sciendo
Polish Journal of Medical Physics and Engineering
The Journal of Polish Society of Medical Physics
ISSN 1898-0309, doi: 10.2478/pjmpe-2024-0026

December 2024
Vol 30, Issue 4

Scientific Paper

The effect of low and moderate myopia on corneal, retinal, and intraretinal layers' thickness by spectral optical coherence tomography

Karina Janina MACIEJEWSKA [1,ABCDF,*], Sara POKORZYŃSKA-ZELEK [2,BEF]

[1]*Faculty of Science and Technology, Institute of Biomedical Engineering, University of Silesia in Katowice, Katowice, Poland*
[2]*St. Barbara Provincial Specialist Hospital no. 5 in Sosnowiec, Sosnowiec, Poland*
[*]*Corresponding author: Dr. Karina Maciejewska; karina.maciejewska@us.edu.pl*

(received 16 April 2024; revised 6 August 2024; accepted 2 October 2024)

Abstract

Introduction: An important goal of biomedical physics and engineering is to study possible confounding factors in diagnosis or treatment to minimize erogenous interpretations due to overestimation or covering pathology-related changes. We aimed to examine the effect of refractive error on corneal thickness, retinal thickness (including its layers), and optic disc parameters in low myopia and moderate myopia, as compared to the emmetropic group.

Material and methods: Sixty eyes from 30 (18 women) young, healthy, physically active, non-smokers, with normal color perception, and no ophthalmological or neurological medical history Caucasians at the age of 24.6 ± 1.5 years were examined. The studied groups were defined based on the SE (spherical equivalent): emmetropia (–0.5 D ≤ SE ≤ 0.75 D, 20 eyes), low myopia (–3 D < SE < -0.5 D, 20 eyes), and moderate myopia (-6 ≤ SE ≤ -3 D, 20 eyes). Spectral optical coherence tomography imaging (SOCT) through SOCT Copernicus HR device (OPTOPOL Technology Sp. z o.o., Poland) was used.

Results: Corneal thickness, peripapillary RNFL thickness, and optic disc parameters didn't change between emmetropic, low myopia, and moderate myopia groups. However, macular retinal thickness decreased with increasing refractive error. Interestingly, particular retinal layers' thicknesses changed differently with increasing spherical equivalent (SE). A thickening of external macular retina layers was observed in the central and inner sectors, while a thinning of internal retinal layers was seen mainly in the outer ring when SE increased from emmetropia to moderate myopia.

Conclusions: Our findings suggest that changes in retinal thickness due to refractive error may appear even in earlier stages than high myopia. Moreover, different retina layers change differently with SE and not every sector behaves in the same manner. These results are especially worth noting, as they point out the necessity of taking into account different behaviors of retinal layers in low and moderately myopic eyes in interpreting the measurement results when diagnosing ocular pathologies or preparing ophthalmologic surgeries.

Keywords: spectral optical coherence tomography (SOCT); myopia; eye imaging; retina; cornea.

Introduction

The goal of using physics and engineering in medicine and biology is to apply physics principles, methods, and techniques in practice and research for the prevention, diagnosis, and treatment of human diseases in a very broad spectrum of branches. This paper is related to the use of a medical optical imaging method: spectral optical coherence tomography (SOCT), which is crucial in the diagnosis of eye disorders, evaluation of therapeutic methods, or visualization of surgical interventions. This technique allows researchers and clinicians to obtain non-invasively, with high-speed, high-resolution images of different structures of the human eye, including the cornea in the anterior segment and the retina in the posterior segment of the eye, in normal and pathological states, enabling direct comparisons of different segments of the eye.[1-5]

In the OCT method, 2D and 3D tomographic images are obtained by measuring the echo time delay of low coherence light emitted by the superluminescent light emitting diode (SLED) source and backscattered from tissue structures. When a tissue has layers with different refractive indexes, light backscatters on the boundaries of the layers. If the pathways of the reference beam (from the mirror) and the study beam (from the tissue) are within the coherence length of the light source, they interfere.[6-8] The first generation of OCT devices worked in the time domain (TdOCT) with a moving mirror. A 1D line giving information about the depth is called A-scan, while 2D images are called B-scans.[1,9,10] More sophisticated and modern

Authors' contribution:
A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article.

devices are Fourier domain OCT (FdOCT or SOCT) based on spectrometers and swept-source OCT (SSOCT), with a swept-source tunable laser as the light source.[9] These techniques give high-resolution images in a shorter time (typically 30,000 - 70,000 in SOCT and 100,000-400,000 A-scans per second in SSOCT, compared to 400 A-scans per second in the TdOCT.[9]

Unfortunately, there are factors that, if not taken into account, may lead to erogenous interpretation of diagnostic images. One of them is myopia. The axial elongation connected to myopia has been reported to produce retinal stretching and thinning, reduce retinal cell density, enlarge photoreceptor inner segments, and may lead to an impairment of retinal function and visual performance.[2,11] Its progression leading to high myopia (defined as SE < 5 or 6 D) is also associated with changes in the morphological structure, biochemical indicators, and support function of the sclera due to its damage, and may transform into pathologic myopia, when characteristic degenerative changes in the sclera, choroid, and RPE (retinal pigment epithelium) occur, with compromised visual function.[11-15] The influence of refractive error on the healthy eye is an important issue, because it may be a confounding factor during diagnosing eye pathologies, and may overestimate their negative impact on the health state of the human eye. There are studies showing changes in some eye structures due to myopia, but the results are often contradictory or incomplete (e.g. macula flattening by thinning at the perifovea and thickening at the foveal pit or parafoveal retina thinning, but either foveal thinning or no difference in foveal thickness in other studies).[2,16-20] There may be several reasons for that, including different techniques used, among which there are techniques that require additional corrections. Many studies are concerned with only selected eye structures, e.g., only the cornea or the optic nerve head (ONH). Moreover, many studies focus only on the central area of the cornea or retina, while the need to take into account the differences between their sectors, as well as between center and periphery, has been recently discussed.[2,3,5] Finally and most importantly, myopia is often not an exclusion factor, or only high and/or pathological myopia is.[3,4,21,22] It is, however, interesting and important to investigate if there are any observable changes in the structures of healthy eyes with a lower degree of myopia, as highly myopic eyes are often accompanied by degenerative changes that may mask any effects related to myopia itself.[12]

Therefore, our work aimed to examine to what extent low and moderate myopia (less than -6D) may influence the thicknesses of several eye structures in healthy eyes, in all accessible sectors. The use of SOCT, a state-of-the-art method of structural assessment of the retina can provide accurate depth-resolved imaging of internal microstructures within the eye tissue.[10] The motivation was the fact that when diagnosing or treating retinal disorders, any effects in the eye structures related to the pathology might overlap with the myopia-related changes, thus making it hard or impossible to disentangle these effects. For this purpose, the thicknesses of central and peripheral corneal sectors, central and peripheral retinal sectors (including retinal layers), and optic disc parameters were compared among low myopia, moderate myopia, and emmetropic groups among young, healthy Caucasians. The correlations of the thicknesses of retinal layers with refractive error were also calculated. Based on our knowledge, this is the first study presenting measurements taken from both: anterior and posterior eye poles, in low and moderate myopia, in central and peripheral sectors. Furthermore, not only the whole retina thickness but also its internal, middle, and external layers were evaluated. If low and moderated myopia causes changes in the thickness of human eye structures, differences between studied myopia groups compared to emmetropic eyes and correlations between these thicknesses and refractive error should be observed. The clinical significance of this study is that if there are any differences in the analyzed retinal structures among the studied groups, it suggests that the thickness of some of the retinal layers, even in healthy eyes with low or moderate myopia, may differ from the emmetropic eyes. This means that special care should be taken when interpreting any results in patients (i.e. in diagnosis or treatment of eye disorders), as any effects found in those patients might be related to the concurrently present myopia (even if it is not high) and not the disorder per se (or at least not entirely).

