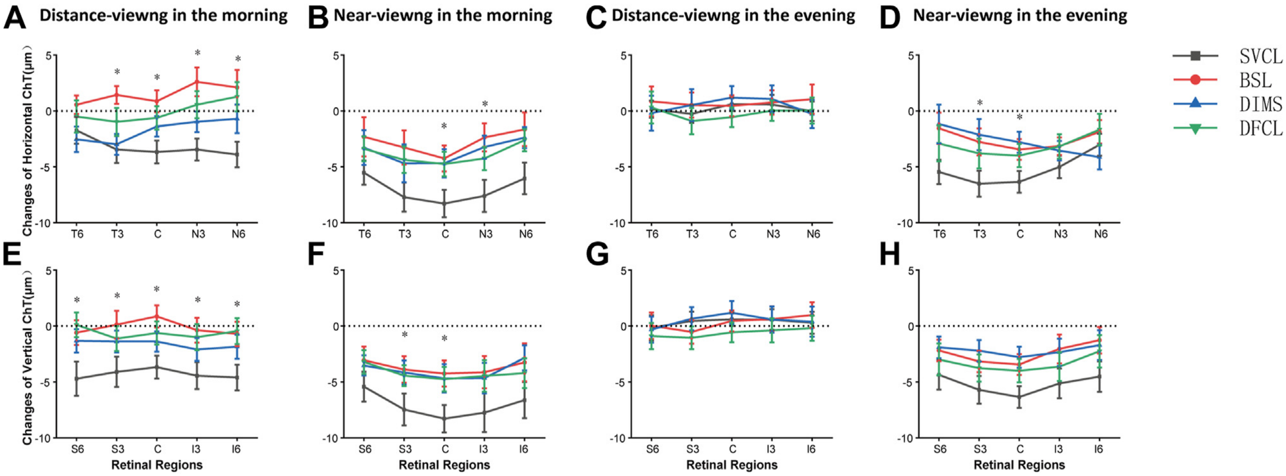

Figure 4. ChT changes in horizontal (A–D) and vertical (E–H) regions. Error bars represent 1 standard error of the mean. *Indicates a significant difference among different lenses ($P < 0.05$). BSL = bifocal spectacle lens; C = 1-mm central foveal; ChT = choroidal thickness; DFCL = dual-focus soft contact lens; DIMS = defocus incorporated multiple segments spectacle lens; I3 = inferior region between 1 mm and 3 mm; I6 = inferior region between 3 mm and 6 mm; N3 = nasal region between 1 mm and 3 mm; N6 = nasal region between 3 mm and 6 mm; SVCL = single-vision soft contact lens; S3 = superior region between 1 mm and 3 mm; S6, superior region between 3-mm and 6-mm; T3 = temporal region between 1 mm and 3 mm; T6 = temporal region between 3 mm and 6 mm.

defocus signals from BSL was concentrated on the superior retinal and in patches. When using a BSL, the imaging in the retina is half clear and half blurred, whereas the imaging with DIMS in the retina is uniform.[17] We speculate there are 3 possible reasons. One is that the superior retina was more sensitive to the defocus signals than other regions, BSL had more signals than DIMS in the superior retina. It is also possible that the defocus signals in patchy that can form a focal point had better effect than scattered defocus signals that cannot form a focal point. Another reason is that the retina might be more sensitive to myopic defocus under competitive defocus, like the upper and lower part of the BSL.[18] However, previous clinical trials showed that bifocal spectacle lenses have not been more effective at preventing myopia progression than DIMS or Misight. In previous studies on myopia control with bifocal spectacle lenses, the additions were all less than +2.00 D, and a +1.50 D addition was commonly used.[19,20] However, a +3.50 D addition was used for comparison with DIMS in this study. This may be the reason why the results of this study differed from previous studies. The ChT changes caused by DIMS and DFCL were not

