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The analysis of macular thickness asymmetry in primary open angle glaucoma using Spectral-Domain Optical Coherence Tomography

Analiza asymetrii grubości plamki u chorych na jaskrę pierwotną otwartego kąta w badaniu spektralnej optycznej tomografii komputerowej

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Abstract:

Purpose: To analyze central retinal thickness asymmetry in patients with known and suspected primary open angle glaucoma. **Material and methods:** A prospective analysis of 21 patients with known glaucoma and 53 patients with suspected glaucoma. A control group consisted of 25 healthy volunteers. Each enrolled patient had a spectral domain optical coherence tomography performed including a circumpapillary retinal nerve fiber layer and central retinal thickness measurements. A central 20 degree area was divided into 64 3° x 3° areas. The mean retinal thickness was measured in each small square and the value obtained in the upper half of every square was compared to the corresponding value in the lower half. A correlation between the mean circumpapillary retinal nerve fiber layer thickness and the central retinal thickness was assessed. **Results:** The mean thickness of circumpapillary retinal nerve fiber layer was significantly lower in patients with known and suspected glaucoma ($92.15 \pm 12.85 \mu\text{m}$; $93.84 \pm 11.45 \mu\text{m}$ vs. $97.82 \pm 7.48 \mu\text{m}$; $P < 0.05$). The mean central retinal thickness did not differ significantly between the groups ($291.05 \pm 15.86 \mu\text{m}$; $290.46 \pm 13.60 \mu\text{m}$ vs. $293.94 \pm 11.07 \mu\text{m}$; $P > 0.05$). Macular asymmetry was detected significantly more frequently in glaucomatous and glaucoma suspected eyes (78%; 66% vs. 32%; $P < 0.05$). An association between the measured values was observed. **Conclusions:** The macular thickness measurements and macular asymmetry analysis may represent a novel strategy in glaucoma diagnosis.

Key words:

glaucoma, Spectral-Domain Optical Coherence Tomography (SD-OCT), macular thickness, macular asymmetry.

Abstrakt:

Cel: ocena asymetrii grubości siatkówki centralnej u chorych na pierwotną jaskrę otwartego kąta oraz u osób, u których podejrzewano jaskrę.

Material i metody: prospektywna analiza 21 przypadków pacjentów, u których rozpoznano jaskrę, oraz 53 osób, u których podejrzewano jaskrę. Za pomocą spektralnej optycznej koherentnej tomografii oceniano grubość warstwy włókien nerwowych wokół tarczy nerwu wzrokowego oraz grubość siatkówki centralnej. Obszar plamki podzielono na 64 pola wielkości 3 x 3 stopnie. Porównano grubości siatkówki w każdym z tych pól z górną półkuli z grubością siatkówki w odpowiadającym mu polu z dolnej półkuli. Oceniono zależność między grubością warstwy włókien nerwowych tarczy nerwu wzrokowego a centralną grubością siatkówki. Grupę kontrolną stanowiło 25 zdrowych ochotników.

Wyniki: średnio warstwa włókien nerwowych była istotnie cieńsza u pacjentów, u których rozpoznano jaskrę, i u osób, u których ją podejrzewano ($92,15 \pm 12,85 \mu\text{m}$; $93,84 \pm 11,45 \mu\text{m}$ wobec $97,82 \pm 7,48 \mu\text{m}$; $P < 0,05$). Nie stwierdzono, aby u badanych z poszczególnych grup istniały statystycznie istotne różnice w grubości siatkówki centralnej ($291,05 \pm 15,86 \mu\text{m}$; $290,46 \pm 13,60 \mu\text{m}$ wobec $293,94 \pm 11,07 \mu\text{m}$; $P > 0,05$). Asymetria grubości plamki istotnie częściej występowała u pacjentów z badanych grup niż u osób z grupy kontrolnej (78%; 66% wobec 32%; $P < 0,05$). Obserwowano zależność między badanymi grubościami siatkówki.

Wnioski: pomiar grubości centralnej siatkówki oraz analiza asymetrii grubości siatkówki w plamce mogą być przydatne do diagnozowania jaskry.

Słowa kluczowe:

jaskra, spektralna optyczna tomografia komputerowa (SD-OCT), grubość plamki, asymetria plamki.

