Subfoveal Scleral Thickness is Associated With Peripheral Retinal Changes in High Myopia in Children and Adolescents

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Research Article

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Abstract

Background This study aims to identify the risk factors in peripheral retinal changes (PRC) associated with high myopes among children and adolescents.

Methods This is a cross-sectional study on children and adolescents diagnosed with high myopia. The subjects involved underwent a series of ocular examinations, including the dilated fundus examination for PRC and the swept-source optical coherence tomography for foveal retinal, choroidal and scleral thickness measurement. Then, the variables were compared among the eyes with high risk, low risk, and no PRC. Spearman correlation was applied to evaluate the relationship between the parameters and the extent of PRC. Logistic regression was performed to identify the potential risk factors.

Results A total of 117 eyes from 117 subjects were recruited. The prevalence of PRC was 57.3% (67 eyes), while that of high-risk PRC was 22.2% (26 eyes). A number of significant differences were observed in the mean subfoveal scleral thickness, spherical equivalent refraction, and axial length among the eyes with high-risk, low-risk, and no PRC ($p < 0.01$, $p < 0.01$, $p = 0.048$, respectively). Compared with spherical equivalent ($r = 0.32$, $p < 0.01$) and axial length ($r = 0.18$, $p = 0.05$), subfoveal scleral thickness exhibited higher correlation coefficient with PRC ($r=-0.38$, $p < 0.01$). Subfoveal scleral thickness and spherical equivalent refraction were identified as the independent risk factors for both PRC and high-risk PRC.

Conclusion It was demonstrated that there was a correlation between subfoveal scleral thickness and PRC. The eyes with thinner subfoveal scleral thickness carried a higher risk of PRC.

Introduction

At present, myopia is known as the most common refractive error worldwide [1]. It is estimated that the number of myopia will reach 4.8 billion by 2050, with nearly one billion being highly myopic [2]. High myopia is not limited to a refractive problem. Instead, it carries an increased risk of chorioretinal leisions complications, including cataract, glaucoma, and chorioretinopathy. In some cases, they may even occur to youngsters, for example, retinal detachment, which has a potential to cause sight impairment[3, 4].

Peripheral retinal changes (PRC) is referred to as a group of disorders occurring at the peripheral retina. It is commonly found in highly myopic eyes. It was once reported that as high as 61.7% of the adolescents with highly myopic eyes suffered PRC in Hong Kong[5]. As for the PRC of some types, such as lattice degeneration (LD) and retinal breaks, it is highly likely that retinal detachment occurs [6–8]. It was previously reported that the prevalence of LD reached 16.9% in highly myopic Singaporeans [9] and 3.3% among the highly myopic adolescents in Hong Kong[5]. Given the high prevalence of PRC in high myopes, it is believed that understanding the risk factors in the development of PRC would be conducive to identifying these high-risk individuals and taking preventative measures to avoid the occurrence of retinal detachment for them.

Currently, the sclera is suggested to play a crucial role in the progression of myopia. In some histological studies, it has been found out that scleral thinning can occur to the posterior pole of highly myopic eyes in both human beings and animals, and posterior scleral thinning is considered as contributory to axial length elongation[10, 11]. In general, the retinal changes in high myopia are believed as resulting from the mechanical elongation of the scleral caused by the excessive axial elongation of the eyeball. In several studies, it has been demonstrated that the increased prevalence of PRC was associated with the rise of either axial length (AL) or spherical equivalent refraction (SER) [5, 12, 13, 9, 14]. Therefore, it is speculated in this study that the thinning of the posterior scleral causes the increase of axial length and elongation of the retinal, thus leading to peripheral retinal changes. Swept-source optical coherence tomography (SS-OCT) could be applied to achieve an *in vivo* visualization of the sclera[15–17]. Up to now, there have been plenty of studies investigating the scleral morphological changes in myopic eyes with SS-OCT [15, 18–20]. However, none of them focus attention on the correlation between sclera and PRC.