Materials and Methods

Participants

The experiment was conducted on 60 eyes from 30 young adults (18 women) at the age of 24.6 ± 1.5 years. They all were healthy, physically active, non-smokers, had normal color perception, and had no ophthalmological or neurological medical history. Refractive error values, defined as SE (spherical equivalent) were obtained from an ophthalmologist's prescription. To evaluate different segments of eye structures in low and moderate myopia compared to emmetropic group, we assigned volunteers with $-0.5\ D \leq SE \leq 0.75\ D$ to emmetropia group (20 eyes), volunteers with $-3\ D < SE < -0.5\ D$ to low myopia group (20 eyes) and volunteers with $-6 \leq SE \leq -3\ D$ to moderate myopia group (20 eyes), based on a systematic review and meta-analysis conducted by Hashemi et al.[23] The mean age (with SD) of the participants for each group was: 24.4 ± 1.2, 24.4 ± 1.9, and 24.9 ± 1.6 years for emmetropia, low myopia, and moderate myopia, respectively, and they did not differ significantly ($F_{2,27} = 0.33$, $P = 0.72$). The eyes with astigmatism were included if its value was not larger than 0.25 D. The experiment was conducted with the understanding and informed, written consent of each subject after an explanation of the nature and possible consequences of the study, according to the Tenets of the Declaration of Helsinki. The studies were approved by the Committee of Ethics of The University of Silesia in Katowice on scientific studies conducted on humans (number 3/2018).

Procedure

Each participant had 3D SOCT scans for the right and left eye taken from 3 eye structures: cornea, macular retina, and optic disc area, using SOCT Copernicus HR device (OPTOPOL Technology Sp. z o.o., Poland), and SOCT Copernicus HR v.4.3.3 software. The 840 nm wavelength SLED source had a tissue axial resolution of 3 μm and a transverse resolution of 18 μm. For the corneal measurements, an additional adapter has been mounted, and axial beam direction used. The scan width and height in cornea, macular retina, and optic disc images were: 4 mm and 1.64 mm, 7 mm and 1.64 mm, 5 mm and 1.64 mm, respectively. The number of A-scans, number of B-scans, and time of single scan were: 2500 × 12 and 1.12 s in cornea images, 743 × 75 and 2.49 s in macular retina images, and 600 × 99 and 2.81 s in optic disc images, respectively.

2D and 3D OCT images are not acquired instantaneously, due to the need for B-scan and C-scans to scan the beam over the tissue in the x-direction and y-direction. Therefore, motion artifacts may occur, which may distort the acquired OCT image and limit the reliability of quantitative measurements.[5] To control for motion artifacts, each scan was visually inspected immediately after the measurement and repeated if the artifacts had occurred.

The following parameters were measured: corneal thickness, macular retinal thickness, peripapillary retina nerve fiber layer (RNFL) thickness around the optic nerve head (ONH), as well as the parameters of the optic disc (disc area, rim area, cup area, cup/disc area ratio, rim volume, cup volume, mean cup depth, and maximal cup depth). Moreover, thicknesses of the following macular retinal layers were also measured (from the inferior to the exterior of the eyeball): RNFL thickness, RNFL-IS/OS junction distance (distance between RNFL and photoreceptor outer/inner segments junction), and IS/OS junction-RPE distance (distance between photoreceptor outer/inner segments junction and retinal pigment epithelium, referred in this paper as IS/OS).

Corneal sectors were automatically detected and ascribed as C – central, S – superior, SN – superior-nasal, N – nasal, IN – inferior-nasal, I – inferior, TI – temporal-inferior, T – temporal, and ST – superior-temporal (**Figure 1a**). Macular retinal sectors were ascribed as C – central, SI – inner superior, NI – inner nasal, II – inner inferior, TI – inner temporal, SO – outer superior, NO – outer nasal, IO – outer inferior, TO – outer temporal (**Figure 1b**). Peripapillary RNFL sectors were ascribed in a 10 o'clock division as S – superior, SN – superior-nasal, N1 – upper nasal, N2 – lower nasal, IN – inferior-nasal, I – inferior, IT – inferior-temporal, T2 – lower temporal, T1 – upper temporal, and ST – superior-temporal (**Figure 1c**). Since automated image segmentation algorithms can fail to accurately delineate corneal or retinal layers,[24] after the automatic layer segmentation process, each scan was visually inspected and manually refined by a specialist. The diameters of central and peripheral areas in the cornea were fixed: 2 and 4 mm, respectively. The diameters of the central area, inner and outer ring in the retina were fixed: 1 mm, 3 mm, and 6 mm, which corresponded to central, pericentral, and near peripheral macular regions, respectively.[25]

To compare horizontal and vertical areas, each sector of the cornea was assigned to superior (S), inferior (I), temporal (T), and nasal (N) hemifields. Both inner and outer rings within the macular retina consist of superior, inferior, temporal, and nasal quadrants. Similarly, each sector of peripapillary RNFL was assigned to superior or inferior horizontal hemifield and: extreme temporal (ET), temporal (T), midline (M), nasal (N), and extreme nasal (EN) vertical sectors (**Figure 1**).

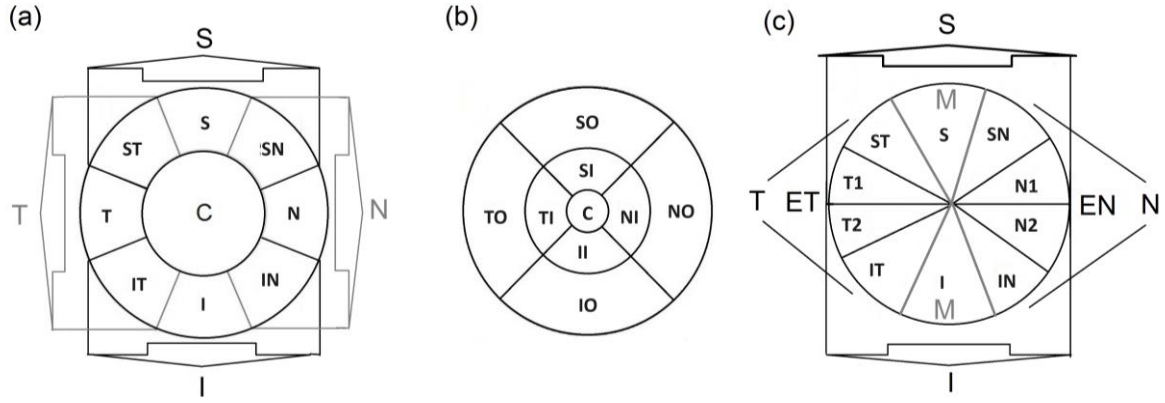

Figure 1. Sectors of cornea (a), macular retina (b), and peripapillary RNFL (c), used for thickness measurements. Corneal sectors were ascribed as C – central, S – superior, SN – superior-nasal, N – nasal, IN – inferior-nasal, I – inferior, IT – temporal-inferior, T – temporal, and ST – superior-temporal. Macular retinal sectors were ascribed as C – central, SI – inner superior, NI – inner nasal, II – inner inferior, TI – inner temporal, SO – outer superior, NO – outer nasal, IO – outer inferior, TO – outer temporal. Peripapillary RNFL sectors were ascribed in a 10 o'clock division as S – superior, SN – superior-nasal, N1 – upper nasal, N2 – lower nasal, IN – inferior-nasal, I – inferior, IT – inferior-temporal, T2 – lower temporal, T1 – upper temporal, and ST – superior-temporal. Moreover, each sector of the cornea was assigned to superior (S), inferior (I), temporal (T), and nasal (N) hemifields, and each sector of peripapillary RNFL was assigned to superior or inferior horizontal hemifield, and: extreme temporal (ET), temporal (T), midline (M), nasal (N) and extreme nasal (EN) vertical sectors.