Introduction

Glaucoma is a progressive optic neuropathy causing damage to retinal ganglion cells and their axons, which may manifest as optic disc cupping and thinning of the retinal nerve fiber layer (RNFL). If diagnosed at the later stage, the course of the disease is usually more severe. Hence, an accurate ear-

ly detection of retinal damage is crucial for better management of glaucoma (1, 2).

The traditional diagnostic management of glaucoma utilizes different imaging devices to assess the optic disc, e.g. measure its cupping and the circumpapillary RNFL (cpRNFL) thickness. RNFL defects are detected the earliest, as they precede all cli-

nically significant changes within an optic disc and the onset of irreversible visual field defects (3).

However, the optic disc size is well known to influence the diagnostic accuracy of many devices (4, 5). Macular ganglion cell count is more stable in healthy patients, because their size and shape are similar in all cases (6, 7), whereas the size and shape of the optic nerve are highly variable. The examination of the macula and paramacular region with Spectral-Domain Optical Coherence Tomography (SD-OCT) may prove to be useful for distinguishing between the early glaucomatous eye and the healthy one.

Ganglion cells form several layers in macular region, so even a 50% loss should not cause any abnormalities in a central visual field. On the other hand, the same loss outside the paramacular region disrupts visual pathway causing visual field defects. We assume that in early glaucoma some ganglion cell loss in a paramacular region must occur, despite normal central vision, which can be detected in an SD-OCT retinal thickness (RT) measurement. This loss is manifested as an asymmetry in the RT between the two hemispheres of the same eye or between the two eyes. RT measurements in a posterior pole and asymmetry analysis are possible owing to the new in-built protocol of Spectralis OCT.

The aim of this study was to compare the diagnostic potential of cpRNFL measurements and macular thickness asymmetry (MTA) measured using spectral-domain optical coherence tomography in patients with known or suspected primary open angle glaucoma (POAG).

Material and methods

The prospective, cross-sectional study was carried out in 41 eyes of 21 consecutive patients with known pre-perimetric POAG and 106 eyes of 53 patients with suspected glaucoma.

The diagnosis of glaucoma was established with baseline tonometry (IOP > 21 mmHg) and dilated fundus exam (disc cupping, C/D ratio > 0.5) with a normal visual field. The glaucoma group (group A) consisted of 21 subjects started on anti-glaucoma medication aiming at achieving a target intraocular pressure (IOP).

53 subjects not using anti-glaucoma medications were enrolled in the study as the suspected glaucoma group (group B), based on the following criteria: A) IOP > 21 mmHg in 3 consecutive measurements without any clinically significant changes to the optic disc or visual field, B) optic disc abnormalities typical of glaucoma seen in a dilated fundus exam with a normal IOP and normal visual field results.

Finally, 50 eyes of 25 volunteers with normal IOP, without macular or perimetric abnormalities were enrolled in the study as a control group (group C).

The exclusion criteria were common for all groups and included: the presence of any macular abnormalities, high myopia and hyperopia (> ±6.0 Dsph), as well as the history of ocular trauma other than uneventful phacoemulsification. Only high quality SD-OCT images were analyzed.

All participants underwent a full ophthalmic examination including best-corrected visual acuity (Snellen), tonometry, biomicroscopy and dilated fundus exam. The visual field was assessed in each subject using Humphrey field analyzer (HFA, Carl Zeiss Meditec Inc, Dublin, California).

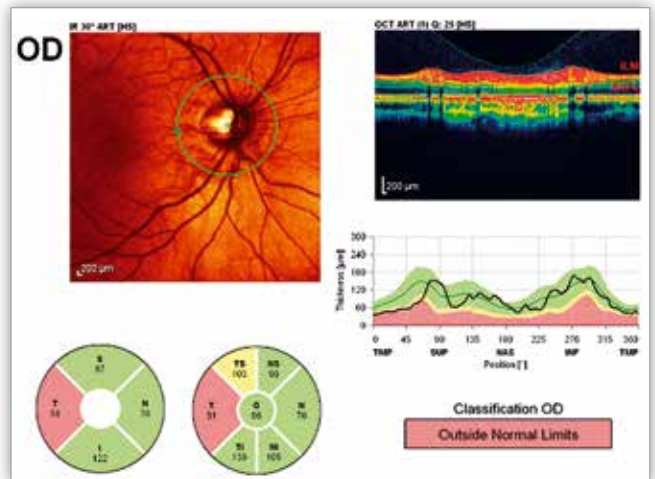


Fig. 1. Automated measurement of the retinal nerve fiber layer thickness using the SD-OCT. The results are then classified as within or outside the reference ranges.