This study is purposed to identify the risk factors in PRC among the children and adolescents with high myopia, including subfoveal scleral thickness (SST), subfoveal choroidal thickness (SCT), foveal retinal thickness (FRT) and other ocular parameters.

Methods

Subject recruitment

This is a cross-sectional study conducted in Joint Shantou International Eye Center, Shantou University and Hongkong Chinese University, from Nov 2018 to Apr 2020. The children and adolescents who were highly myopic and aged from 7 to 17 were recruited. High myopia was defined as SER (spherical power + 1/2*cylindrical power) of -5.00D or higher[21]. The subjects with either past or present severe ocular diseases, such as manifest deviation, ptosis, glaucoma, cataract, other retinopathy except for PRC, media opacities or a medical history of ocular surgery were excluded from this study. In addition, the subjects unfit for the fundus examination were excluded as well. For the subjects with bilateral high myopia, only the eyes with higher SER were included in this study.

In line with the tenets of the Declaration of Helsinki, the study was granted approval from the Institutional Review Board. Written consent was obtained from their parents in advance.

Data Collection And Ocular Examination

The data used in this study, including age, gender, ethnicity, ocular history, systemic diseases, and the family history of high myopia, was recorded in detail. Besides, their heights and weights were also measured. All of the participants underwent a range of comprehensive ocular examinations, including uncorrected and best-corrected visual acuity (BCVA), intraocular pressure (IOP) measured by noncontact tonometer (TX-F, Canon, Japan), slit-lamp examination (BM900, Haag-Streit AG, Koeniz, Switzerland), axial length and corneal curvature measurement, refraction, fundus examination and SS-OCT.

Corneal Curvature, Axial Length And Refractive Error Assessment

Prior to cycloplegia, both axial length and corneal curvature were measured using ocular biometry (IOL Master 500, ZEISS, German). Refractive error was determined by an autorefractor machine after cycloplegia (KR-8 Topcon, Japan). Cycloplegia was induced by adding four drops of 0.5% Tropicamide, with a 5-min interval[22]. The pupillary light reflex and pupil size were examined at least 20 min after the last drop of Tropicamide was administered. The criterion of cycloplegia was determined as the absence of a pupillary light reflex and a pupil size of at least 6 mm. Subsequently, subjective cycloplegic refraction tests were conducted by the trained, certified study optometrists to achieve BCVA, with the results of subjective refraction taken as the final refraction for analysis.

Peripheral Retinal Changes Assessment

Dilated fundus examination was performed with binocular indirect ophthalmoscopy by an ophthalmologist (WZ). Then, widefield laser scanning ophthalmoscope (Daytona P200T, Optomap, German) imaging of the central fundus and the orientation of PRC were performed. Peripheral retinal changes were recorded and confirmed by the second opthalmologist (TS) before being classed as either high-risk or low-risk PRC depending on the predisposition of retinal detachment. High-risk PRC included LD, snail-track degeneration, retinal hole or tear, while low-risk PRC included white without pressure (WWOP), snowflake degeneration, microcystoid degeneration, peripheral pigmentary degeneration[8, 23–26].