Statistical Analysis

Statistical analyses were performed using Statistica v.13 software (Tibco Software Inc). According to statistical guidelines for the analysis of data obtained from one or both eyes,[26] only one eye of each participant was randomly included in the analysis (the number of left and right eyes was equal). Shapiro-Wilk's, Levene's, and Mauchley's tests were used to check the normality of data distribution, variation homogeneity, and data sphericity, respectively.

A comparison of corneal thicknesses between emmetropic and myopia groups was conducted using two-way ANOVA with between-subject factor GROUP (emmetropic, low myopia, and moderate myopia), and within-subject factor SECTOR (described in section Procedure) for the comparison of all studied sectors. In addition, within-subject factors HORIZONTAL (superior and inferior) and VERTICAL (temporal and nasal) were used to compare hemispheric asymmetries in peripheral areas of the cornea.

A comparison of retinal thicknesses between emmetropic and myopia groups was conducted using two-way ANOVA with between-subject factor GROUP (emmetropic, low myopia, and moderate myopia) and within-subject factor SECTOR for the comparison of all studied sectors. To take into account horizontal and vertical differences between rings, three-way ANOVA with between-subject factor GROUP (emmetropic, low myopia, and moderate myopia), and within-subject factors: RING (inner, outer) and QUADRANT (superior, inferior, temporal, and nasal) was used.

For the comparison of the 10 o'clock sectors within peripapillary RNFL, two-way ANOVA with between-subject factor GROUP (emmetropic, low myopia, and moderate myopia) and within-subject factor SECTOR was used. In addition, within-subject factors HORIZONTAL (superior and inferior) and VERTICAL (extreme temporal, temporal, midline, nasal, and extreme nasal) for the comparison of the peripapillary RNFL hemifield asymmetries were used.

Comparison of retinal layers' thicknesses between analyzed groups was conducted using repeated measures ANOVA with between-subject factor GROUP (emmetropic, low myopia, and moderate myopia) and within-subject factors: LAYER (RNFL, RNFL-IS/OS, and IS/OS), RING (inner, outer) and SECTOR. Post-hoc comparisons were analyzed with Bonferroni correction. Greenhouse-Geisser correction for violation of sphericity was used if needed.

Correlations were measured using Pearson's r coefficient using a general regression model. Nonparametric tests were used when data did not fulfill assumptions for parametric tests. In all analyses, $P<0.05$ was regarded as statistically significant.

Results

SOCT Scans

Exemplary, representative scans of the cornea, macular retina, and optic disc from one emmetropic eye are presented in **Figure 2**.

The scan of the cornea shows epithelium and stroma, split by Bowman's layer, Descemet's membrane, and endothelium. In the retina image, the brightest are RPE and IS/OS junction and, more faintly, RNFL. In the scan of an optic disc, one can see bright RNFL, RPE, and IS/OS junction layers.

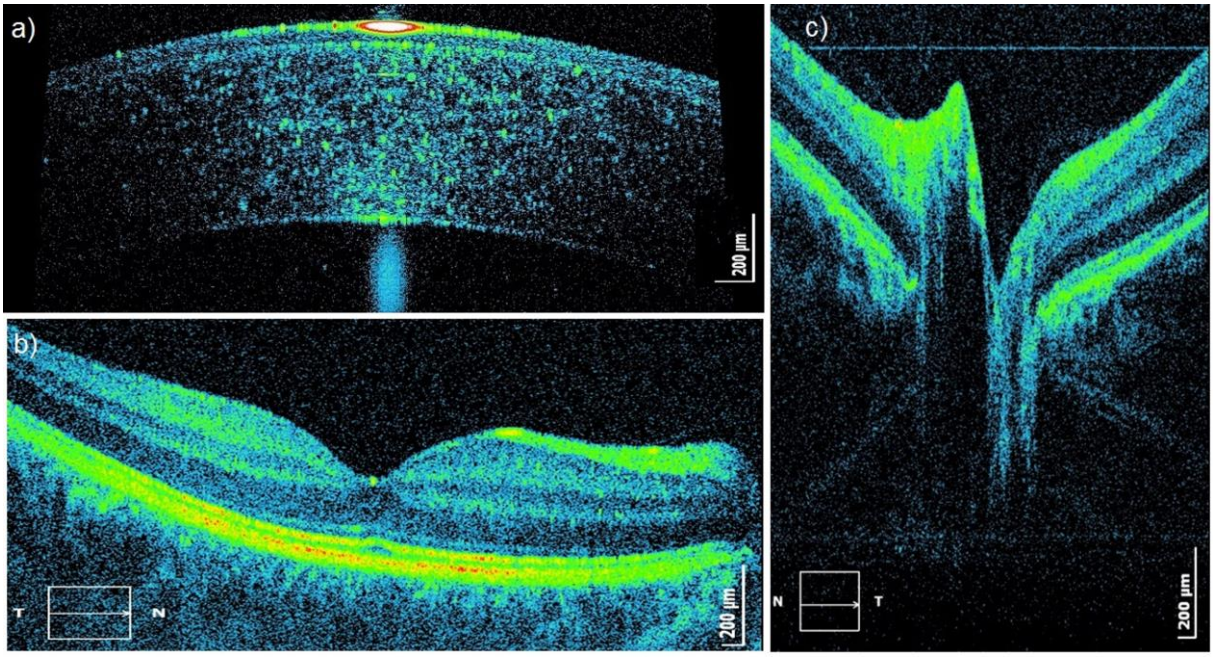

Figure 2. Corneal (a), macular retinal (b), and optic disc (c) scans from a representative emmetropic eye. T – temporal, N – nasal. Note the typical central artifact (vertical hyperreflective stripe) observed in corneal imaging, related to the repetitive pattern of back-reflections from the air-tear(-epithelial) interface and endothelium-aqueous interface in panel 2a

Differences in corneal and retinal thicknesses between myopia groups

Cornea

Corneal thickness didn't differ between the myopia group, either in the center ($F_{2,27} = 0.66$, $P = 0.52$, $\eta^2_P = 0.047$) or in the periphery (main effect: $F_{2,108} = 3.1$, $P = 0.051$, $\eta^2_P = 0.053$, interactions: $F_{2,108} = 0.17$, $P = 0.84$, $\eta^2_P = 0.003$, $F_{2,108}=0.0$, $P = 0.99$, $\eta^2_P = 0.00007$, $F_{2,108} = 0.13$, $P = 0.88$, $\eta^2_P = 0.002$ for GROUPxVERICAL, GROUPxHORIZONTAL and GROUPxVERICALxHORIZONTAL, respectively). However, the temporal corneal thickness was significantly lower than the nasal one (**$F_{1,108} = 6.12$, $P = 0.015$, $\eta^2_P = 0.054$**). Averaged corneal thicknesses in normal, low myopia, and moderate myopia groups were: 550±31, 559±24 and 544±29 µm, respectively. Mean corneal thicknesses in central and peripheral corneal in emmetropic and myopia groups are presented in **Figure 3**.

Macular Retina

A comparison of macular retinal thickness between analyzed groups revealed a significant effect GROUP (**$F_{2,243} = 3.7$, $P = 0.025$, $\eta^2_P = 0.03$, significant post hoc $P = 0.025$** between low and moderate myopia group) as well as SECTOR (**$F_{8,243} = 127.7$, $P < 0.0001$, $\eta^2_P = 0.81$**). The central macular retina was significantly lower than all other sectors (**post hoc $P < 0.0001$** in all cases). Including ring and quadrant factors, the analysis showed RING (**$F_{1,216} = 521$, $P < 0.0001$, $\eta^2_P = 0.71$**) and QUADRANT (**$F_{3,216} = 49$, $P < 0.0001$, $\eta^2_P = 0.41$**, with all post hoc **$P < 0.05$**) main effects as well as RINGxQUADRANT (**$F_{3,216} = 11$, $P = 0.000001$, $\eta^2_P = 0.13$**, with significant post hoc difference in inner ring between S and T: **$P = 0.0002$** and between N and T: **$P = 0.00004$**, and in the outer ring between all quadrants with **$P < 0.05$** except for S and I: $P = 0.49$) interaction effect. Averaged macular retina thicknesses in normal, low myopia, and moderate myopia groups were: 286±31, 287±29 and 282±30 µm, respectively. Mean retinal thicknesses in emmetropic, low myopia, and moderate myopia groups (averaged over sectors), as well as in all quadrants of inner and outer rings of the peripheral retina are presented in **Figure 4**.