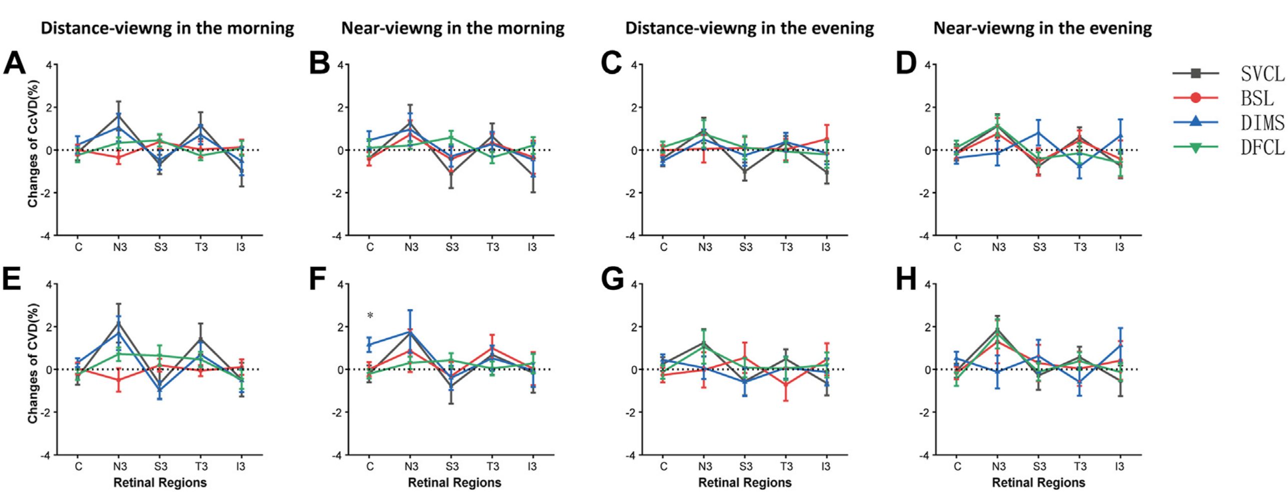

Figure 5. Changes in CcVD in the morning (A, B) and evening (C, D) and changes in CVD in the morning (E, F) and evening (G, H). Error bars represent 1 standard error of the mean. BSL = bifocal spectacle lens; C = 1-mm central foveal; CcVD = choriocapillary vessel density; CVD = choroidal vessel density; DFCL = dual-focus soft contact lens; DIMS = defocus incorporated multiple segments spectacle lens; I3 = inferior region between 1 mm and 3 mm N3 = nasal region between 1 mm and 3 mm; S3 = superior region between 1 mm and 3 mm; SVCL = single-vision soft contact lens; T3 = temporal region between 1 mm and 3 mm.