Ss-oct Examination And Measurements

All the eyes were subject to examination by SS-OCT (DRI OCT-1 Atlantis, Topcon, Japan) according to the protocol of 12 mm line scan with an average of 128 consecutive, overlapping single B-scan OCT images. Besides, the line scan was made horizontal. An image quality score ranging from 0 to 100 was given by software for each volumetric OCT scan, with any scores below 60 excluded. There are also other significant image artifacts excluded from analysis, including(1) motion artifacts, (2) blur affecting 20% or more of the image (eg, due to tilted images, defocus, or axial movement), (3) signal loss (eg, due to eye blinking), or (4) poor centration (ie, fovea displaced from the center). After cycloplegia, the same examiner performed all the SS-OCT examinations. We recognized the fovea to be at the center of the vessel-free area during the scaning of the images. The fovea in the OCT images was defined as the area where the inner retinal layers (the nerve fibre layer, ganglion cell layer, inner plexiform layer and inner nuclear layer) were absent. FRT, SCT and SST were measured by a trained grader without knowledge of information about the participants. Retinal thickness was defined as the vertical distance between the internal limiting membrane and the outer border of the retinal pigment epithelium (RPE), choroidal thickness was defined as the vertical distance between the outer border of the RPE and the choroidal–sclera interface, while scleral thickness was defined as the vertical distance between the choroidal–sclera interface and the outer scleral border, as shown in Fig. 1. In order to determine the repeatability and reproducibility of SST measurement, a total of 23 OCT images randomly selected were measured by two ophthalmologists independently and twice by an ophthalmologist.

Statistical Analysis

All statistical analyses were conducted using SPSS version 19 (SPSS, Chicago, IL, USA). Bland–Altman analyses were carried out to assess the consistence between the intraobserver and the interobserver in SST, SCT and FRT measurement. The one-way analysis of variance (ANOVA) and Chi-square was conducted to analyze continuous variables and categorical variables respectively. Bonferroni method was adopted for the post hoc test. The correlation between FRT, SCT, SST and AL, SER as well as the correlation between PRC and AL, SER, SST were analyzed using Spearman correlation. Stepwise logistic regression was also performed for the potential risk factors of PRC and high-risk PRC. The level of $p < 0.05$ was considered as statistically significant.

Results

Baseline characteristics

Initially, there were 145 participants meeting the inclusion criteria and seven participants excluded for their inability to cooperate with the examinations. Besides, another twenty-one were excluded for the outer scleral border beyond recognition. Finally, 117 eyes of 117 participants were included in data analysis. Among them, 52 were right eyes (44.4%), and 65 were left eyes (55.6%). There were 56 boys (47.9%) and 61 girls (52.1%). All of the participants were Chinese. The baseline characteristics of these eyes are shown in Table 1. The mean age was 11.4 ± 3 years.

Table 1
Baseline characteristics of study eyes

Parameters	All	High-risk PRC	Low-risk PRC	Without PRC	p value
n	117	26	41	50	
Age (years)	11.4 ± 3.0	11.3 ± 2.9	12.0 ± 3.0	11.0 ± 2.9	0.33*
Gender (Male: Female)	56:61	13:13	18:23	25:25	0.84#
Height (cm)	146.2 ± 16.0	147.0 ± 16.0	145.3 ± 16.0	146.4 ± 16.2	0.79*
Weight (kg)	38.7 ± 12.4	39.4 ± 12.6	38.3 ± 11.6	38.7 ± 13.1	0.8*
Body mass index (kg/m2)	17.6 ± 3.1	17.7 ± 2.9	17.8 ± 3.1	17.5 ± 3.2	0.92*
Family history of high myopia	21 (17.9%)	8 (30.7%)	3 (7.3%)	10 (20.0%)	0.09#
Intraocular pressure (mmHg)	17.4 ± 2.8	18.0 ± 2.3	17.6 ± 2.9	17.0 ± 2.9	0.35*
Spherical equivalent (Diopter)	-9.0 ± 2.8	-10.6 ± 3.6	-9.0 ± 2.6	-8.2 ± 2.2	< 0.01*
BCVA (LogMAR)	0.21 ± 0.31	0.32 ± 0.46	0.18 ± 0.21	0.16 ± 0.27	0.11*
Axial length (mm)	26.77 ± 1.36	27.22 ± 1.74	26.86 ± 1.33	26.47 ± 1.09	0.048*
Corneal curvature (Diopter)	43.0 ± 1.1	42.9 ± 1.1	42.9 ± 1.1	43.2 ± 1.2	0.49*
Foveal retinal thickness (um)	212.9 ± 20.4	209.0 ± 17.9	211.7 ± 19.1	216.0 ± 22.6	0.37*
Subfoveal choroidal thickness (um)	183.7 ± 64.2	176.1 ± 65.7	175.5 ± 60.5	194.4 ± 66.0	0.27*
Subfoveal scleral thickness (um)	351.4 ± 51.5	328.1 ± 45.1	337.2 ± 42.9	375.3 ± 52.0	< 0.01*