Peripapillary RNFL

A comparison of peripapillary RNFL thickness revealed VERTICAL difference (**$H_{4,283}=220$, $P=0.0000$** with significant post hoc difference between all sectors except for nasal and temporal: $P = 0.6$ and between extreme nasal and extreme temporal: $P = 0.8$), but no HORIZONTAL ($H_{1,283} = 3.4$, $P = 0.07$) or GROUP ($H_{2,283} = 0.3$, $P = 0.9$) effect was observed (**Figure 5**).

Disc Parameters

There were no myopia-related differences in any optic disc parameters: area ($F_{2,26} = 0.4$, $P = 0.7$), volume ($F_{2,26} = 1.1$, $P = 0.4$), or cup depth ($F_{2,26} = 1.4$, $P = 0.3$).

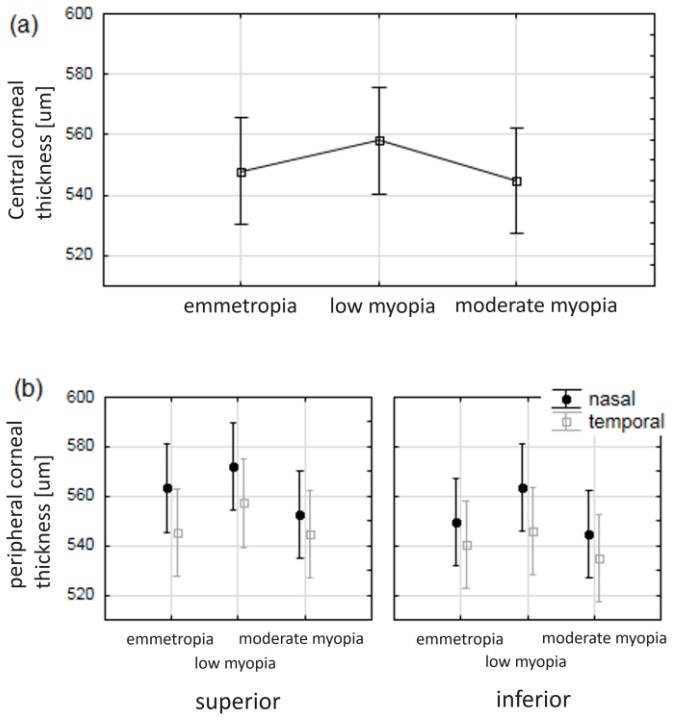

Figure 3. Mean corneal thicknesses in central (a) and peripheral (b) cornea in emmetropic and myopia groups (bars – 95% confidence level)

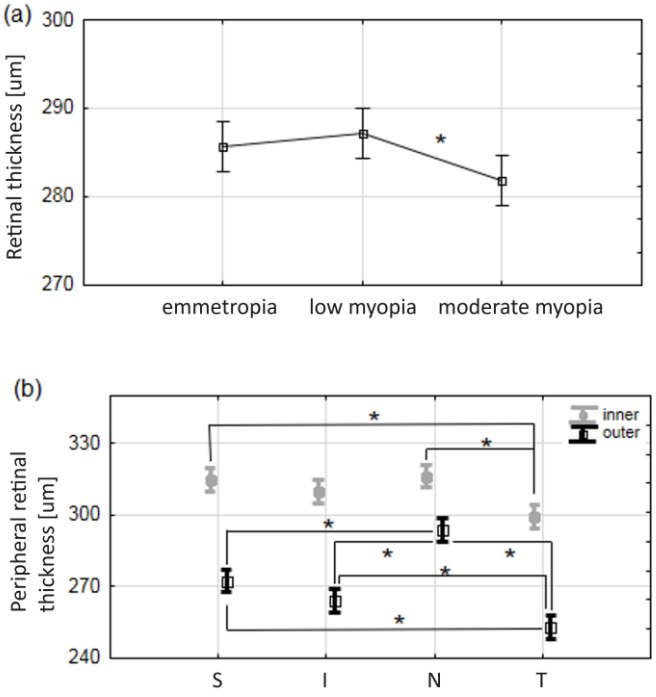

Figure 4. Mean retinal thicknesses in emmetropic, low myopia, and moderate myopia groups (averaged over sectors) (a), as well as in all quadrants (S – superior, I – inferior, N – nasal, T – temporal) of inner and outer rings of peripheral retina (b). * - significant differences with P < 0.05, bars – 95% confidence level.

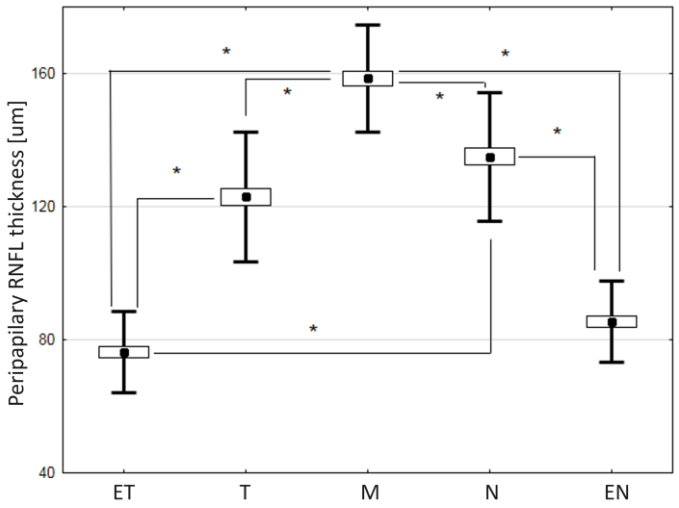

Figure 5. Mean peripapillary RNFL thicknesses in vertical sectors (ET – extreme temporal, T – temporal, M – midline, N – nasal, EN – extreme nasal). * - significant differences with P < 0.05, box – standard error, whisker – standard deviation.

Comparisons of the thicknesses of macular retinal layers

To better understand the changes in retinal thickness due to increasing myopia, the next step of analysis included its layers: RNFL, RNFL-IS/OS distance, and IS/OS.

Figure 6 presents a comparison of mean RNFL, RNFL-IS/OS, and IS/OS thicknesses between study groups as well as between sectors. Repeated measures ANOVA revealed the main effect of LAYER ($F_{2,486}$ **= 44700,** P **< 0.0001**). LAYERxSECTOR ($F_{16,486}$ **= 172,** P **< 0.0001**) and LAYERxGROUP ($F_{4,486}$ **= 9.6,** P **= 0.00003** with significant post hoc difference in RNFL-IS/OS between emmetropic and moderate myopia group: P **= 000002**) interaction effects were also observed (**Figure 6a**, **6c**).

Significant differences in RNFL-IS/OS thickness (**Figure 6b**) were observed between C and the following sectors: SI (P **= 0.0000**), II (P **= 0.0000**), NI (P **= 0.0000**), TI (P **= 0.0000**) and IO (P **= 0.00007**). Moreover, in the inner ring, there was a difference between II and NI (P **= 0.005**) and between TI and NI (P **= 0.00005**), while in the outer sector between SO and IO (P **= 0.045**), between IO and NO (P **= 0.0000**) and between IO and TO (P **= 0.0006**).