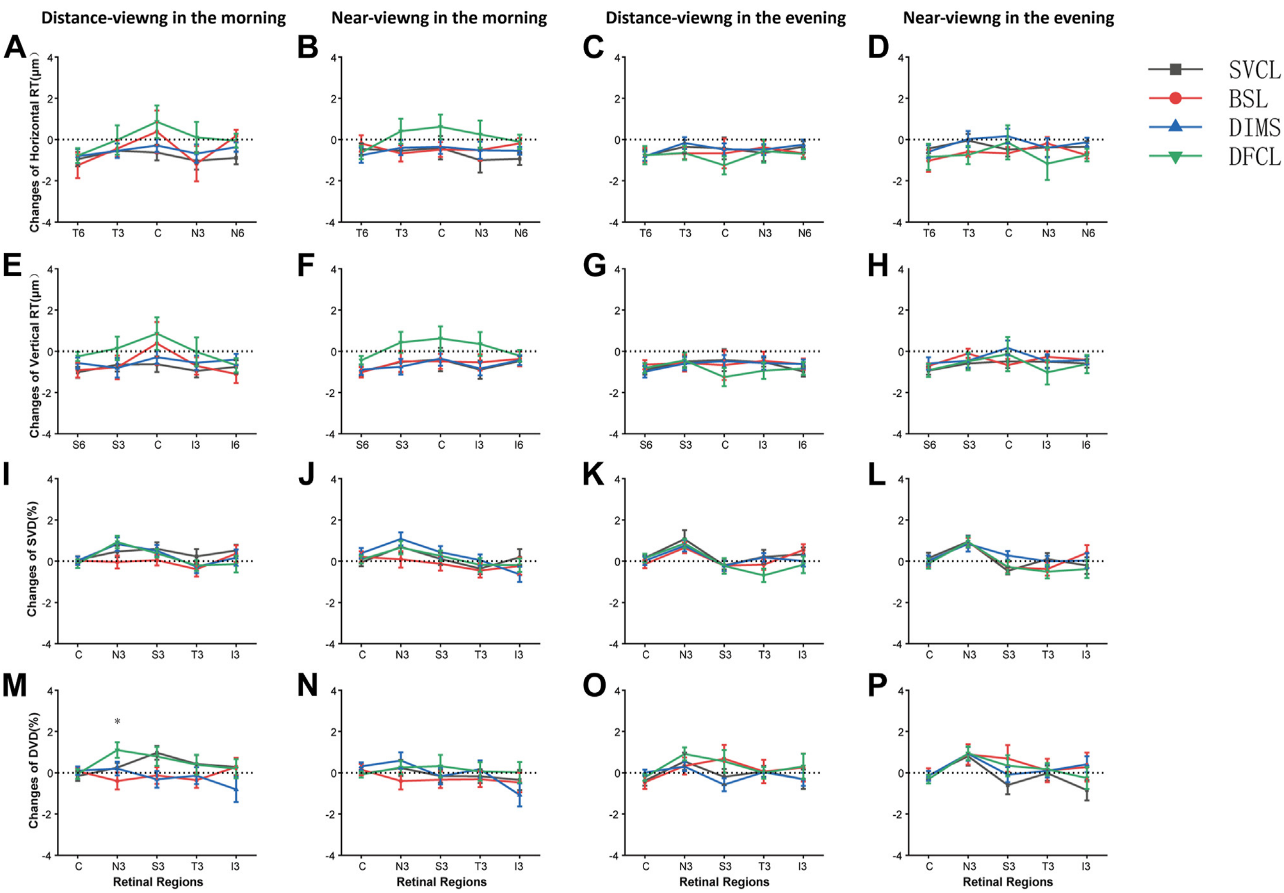

Figure 6. Changes in RT (A-H), RSVD (I-L) and RDVD (M-P) for different lenses, times and after distance- or near-viewing. Error bars represent 1 standard error of the mean. BSL = bifocal spectacle lens; C = 1-mm central foveal; DFCL = dual-focus soft contact lens; DIMS = defocus incorporated multiple segments spectacle lens; I3 = inferior region between 1 mm and 3 mm; I6 = inferior region between 3 mm and 6 mm N3 = nasal region between 1 mm and 3 mm; N6 = nasal region between 3 mm and 6 mm; RT = retinal thickness; RSVD = retinal superficial vessel density; RDVD = retinal deep vessel density; SVCL = single-vision soft contact lens; S3 = superior region between 1 mm and 3 mm; S6 = superior region between 3-mm and 6-mm; T3 = temporal region between 1 mm and 3 mm; T6 = temporal region between 3 mm and 6 mm.