PRC = peripheral retinal changes, BCVA = best-corrected visual acuity, * one-way ANOVA, # Chi-square

Figure 2 shows the repeatability and reproducibility of SST, SCT, FRT measurement. The mean difference between the intraobserver and the interobserver was 0.9μm (95% limits: -6.1 to 7.9) and − 0.1 (95% limits: -7.1 to 6.9), -0.9μm (95% limits: -13.5 to 11.6) and − 1.9 μm (95% limits: -14.5 to 10.6), 2.1 μm (95% limits: -26.3 to 30.5) and 1.1 μm (95% limits: -27.3 to 29.5)in SST, SCT and FRT respectively. The outer borders of sclera drawn manually were verified as reliable.

Frequencies Of Peripheral Retinal Changes

PRC was detected in 67 eyes (57.3%), and there were 26 eyes (22.2%) with high-risk PRC. The commonest PRC was WWOP, as observed in 31 eyes (26.5%). Snowflake degeneration, LD and Snail-track degeneration were observed in 29 (24.8%), 21 (17.9%) and 5 (4.3%) eyes, respectively. While retinal hole, microcystoid degeneration, peripheral pigmentary degeneration and retinal thinning were observed in 1 eye (0.8%), respectively. There was no retinal detachment, paving stone degeneration or retinal tuft in our subjects.

Comparisons Among Eyes With High-risk, Low-risk And Without Prc

Table 1 shows the mean values of parameters in the eyes with high-risk PRC, eyes with low-risk PRC and the eyes without PRC, respectively. The differences in mean SER (-10.6 ± 3.6, -9.0 ± 2.6, -8.2 ± 2.2), AL (27.22 ± 1.74, 26.86 ± 1.33, 26.47 ± 1.09), SST (328.1 ± 45.1, 337.2 ± 42.9, 375.3 ± 52.0) among the three groups were identified as significant (one-way ANOVA, $p < 0.01$, $p = 0.048$, $p < 0.01$, respectively). Though SCT in the eyes with high-risk PRC and eyes with low-risk PRC was thinner than without PRC, the difference was not found statistically significant. There was no significant difference observed either for age, gender, height, weight, BMI, the family history of high myopia, IOP, BCVA, corneal curvature, and FRT among the three groups (one-way ANOVA, $p > 0.05$).

The results of the post-hoc analysis was presented in Table 2. The eyes with high-risk PRC and the eyes with low-risk PRC had significantly thinner sclera than without PRC (328.1, 337.2 V.S 375.3, both $p = 0.001$). N significant difference was observed between the high-risk PRC group and the low-risk PRC group in both SST and AL. The eyes with high-risk PRC showed significantly higher SER and longer AL than without PRC ($p < 0.001$ and $p = 0.04$, respectively). In contrast, there was no significant difference found in SER and AL between the eyes with low-risk PRC and the eyes without PRC. However, a significant difference was observed in SER between the high-risk and low-risk PRC groups ($p = 0.02$).

Table 2
Pairwise comparisons between high-risk PRC, low-risk PRC, and without PRC in SER, AL, SST

	SER	AL	SST
High-risk PRC versus low-risk PRC	0.02	0.67	1
High-risk PRC versus without PRC	< 0.001	0.04	0.001
Low-risk PRC versus without PRC	0.63	0.53	0.001
PRC = peripheral retinal changes, SER = spherical equivalent refraction, AL = axial length, SST = subfoveal scleral thickness.			
The Bonferroni method was used for post hoc tests; the numbers are p-values.			