Significant differences in the RNFL layer (**Figure 6d**) were observed between C and all other sectors (P **= 0.0000**), in the inner ring between TI and SI (P **= 0.0002**) and between TI and II (P **= 0.006**), and in outer ring NO was significantly thicker than all other sectors (P **= 0.0000**) and TO was significantly thinner than all other sectors (P **= 0.0000**).

No differences between sectors were observed in IS/OS thickness (**Figure 6d**).

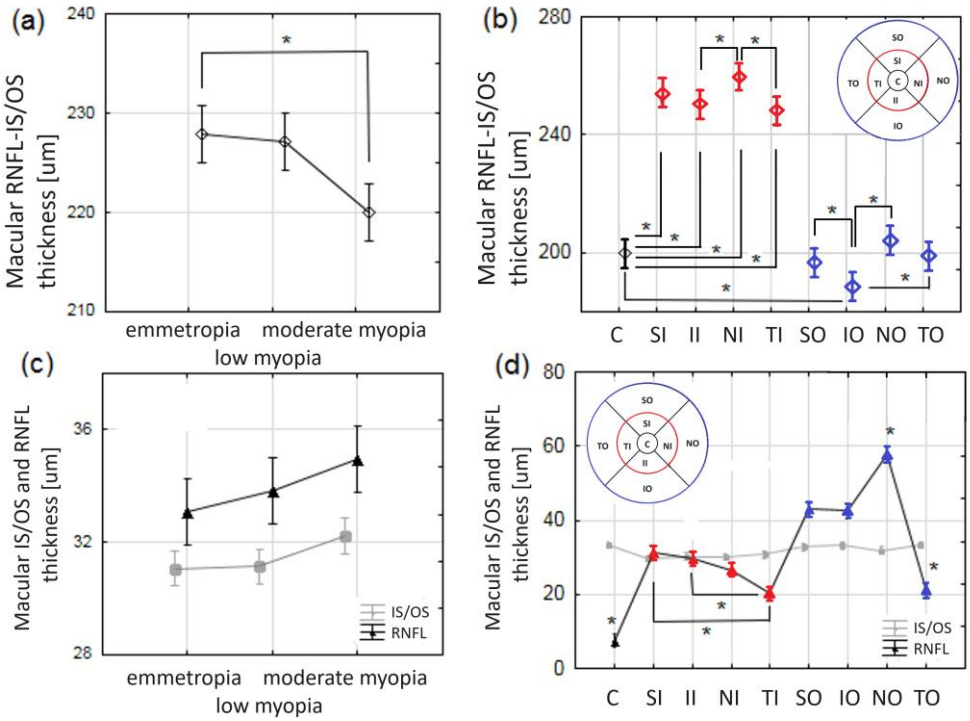

Figure 6. A comparison of mean RNFL-IS/OS, IS/OS, and RNFL thicknesses between emmetropia, low myopia, and moderate myopia groups (a) and (c), as well as between sectors (b) and (d). Retinal sectors: C – central, SI – inner superior, II – inner inferior, NI – inner nasal, TI – inner temporal, SO – outer superior, IO – outer inferior, NO – outer nasal, TO – outer temporal. * - significant differences with P<0.05, bars – 95% confidence level. Charts (b) and (d): the position of the macular sectors used for thickness measurements have been shown in the insets to visualize the differences better; markers in red and blue represent the inner and outer rings, respectively.

Table 1. Correlation results between retinal layers' (RNFL, IS/OS, and RNFL-IS/OS) thicknesses and refractive error in the sectors that obtained significance. Retinal sectors: C – central, NI – inner nasal, II – inner inferior, SO – outer superior, TO – outer temporal, NO – outer nasal.

Retinal layer	Sector	Model coefficient	Standard error	*P* value	95% Confidence Interval	Pearson's *r*	Corrected r^2
RNFL	II	-0.91	0.42	**0.039**	-1.77 ÷ -0.05	0.38	0.11
	NI	-0.72	0.30	**0.025**	-1.34 ÷ -0.10	0.41	0.14
IS/OS	C	-0.40	0.16	**0.022**	-0.73 ÷ -0.06	0.42	0.14
	NI	-0.55	0.23	**0.022**	-1.02 ÷ -0.09	0.42	0.14
RNFL-IS/OS	II	2.62	1.12	**0.028**	0.30 ÷ 4.93	0.40	0.14
	SO	2.67	1.22	**0.038**	0.17 ÷ 5.18	0.38	0.11
	TO	3.04	1.12	**0.010**	0.75 ÷ 5.33	0.46	0.18
	NO	2.66	1.28	**0.047**	0.03 ÷ 5.28	0.36	0.10

In addition, the correlation between SE and all macular retina layers was calculated using a general regression model. **Table 1** presents statistical results of significant correlations observed in the RNFL-IS/OS layer in: SO, TO, NO, and II sectors, in the IS/OS layer in C and NI sectors, and RNFL in II and NI sectors. **Figure 7** shows the scattering plots with significant correlations of the thicknesses of the following layers with SE: retina (**Figure 7a**), RNFL-IS/OS (**Figure 7b-e**), IS/OS (**Figure 7f-g**) and RNFL (**Figure 7h-i**). All the correlations were medium (Pearson's r between 0.36 and 0.46). The refractive error correlated with the RNFL and IS/OS layers mostly in the inner inferior-nasal regions, whereas the correlations with the RNFL-IS/OS layer were mostly observed in the outer regions of the macula (with a higher correlation in the temporal segment).

Discussion

Spectral optical coherence tomography (SOCT) is a perfect tool for the diagnosis of eye disorders, evaluation of therapeutic methods, or visualization of surgical interventions. However, as in any other imaging technique, there are factors (e.g. myopia) which, if not taken into account, may lead to erogenous interpretation of the images.

Differences in corneal and retinal thicknesses related to the degree of myopia

Cornea

In our study, the thickness of the temporal corneal segment was significantly lower than the nasal segment (**Figure 3**). However, corneal thickness didn't change with increasing spherical equivalent in any of the studied sectors, which is in concordance with previously reported findings.[11,27,28]

Macular retina and its layers

The analysis of macular retinal thickness due to refractive error showed some interesting findings. When the whole retinal thickness was analyzed, we found its decrease in moderate myopia, compared to the emmetropic group (**Figure 4**). Previous studies in humans have determined that the macula generally flattens in high myopia by thinning at the perifovea and thickening at the foveal pit.[16,17] However low and moderate myopia has been studied less in terms of retinal thickness. While many studies have focused on highly myopic eyes, in which pathologic myopia may occur, it is extremely important to determine the extent to which low or moderate myopia in healthy people may influence the measurements of eye structures and their parameters.

Tan[2] observed that the thickness of the retinal central subfield was similar among different refractive error groups, whereas the parafoveal subfields thinned progressively with increasing severity of myopia. Other studies, however, found either foveal thinning or no difference in foveal thickness.[18-20] This discrepancy of the previous findings doesn't necessarily mean some of them are right and others are wrong. It is more likely that they capture different mechanisms related to these changes, but the diversity of used imaging protocols and analyzed locations within the retina doesn't allow for comparison of these findings. Our results shed more light on the changes in retinal thickness with increasing SE in low and moderate myopia.

Interestingly, when analyzing individual macular retina layers (**Figure 6** and **7**), we observed different changes in the thicknesses of particular retinal layers with increasing SE: a thinning of RNFL-IS/OS distance mostly in the near peripheral retina and a thickening of external layers: RNFL and IS/OS junction in the pericentral region. All the correlations were medium with *r* ranging from 0.36 in RNFL-IS/OS distance in the near peripheral nasal sector up to 0.46 in RNFL-IS/OS distance in the near peripheral temporal sector. This different behavior of retinal layers may explain the lack of myopia-related effects on retinal thickness in low and moderate stages in previous findings. We suggest that different directions of thickness changes in different retina layers may cancel each other and therefore significant change may not be observed when the whole retina thickness is analyzed. This might explain the discrepancies in findings present in the literature.