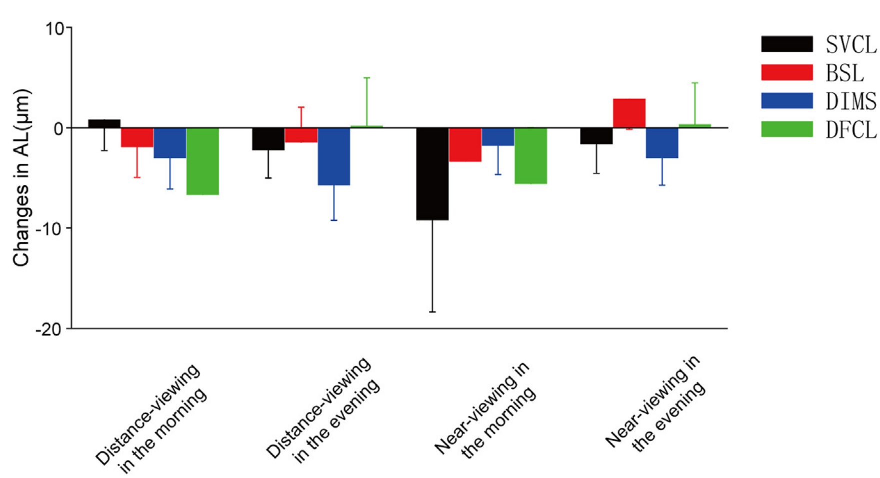

Figure 7. Axial length (AL) changes with different lenses. Error bars represent 1 SE of the mean; BSL = bifocal spectacle lens; DFCL = dual-focus soft contact lens DIMS = defocus incorporated multiple segments spectacle lens; SVCL = single-vision soft contact lens.

significantly different; therefore, no effect of defocus amount (+3.50 D vs. +2.00 D) on the choroid was found in this study. It could be attributed to the optical design of the DIMS and DFCL, along with their wearing effects. When wearing DIMS, there is a vertex distance between the spectacle lenses and the eyes. The defocus incorporated multiple segments lens features a dispersed lenslets design, whereas DFCL uses an intermittent ring design. Consequently, the defocus signals from DIMS reaching the retina may not exceed those from DFCL. Additionally, more participants are needed to verify this.

As in previous studies, we chose 10 AM and 5 PM because opposite ChT changes in diurnal rhythm are achieved at these times.[10] Significant difference was found between lenses in the morning but not in the evening after distance-viewing. There were 2 possible conjectures. One is that the retina is less sensitive to defocus in the evening than in the morning. However, Moderiano et al[12] found that myopic defocus had greater effects in the evening, whereas hyperopic defocus was more effective in the morning. Another possible reason is that the effect of the lens can only be significant when there is choroid thinning. Therefore, after morning distance-viewing and both morning and evening near-viewing, defocus lenses can reduce thinning. This study also investigated the impact of circadian rhythm along on the choroid. Participants had distance-viewing in the morning with single-vision lenses showed significant choroid thinning, which represented the morning diurnal rhythm. However, the choroid did not show significant thickening with the evening diurnal rhythm. This would lead to a problem. The washout period was designed to have distance-viewing with single-vision lenses, but the circadian rhythms in the morning and evening may have different effects on the washout period, especially the morning circadian rhythms, which may lead to sustained thinning of the choroid. The comparison of different lenses is carried out through the same experimental process, including the washout period, and at the same time on different days. Although circadian rhythms may also cause changes in the choroidal thickness, the changes between different lenses are the same, which did not affect the comparison between lenses, but may have an impact on the comparison between the morning and evening. This is one of the limitations in this study, and a better washout method needs to be designed.

All 3 myopic defocus lenses significantly inhibited the choroidal thinning caused by accommodation with respect to the SVCL; however, none of the lenses could completely inhibit the thinning. The accommodative stimulus in this study was +5.00 D, whereas the defocus amounts of the lenses were +3.50 D and +2.00 D, which was insufficient to offset the effect of accommodation. Bao et al[21] demonstrated that the working distances when playing video games, writing, and reading was 21.3 ± 5.2 cm, 24.9 ± 5.8 cm, and 27.2 ± 6.4 cm, respectively, for myopic schoolchildren (6−13 years old), and gradually decreasing over time for reading and writing tasks. The results of this study suggest the necessity of considering the near work distance of children when designing the amount of defocus to impart to myopic control lenses.