Correlation And Regression

Furthermore, Spearman's correlation was applied to explore the correlation between PRC and SST, SER, AL. SST ($r = -0.38$, $p < 0.01$) and SER ($r = -0.32$, $p < 0.01$) were found to be negatively correlated with PRC, respectively, while AL was observed to be positively associated with PRC ($r = 0.18$, $p = 0.05$). Besides, the correlation between SST and PRC was found closer than between PRC and AL or SER. The eyes with PRC showed thinner SST, higher SER and longer AL.

In addition, there was no correlation observed between FRT and SER or AL. However, SCT exhibited moderate correlation with both SER ($r = 0.59$, $p < 0.01$) and AL ($r = -0.624$, $p < 0.01$). While there was only weak correlation found between SST and AL ($r = -0.19$, $p = 0.04$).

According to stepwise logistic regression, SST and SER were independently and significantly associated with both PRC and high-risk PRC. Every 1μm increase in SST contributed to 1.8% and 1% reduction to the risk of PRC and high-risk PRC, respectively. Additionally, every one diopter increase in SER was associated with 16.6% and 21.1% decrease in the risk of PRC and high-risk PRC, respectively, as shown in Table 3.

Table 3
Risk factors for peripheral retinal changes and high-risk peripheral retinal changes by stepwise logistic regression

	Risk factors	OR (95% CI)	p-value
peripheral retinal changes	spherical equivalent refraction	0.834(0.710, 0.980)	0.028
	subfoveal scleral thickness	0.982(0.972, 0.991)	< 0.001
high-risk peripheral retinal changes	spherical equivalent refraction	0.789(0.678, 0.989)	0.002
	subfoveal scleral thickness	0.990(0.980, 1.000)	0.05

Discussion

To our knowledge, this is the first study exploring the correlation between PRC and foveal retinal, choroidal, scleral thickness in both children and adolescents. The eyes with PRC was found to have significantly thinner SST, higher SER and longer AL than without PRC. In contrast, SCT and FRT were identified as irrelevant to PRC. The correlations between PRC and SER, AL and SST were confirmed in univariate analyses. In stepwise logistic regression, SST and SER were taken as the independent risk factors for both PRC and high-risk PRC.

Different from most published studies focusing on the adult population, the study conducted on a young adult population in Singapore revealed that the prevalence of PRC in high myopes was 67.1%, and the most frequent PRC was WWOP (57.2%), followed by LD (16.9%) and retinal hole (4.4%)[9]. Lai et.al.

observed pigmentary peripheral retinal degeneration, WWOP, LD and retinal break in 37.7%, 21.1%, 13.2% and 6.2% highly myopic eyes in an adult population in Hong Kong, respectively [13]. In another study on an adolescent population in Hongkong, it was found out that the four most prevalent findings were WWOP (51.7%), microcystoid degeneration (5%), peripheral pigmentary degeneration (4.2%) and LD (3.3%) with PRC prevalence of 61.7%. Compared with prior literature, the frequency of PRC (57.3%) in our study was lower than in other reports, which may be attributed to the younger age of our study population compared with previous studies. The prevalence of PRC increases with the progression of myopia over time. Likewise, this also explains the lower prevalence of retinal hole or tear in our study (0.8%) despite the higher prevalence of LD (17.9%). There is barely vitreous liquefaction found in the children and adolescents with mild tractional forces to the retina, which may be another reason for the lower prevalence of retinal hole or tear.

In a number of studies, investigation has been conducted into the risk factors for PRC in highly myopic eyes. According to Cheng et al., an AL of 26.5mm or longer was the significant risk factor for PRC while it was not the case for SER[5], which is consistent with the results of a study conducted in Singapore[9]. In the research of Zhang et al, PRC was demonstrated as significantly associated with a longer AL and a higher SER[27]. In contrast, Celorio et al. reported that the peak prevalence of LD was related to the eyes with a range of AL from 26.0mm to 26.9 mm, which suggests an inverse relationship between the prevalence of LD and AL when the AL > 27.0mm[14]. The conflicting results of these studies might be attributable to the differences in the age spectrum of the study population. In our study, higher SER and longer AL were found to be associated with the increase of PRC in univariate analyses. Differently, SER rather than AL was the independent risk factor in stepwise logistic regression.