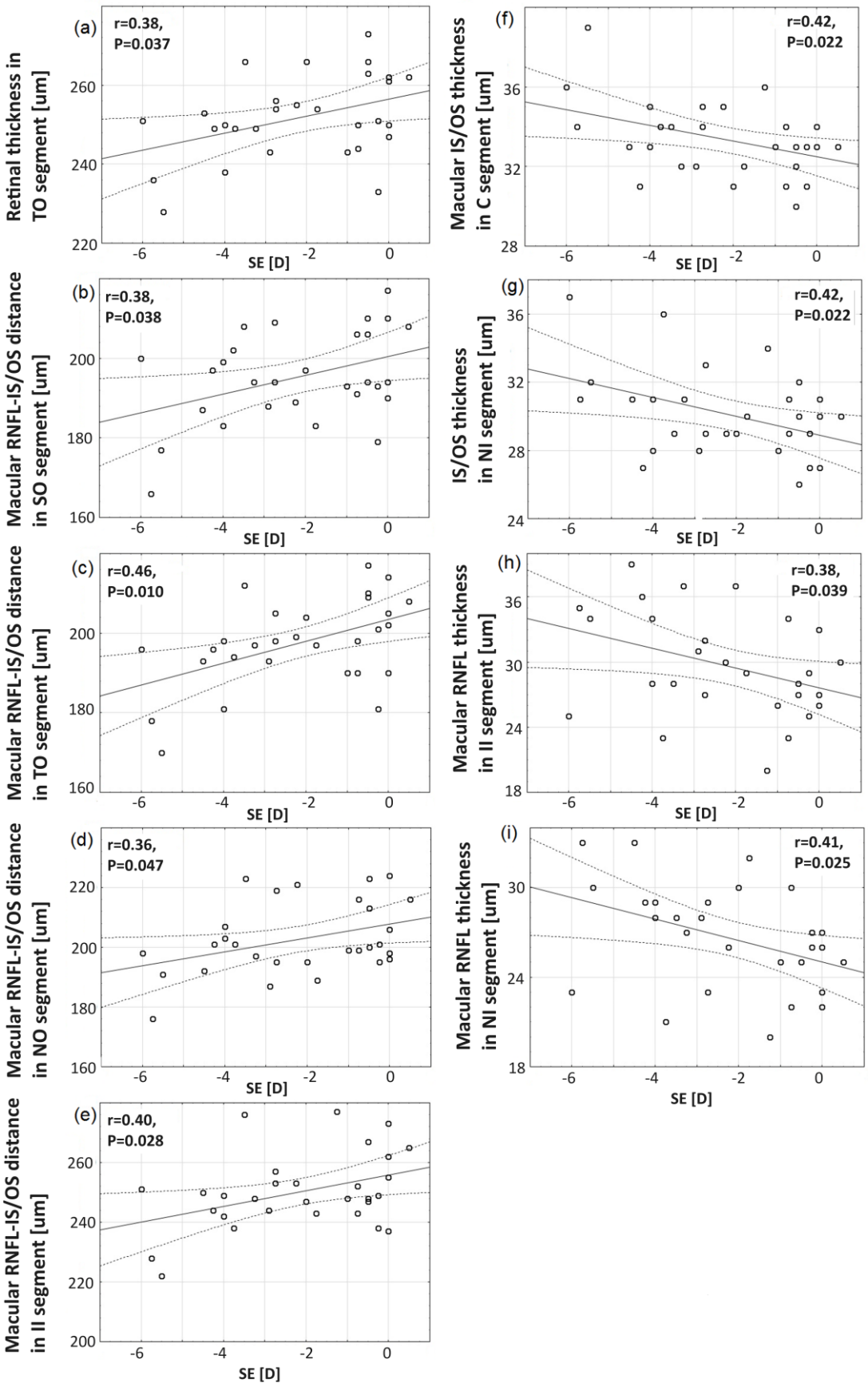

Figure 7. The scattering plots showing significant correlations of the macular retina and its layers with SE: macular retina in TO (a), RNFL-IS/OS distance in SO (b), RNFL-IS/OS distance in TO (c), RNFL-IS/OS distance in NO (d), RNFL-IS/OS distance in II (e), IS/OS thickness in C (f), IS/OS thickness in NI (g), macular RNFL thickness in II (h) and macular RNFL thickness in NI (i).

The fact that different retinal layers change differently due to myopia has been pointed out in the literature. Abbott[29] showed that inner plexiform, inner nuclear, and outer plexiform layers thinned the most in the high myopia group in mammalian model studies, compared to control, and that all neuronal cell types are involved in retinal thinning. Garcia-Valenzuela et al.[30] suggested that the various layers of the sensory retina may be differentially affected by axial length–related tissue stretching.

What is worth noting, we also found differences in retinal layers' thicknesses between sectors. The most evident change was observed in the near peripheral temporal sector of RNFL-IS/OS distance, which may suggest that this region is the most prone to changes due to eye elongation. This, however, needs further investigation.

Our results suggest that even when no changes in the whole retina thickness with increasing degrees of myopia are observed, it is important to take into account changes in particular retina layers, as their thickness may significantly change due to refractive error. These changes might be observed not only in a high degree of myopia but also in its earlier stages. These findings are especially worth noting, as they suggest the need for taking into account the different behavior of retina layers in low and moderately myopic eyes in diagnosing ocular pathologies or in preparing ophthalmologic surgeries to prevent erogenous interpretation of the images.

Peripapillary retina and optic disc

There were no changes in papillary RFNL thickness and optic disc parameters with SE in our study. Papillary RFNL was the thinnest in temporal and nasal sectors and the thickest in superior and inferior sectors (**Figure 5**), similar to the findings reported earlier.[31,32] Moreover, it was symmetrical, both horizontally and vertically. The literature generally shows no or minimal effect of refractive error on peripapillary RNFL thickness or optic disc parameters, especially in low and moderate myopia.[22,33–36] A recent study by Tai et al.[37] compared peripapillary RNFL thickness between four myopia groups and found significant thinning in superior and inferior quadrants, but only in high myopia, compared to the other groups. Superior and inferior peripapillary RNFL is much thicker than nasal and temporal areas, which was also observed in our study. These results suggest that different regions of peripapillary RNFL may be differently susceptible to myopia-related changes, but not likely in low or moderate myopia.

When comparing the corneal and retinal thicknesses among different degrees of myopia measured by OCT, one may question whether any observed effects are due to clinical differences or image distortions, as there have been studies showing statistically, but not clinically significant effects of refractive error on OCT measurements ([38,39]). Moreover, the need for quantitative image corrections in OCT has been suggested ([40–42]). This, however, is not the issue in this study, for the following reasons. The need for correction of the OCT images discussed in [40,41] was presented more than 20 years ago, even before the first spectral OCT was introduced, which has many improvements in image acquisition, including stationary reference arm which eliminates motion errors discussed in the above-mentioned works. The SOCT device used in our research has refraction compensation and correction of focus included in the measurement mode of the software, based on the refraction power set for each studied eye during the examination. Another suggestion that our result are not generated by the image distortions is that Podoleanu et al.[41] observed image distortion of the cornea. However, we did not observe differences in corneal thickness between the studied group or in the peripapillary retina and optic disc. If the observed changes were due to the image distortions, we should not only observe changes in the corneal thickness but also the optical disc. On the contrary, the effects that we observed were present in the macula, in the central region of the retina, with the diameter of the studied sector up to 6 mm only. The more recent study by Tan et al.[42] was related to the refractive distortions in whole-eye OCT imaging, which is not relevant to our study, where only small areas (but clinically significant) were imaged in a single measurement. Such errors are particularly important in ultra-wide field OCT or biometry, where not only linear distances but also curvilinear surfaces, interfaces, and enclosed areas must be accurately obtained.[40] Nevertheless, one should be aware of any possible confounding factors that may result in a wrong interpretation of the obtained results. However, taking into account the previous considerations and the fact that the SOCT method has a long history, its construction, and the new imaging algorithms are being developed constantly, we believe that these imaging errors don't contribute to the effects presented in this paper.