There are some limitations in this study. First, the sample size in this study consisted of 21 participants, which is relatively small. However, this exploratory investigation provides new insights into the possible factors influencing the efficacy of myopia intervention based on induced myopic defocus signals. Second, we included myopic adults as participants, whereas defocus lenses are designed primarily for children. The study was designed to include adults because of strict experimental time and subject compliance requirements, but children and emmetropia may have different reactions.[22] Future studies should include children to determine whether they have the same responses to defocus as adults. Third, the visual task for near-viewing was set straight ahead, whereas, in real scenarios, most near work is performed while looking down and converging. Differences in eye position will change the defocus distribution, with more defocus in the nasal and inferior visual fields. This study used the primary gaze to determine the effect of accommodation alone, and the effect of near work in real life should be determined in future studies. Fourth, we only chose the superior retina to verify the effect of defocus region. However, previous studies have found that orthokeratology lenses have better myopia control effect when the lenses were decentration.[23] We speculate that sufficient defocus at the temporal retina would also have a better effect and should be verified in future studies. Fifth, the intervention time in this study was only 20 minutes, and it is possible that the effect of defocus signals on the choroid did not reach its peak. However, in the pilot study, we compared the changes in the choroid after intervention for 20 minutes, 40 minutes, and 60 minutes and found no difference. Therefore, we ultimately chose to intervene for 20 minutes. A 20-minute intervention cannot be associated with the impact of long-term intervention on myopia control, the results of this study do not demonstrate the effect of defocus on myopia control. However, due to the rapid response of the choroid, this study can explore the factors influencing the effect of defocus signal, and provide some ideas for the design and the use of defocus lenses. The last one is the need for improvement in the washout methodology, which has been mentioned above.

Conclusion

The choroid thinned less in response to myopic defocus in the superior retinal region than to full-field myopic defocus. Furthermore, exposure to myopic defocus in the morning could be more efficacious. A +3.50 D myopic defocus was insufficient to offset the effect of 20-cm near work. Thus, when designing lenses, we suggest ensuring sufficient myopic defocus signals in the inferior field, and the defocus amounts account for the near work distance of children. We also suggest that children wear lenses with myopic defocus for myopia control more in the morning and for near work.

Footnotes and Disclosures

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HUMAN SUBJECTS: Human subjects were included in this study. Written informed consent was obtained from each participant. This study was approved by the Ethics Committee of the Eye Hospital of Wenzhou Medical University (Approval number: 2022-005-K-03) and all work was carried out following the tenets of the Declaration of Helsinki.

No animal subjects were used in this study.

Author Contributions

Conception and design: Huang, Zhang, Chen, Bao

Data collection: Zhang, Li

Analysis and interpretation: Huang, Zhang, Li

Obtained funding: Bao

Overall responsibility: Huang, Bao

Abbreviations and acronyms:
AL = axial length; **BSL** = bifocal spectacle lens; **ChT** = choroidal thickness; **CcVD** = choriocapillary vessel density; **CVD** = choroidal vessel density; **D** = diopters; **DFCL** = dual-focus soft contact lens; **DIMS** = defocus incorporated multiple segments spectacle lens; **I3** = inferior region between 1 mm and 3 mm; **I6** = inferior region between 3 mm and 6 mm; **IPL/INL** = inner plexiform layer/inner nuclear layer; **N3** = nasal region between 1 mm and 3 mm; **N6** = nasal region between 3 mm and 6 mm; **OCTA** = OCT angiography; **RDVD** = retinal deep vessel density; **RSVD** = retinal superficial vessel density; **RT** = retinal thickness; **SVCL** = single-vision soft contact lens; **S3** = superior region between 1 mm and 3 mm; **S6** = superior region between 3 mm and 6 mm; **T3** = temporal region between 1 mm and 3 mm; **T6** = temporal region between 3 mm and 6 mm.

Keywords:
Myopic defocus, Choroid, Accommodation, Diurnal rhythm.

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