So far, the underlying mechanism of PRC in patients with high myopia is still not fully understood. A widely accepted view is that the mechanical elongation of the eyeball due to excessive axial elongation may be contributory to the development of PRC. Starting at the equator, the sclera thinning is most marked at the posterior pole owing to the axial elongation occurring in the course of myopization [28]. It is speculated that scleral thinning results from the mechanical elongation caused by axial elongation since the scleral volume showed no obvious increase during the process of myopization, which is accompanied by the remodeling of existing scleral tissue[29]. In our study, it was found out that the eyes with PRC had a thinner SST than the eyes without PRC. The significance of the correlation between PRC and SST was increased than between PRC and SER or AL. In stepwise logistic regression, SST was the risk factor associated with both PRC and high-risk PRC, which has not been reported yet. Considering the findings of our study and others, it is speculated that the equatorial expansion resulting from axial elongation produces mechanical tractional forces on a continued basis for the peripheral retina, thus promoting the development of PRC.

While choroidal thinning potentially results in the reduction to choroidal perfusion and ischemia, which may be related to PRC. As revealed by Ujiie, the thickness of the peripheral eyeball is small and vascular obstruction may occur due to the mechanical stretching during the axial elongation. It was also suggested that choroidal circulation allows the supply of blood for the total layer of the peripheral retina.

The retina will suffer damage when choroidal perfusion is reduced. Nonetheless, SCT in eyes with PRC was thinner than without PRC, despite no statistical significance. The findings of our study are consistent with that of Chen et al[9]. As we know, the choroidal blood vessels become increasingly thinner from the posterior pole to the periphery[30], which may make the peripheral blood vessels less able to withstand mechanically tractional forces. Thus, it is necessary to conduct a further study on peripheral choroidal thickness for confirming our speculation. In our study, the FRT was shown not to be significantly different among the three groups. It was reported that the occurrence of retinal thinning in the equatorial and retroequatorial region was attributed to a tube-like enlargement of the eyeball, and retinal thickness in the macular region was irrelevant to axial length[28], which may explain the lack of association between FRT and PRC. It should be emphasized that choroidal thickness of all subjects were measured after cyclopegia in our study. Choroidal thickness might be modified by cyclopegia reported by some studies, although the results were inconsisitent, one of them found a decrease of CT with cyclopegia[31]; another demonstrated an increase[32].

There are several limitations in our study. Firstly, only the children with high myopes were recruited, and the representation of AL and SST was restricted, which might be related to the weak correlation between SST and AL. Secondly, the exclusion of subjects with unrecognizable outer scleral border may lead to the underestimate of mean SST, especially in the eyes without PRC. Thirdly, this is a cross-sectional study, as a result of which causality cannot be confirmed.

In conclusion, SST is an independent risk factor for peripheral retinal changes. High myopes with thinning sclera may require detailed fundus examination, particularly in the peripheral retina. The SS-OCT measurement of subfoveal scleral thickness in high myopes would assist the identification of people at risk of peripheral retinal changes.

Declarations

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Ethics approval and consent to participate: All patients gave their informed consent for their anonymized data to be submitted for audit and publication. The Joint Shantou International Eye Center Institute Ethics

Committee approved this study.

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Competing interests: The authors declare that there is no conflict of interests.