In addition, the effects found in [38] and [39] were observed for high myopia, where SE is larger than 6 D, and the older population (above 40 years old), which makes this group much more prone to imaging errors, due to the presence of pathologic myopia (i.e. degenerative macular changes) and increase in age-related pathologies, which may distort the image even more. Moreover, in the study by Hwang,[38] half of the study group of 15 participants was Asians, and the other was Caucasians, which may introduce a bias in the results, as there are differences in the retinal parameters between these ethnic groups.[43] Finally, the statistically but not clinically significant changes observed by the Authors were based on the measurements with and without contact lenses, which itself may introduce additional confounds such as the contact surface between the contact lens and the eye, or the positioning of the contact lens, which the Authors themselves pointed out as one of the possible reason. Interestingly though, while the results discussed in[39] at first might suggest that differences in the retinal structures in the myopic eyes are more related to imaging errors in OCT than the true effect, this work however perfectly emphasizes the importance of our results. This is because the 'OCT

measurement distortions' described in[39] relate not to the imaging errors but to the automatic comparisons of the retinal measurements taken from myopic eyes with the built-in normative databases in the OCT software (which are based on the emmetropic eyes), which may lead to false positive or false negative results because, as we showed, the retinal layers differ in thickness between myopic and emmetropic eyes. Thus, these findings support the rationale of our study that myopia should be taken into account in the diagnosis and treatment of ophthalmologic patients.

Study Advantages and Limitations

Our study has several advantages. First, the use of the high-resolution SOCT method allowed us to get direct cross-sectional images of both: the anterior and posterior poles of the eye. Secondly, all scans were obtained for all sectors at once for every examined volunteer. Thirdly, visual careful inspection and manual correction of layer delineation allowed us to minimize the methodology artifacts of SOCT imaging (including motion and automatic segmentation artifacts). Moreover, to investigate different locations of the retina, we analyzed both central and peripheral areas of the studied structures. Lastly, uniform age groups prevented any age-related confounds, as the mean age of the participants among the studied groups did not differ significantly ($F_{2,27} = 0.33$, $P = 0.72$). However, our study has also some limitations, among which are: not taking into account gender (though a similar number of men and women were studied) and measurements performed only on Caucasian people. Nevertheless, we believe our results show how using spectral optical coherence tomography imaging can have a meaningful contribution to the knowledge of the influence of refractive error in healthy myopic eyes with low and moderate degrees on corneal and retinal measurements.

Conclusions

It is extremely important to determine the extent to which low or moderate myopia in healthy people may influence the thickness of eye structures. There was no relationship between corneal thickness and SE. Macular retina thickness decreased with increasing refractive error. Interestingly, different behaviors of changes in macular retinal layer thicknesses with increasing refractive error have been found. A thickening of external macular retina layers (IS/OS and RFNL) was observed in central and pericentral segments, while a thinning of internal retina layers (RFNL-IS/OS distance) was seen mainly in the near periphery, when SE increased from emmetropia to moderate myopia. There was no correlation between papillary RFNL thickness or optic disc parameters and SE. The observed effects may rearrange previously reported findings on the influence of refractive error on the thickness of eye structures in healthy eyes and suggest that changes in the retina due to myopia may appear earlier than in high myopia. Moreover, different retina layers change differently. Thirdly, not every sector behaves in the same manner. These results indicate the need to take into account the different behaviors of retina layers in low and moderately myopic eyes. It is especially important in diagnosing ocular pathologies or in preparing ophthalmologic surgeries to prevent erogenous interpretation of diagnostic results.

References

1. Ang M, Baskaran M, Werkmeister RM, et al. Anterior segment optical coherence tomography. Progress in Retinal and Eye Research. 2018;66:132-156. https://doi.org/10.1016/j.preteyeres.2018.04.002
2. Tan CS, Li KZ, Tan M, et al. Relationship between Myopia Severity and Macular Retinal Thickness on Visual Performance under Different Lighting Conditions. Ophthalmology Retina. 2017;1(4):339-346. https://doi.org/10.1016/j.oret.2017.01.009
3. Tsai CY, Hung KC, Wang SW, Chen MS, Ho TC. Spectral-domain optical coherence tomography of peripheral lattice degeneration of myopic eyes before and after laser photocoagulation. Journal of the Formosan Medical Association. 2019;118(3):679-685. https://doi.org/10.1016/j.jfma.2018.08.005
4. Jankowska-Lech I, Wasyluk J, Palasik W, Terelak-Borys B, Grabska-Liberek I. Peripapillary retinal nerve fiber layer thickness measured by optical coherence tomography in different clinical subtypes of multiple sclerosis. Multiple Sclerosis and Related Disorders. 2019;27(November 2018):260-268. https://doi.org/10.1016/j.msard.2018.11.003
5. Quinn N, Csincsik L, Flynn E, et al. The clinical relevance of visualising the peripheral retina. Progress in Retinal and Eye Research. 2019;68(June 2018):83-109. https://doi.org/10.1016/j.preteyeres.2018.10.001
6. Huang D, Swanson EA, Lin CP, et al. Optical Coherence Tomography. Science. 1991;254(5035):1178-1181. https://doi.org/10.1126/science.1957169
7. Wojtkowski M, Kowalczyk A, Targowski P, Gorczyńska I. Fourier-domain optical coherence tomography: Next step in optical imaging. Optica Applicata. 2002;32(4):569-580.
8. Wojtkowski M, Srinivasan VJ, Ko TH, Fujimoto JG, Kowalczyk A, Duker JS. Domain Optical Coherence Tomography and. Optics express. 2004;12(11):707-709.
9. Bhende M, Shetty S, Kuppuswamy Parthasarathy M, Ramya S. Optical coherence tomography: A guide to interpretation of common macular diseases. Indian Journal of Ophthalmology. 2018;66:20-35. https://doi.org/10.4103/ijo.IJO_902_17