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Figures

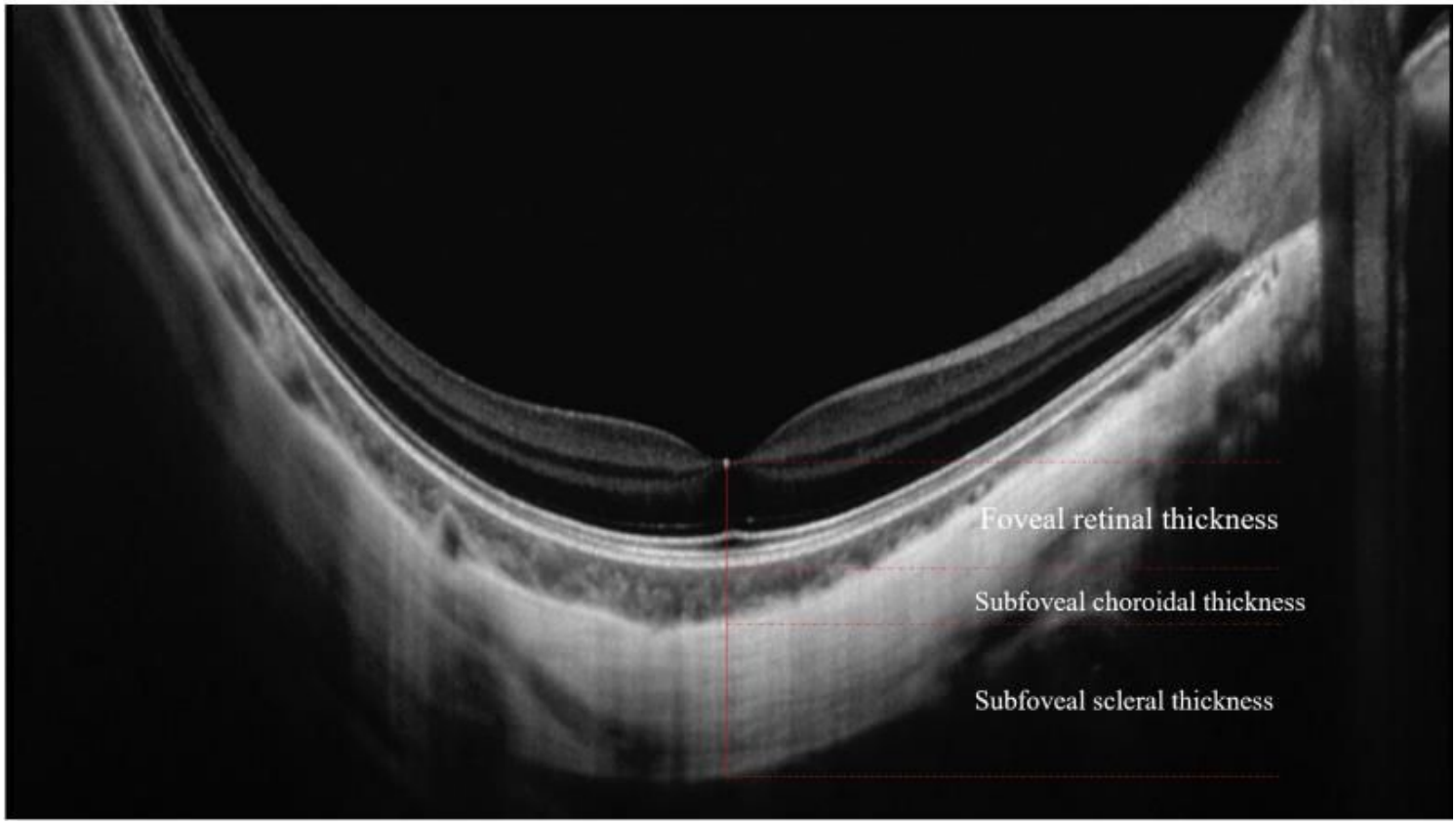

Figure 1

SS-OCT of a highly myopic eye, depicting the measurement of foveal retinal thickness, subfoveal choroidal thickness and subfoveal scleral thickness

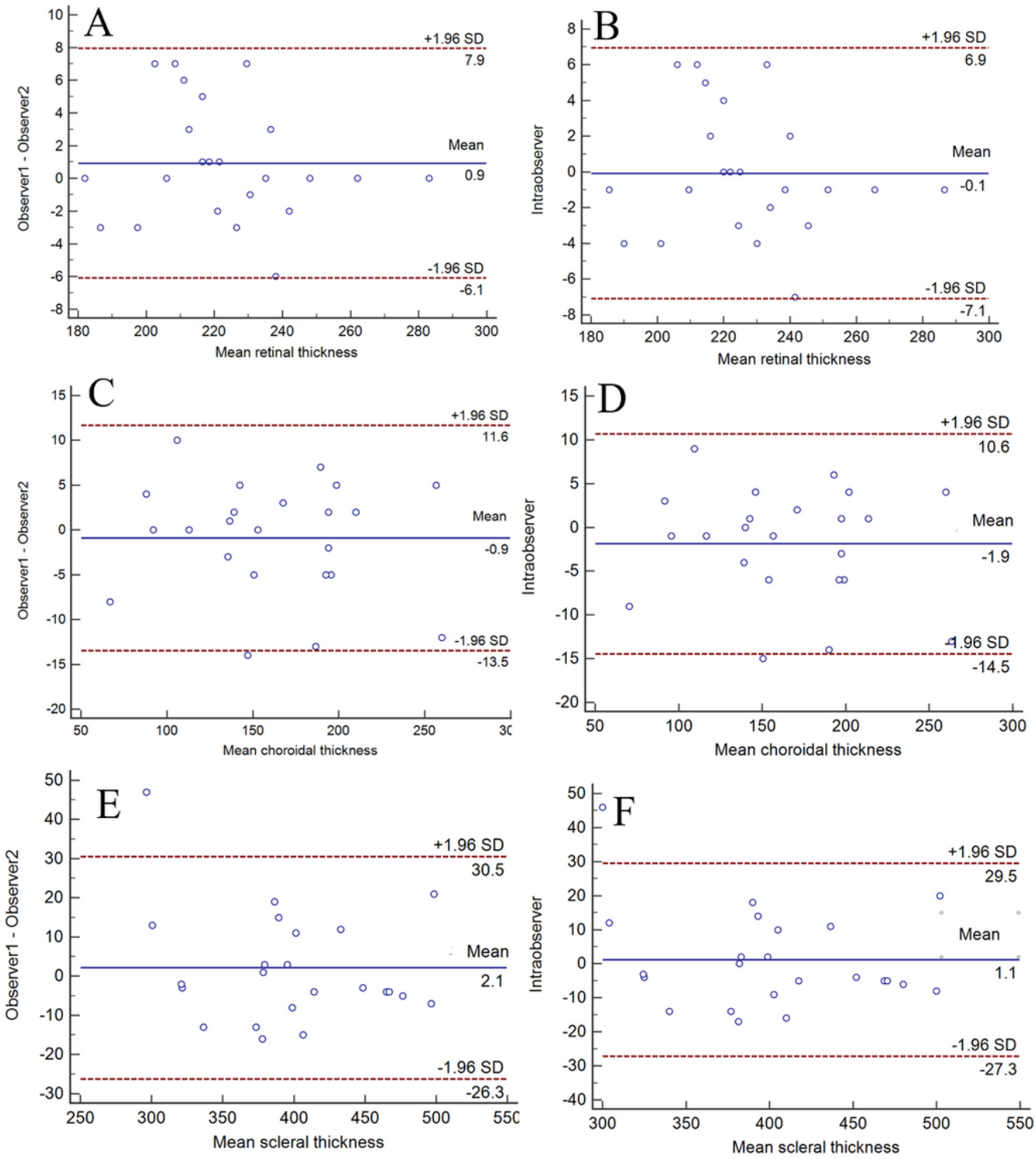

Figure 2

Bland-Altman plots show the intraobserver (a) and interobserver (b) agreements of the subfoveal scleral thickness□subfoveal choroidal thickness and foveal retinal thickness measurements.