10. Bian H, Gao W. Measurement and compensation of motion artifacts in spectral domain optical coherence tomography. Optik. 2019;183(January):24-29. https://doi.org/10.1016/j.ijleo.2019.01.102
11. Ortiz S, Mena L, Rio-San Cristobal A, Martin R. Relationships between central and peripheral corneal thickness in different degrees of myopia. Journal of Optometry. 2014;7(1):44-50. https://doi.org/10.1016/j.optom.2013.03.005
12. Ueta T, Makino S, Yamamoto Y, Fukushima H, Yashiro S, Nagahara M. Pathologic myopia: an overview of the current understanding and interventions. Global Health & Medicine. 2020;2(3):151-155. https://doi.org/10.35772/ghm.2020.01007
13. Morgan IG, Ohno-Matsui K, Saw SM. Myopia. The Lancet. 2012;379(9827):1739-1748. https://doi.org/10.1016/S0140-6736(12)60272-4
14. Minkevich NI, Morozova-Roche LA, Iomdina EN, et al. Abnormal pigment epithelium-derived factor processing in progressive myopia. Experimental Eye Research. 2016;152:1-9. https://doi.org/10.1016/j.exer.2016.08.017
15. Metlapally R, Wildsoet CF. Scleral Mechanisms Underlying Ocular Growth and Myopia. Vol 134. 1st ed. Elsevier Inc.; 2015. https://doi.org/10.1016/bs.pmbts.2015.05.005
16. Wolsley CJ, Saunders KJ, Silvestri G, Anderson RS. Investigation of changes in the myopic retina using multifocal electroretinograms, optical coherence tomography and peripheral resolution acuity. Vision Research. 2008;48(14):1554-1561. https://doi.org/10.1016/j.visres.2008.04.013
17. Wu PC, Chen YJ, Chen CH, et al. Assessment of macular retinal thickness and volume in normal eyes and highly myopic eyes with third-generation optical coherence tomography. Eye. 2008;22(4):551-555. https://doi.org/10.1038/sj.eye.6702789
18. Mrugacz M, Bakunowicz-Lazarczyk A, Sredzinska-Kita D. Use of Optical Coherence Tomography In Myopia. . J Pediatr Ophthalmol Strabismus. 2004;41(3):159-162. https://doi.org/https://doi.org/10.3928/0191-3913-20040501-08
19. Wakitani Y, Sasoh M, Sugimoto M, Ito Y, Ido M, Uji Y. Macular thickness measurements in healthy subjects with different axial lengths using optical coherence tomography. Retina. 2003;23(2):177-182. https://doi.org/10.1097/00006982-200304000-00007
20. Choi JA, Kim JS, Park HYL, Park H, Park CK. Retinal nerve fiber layer thickness profiles associated with ocular laterality and dominance. Neuroscience Letters. 2014;558:197-202. https://doi.org/10.1016/j.neulet.2013.10.054
21. Uzun F, Karaca EE, Yıldız Yerlikaya G, Fındık H, Akın M. Retinal nerve fiber layer thickness in children with β-thalassemia major. Saudi Journal of Ophthalmology. 2017;31(4):224-228. https://doi.org/10.1016/j.sjopt.2017.10.001
22. Lee MW, Kim J mi, Shin Y Il, Jo YJ, Kim JY. Longitudinal Changes in Peripapillary Retinal Nerve Fiber Layer Thickness in High Myopia: A Prospective, Observational Study. Ophthalmology. 2019;126(4):522-528. https://doi.org/10.1016/j.ophtha.2018.07.007
23. Hashemi H, Fotouhi A, Yekta A, Pakzad R, Ostadimoghaddam H, Khabazkhoob M. Global and regional estimates of prevalence of refractive errors: Systematic review and meta-analysis. Journal of Current Ophthalmology. 2018;30(1):3-22. https://doi.org/10.1016/j.joco.2017.08.009
24. Mansberger SL, Menda SA, Fortune BA, Gardiner SK, Demirel S. Automated Segmentation Errors When Using Optical Coherence Tomography to Measure Retinal Nerve Fiber Layer Thickness in Glaucoma. American Journal of Ophthalmology. 2017;174:1-8. https://doi.org/10.1016/j.ajo.2016.10.020
25. Liu X, Shen M, Yuan Y, et al. Macular thickness profiles of intraretinal layers in myopia evaluated by ultrahigh-resolution optical coherence tomography. American Journal of Ophthalmology. 2015;160(1):53-61.e2. https://doi.org/10.1016/j.ajo.2015.03.012
26. Armstrong RA. Statistical guidelines for the analysis of data obtained from one or both eyes. Ophthalmic and Physiological Optics. 2013;33(1):7-14. https://doi.org/10.1111/opo.12009
27. Chen YC, Kasuga T, Lee HJ, Lee SH, Lin SY. Correlation between central corneal thickness and myopia in Taiwan. Kaohsiung Journal of Medical Sciences. 2014;30(1):20-24. https://doi.org/10.1016/j.kjms.2013.08.008
28. Mumcuoglu T, Townsend KA, Wollstein G, et al. Assessing the Relationship Between Central Corneal Thickness and Retinal Nerve Fiber Layer Thickness in Healthy Subjects. American Journal of Ophthalmology. 2008;146(4):561-566. https://doi.org/10.1016/j.ajo.2008.05.038
29. Abbott CJ, Grünert U, Pianta MJ, McBrien NA. Retinal thinning in tree shrews with induced high myopia: Optical coherence tomography and histological assessment. Vision Research. 2011;51(3):376-385. https://doi.org/10.1016/j.visres.2010.12.005
30. Garcia-Valenzuela E, Mori M, Edward DP, Shahidi M. Thickness of the peripapillary retina in healthy subjects with different degrees of ametropia. Ophthalmology. 2000;107(7):1321-1327. https://doi.org/10.1016/S0161-6420(00)00166-4
31. Ahuja S, Anand D, Dutta TK, Roopesh Kumar VR, Kar SS. Retinal nerve fiber layer thickness analysis in cases of papilledema using optical coherence tomography - A case control study. Clinical Neurology and Neurosurgery. 2015;136:95-99. https://doi.org/10.1016/j.clineuro.2015.05.002
32. Gupta P, Cheung CY, Baskaran M, et al. Relationship between Peripapillary Choroid and Retinal Nerve Fiber Layer Thickness in a Population-Based Sample of Nonglaucomatous Eyes. American Journal of Ophthalmology. 2016;161:4-11.e2. https://doi.org/10.1016/j.ajo.2015.09.018
33. Hoh ST, Lim MCC, Seah SKL, et al. Peripapillary Retinal Nerve Fiber Layer Thickness Variations with Myopia. Ophthalmology. 2006;113(5):773-777. https://doi.org/10.1016/j.ophtha.2006.01.058

34. Wu RY, Wong TY, Zheng YF, et al. Influence of refractive error on optic disc topographic parameters: The Singapore malay eye study. American Journal of Ophthalmology. 2011;152(1):81-86. https://doi.org/10.1016/j.ajo.2011.01.018
35. Samarawickrama C, Hong T, Jonas JB, Mitchell P. Measurement of Normal Optic Nerve Head Parameters. Survey of Ophthalmology. 2012;57(4):317-336. https://doi.org/10.1016/j.survophthal.2011.12.001
36. Kuang TM, Liu CJL, Ko YC, Lee SM, Cheng CY, Chou P. Distribution and associated factors of optic disc diameter and cup-to-disc ratio in an elderly Chinese population. Journal of the Chinese Medical Association. 2014;77(4):203-208. https://doi.org/10.1016/j.jcma.2014.01.006
37. Tai ELM, Ling JL, Gan EH, Adil H, Wan-Hazabbah WH. Comparison of peripapillary retinal nerve fiber layer thickness between myopia severity groups and controls. International Journal of Ophthalmology. 2018;11(2):274-278. https://doi.org/10.18240/ijo.2018.02.16
38. Hwang AM, Salchow DJ. Refractive Error and Optical Coherence Tomography (OCT) of the Retina. Investigative Ophthalmology & Visual Science. 2009;50(13):1081.
39. Refractive Error Distorts OCT Measurements. Review of Optometry. Published 2021. https://www.reviewofoptometry.com/article/refractive-error-distorts-oct-measurements
40. Westphal V, Rollins A, Radhakrishnan S, Izatt J. Correction of geometric and refractive image distortions in optical coherence tomography applying Fermat's principle. Optics Express. 2002;10(9):397. https://doi.org/10.1364/oe.10.000397
41. Podoleanu A, Charalambous I, Plesea L, Dogariu A, Rosen R. Correction of distortions in optical coherence tomography imaging of the eye. Physics in Medicine and Biology. 2004;49(7):1277-1294. https://doi.org/10.1088/0031-9155/49/7/015
42. Tan J, Qiu R, Ding X, et al. Correction of refractive distortion in whole-eye optical coherence tomography imaging of the mouse eye. Journal of Biophotonics. 2022;15(12):e202200146. https://doi.org/10.1002/jbio.202200146
43. Samarawickrama C, Wang JJ, Huynh SC, et al. Ethnic differences in optic nerve head and retinal nerve fibre layer thickness parameters in children. British Journal of Ophthalmology. 2010;94(7):871-876. https://doi.org/10.1136/bjo.2009.158279