Ryc. 1. W badaniu spektralnej optycznej koherentnej tomografii w sposób automatyczny zmierzono grubość warstwy włókien nerwowych. Następnie wyniki klasyfikowano jako w granicach normy lub poza granicami normy.

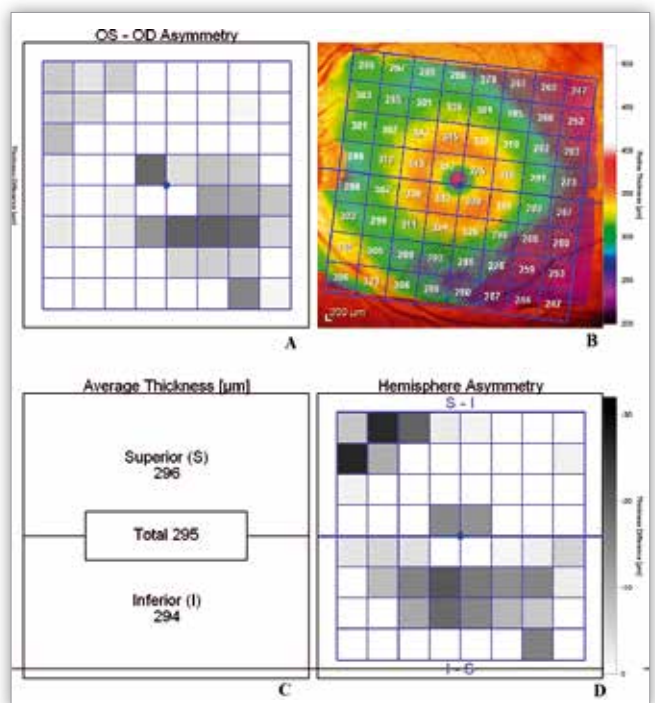


Fig. 2. SD-OCT macular asymmetry analysis report. The central 20-degree area is divided into 64 units (squares) and the obtained colour-coded map is projected onto fundus photograph (B). Every small square (3 x 3 degrees) of one hemisphere is weighed against the corresponding square of the other eye (A) and of the other hemisphere in the same eye (D); the difference is presented in a gray scale. The graph shows the mean central retinal thicknesses: global value and separate values for each hemisphere (C).

Ryc. 2. Wynik badania asymetrii plamki. Centralne 20 stopni jest podzielone na 64 pola; mapa, która powstała, jest prezentowana na fotografii plamki (B). Każde z małych pól jest porównywane z odpowiadającym polem z drugiego oka (A) oraz z drugiej półkuli tego samego oka (D), wyniki są prezentowane w skali szarości. Diagram prezentujący średnią grubość siatkówki centralnej oraz obu półkul plamki (C).

The SD-OCT was performed using Spectralis HRA+OCT (Heidelberg Engineering, Heidelberg, Germany) capable of measuring the cpRNFL and macular thickness.

CpRNFL thickness was assessed globally and in 6 zones: superior temporal, temporal, inferior temporal, inferior nasal, nasal and superior nasal (Fig. 1). These measurements were weighed against a normative database incorporated into the SD-OCT device and classified as within or outside the reference range.

A novel retinal thickness protocol was used for macular imaging (8). The mean RT in two hemispheres of the same eye was analyzed. The central 20 degree area was divided into 64 smaller units, each sized 3° x 3°. The mean RT was measured separately for each small square in the upper half and the results were weighed against the mean RT in the corresponding squares in the lower half (Fig. 2). A significant asymmetry was defined as the RT reduction by 10–20 microns in at least 4 adjacent 3° x 3° units, as well as the RT reduction by more than 20 microns in at least 2 adjacent units and their counterparts in the other hemisphere. 6 outermost zones of the nasal superior and nasal inferior quadrants of each eye were excluded from analysis due to the physiology of retinal vasculature in the scanned areas, as a slight asymmetry between the upper and lower temporal arcades yielded a significant RT asymmetry, which could be easily identified as a false positive result when a colour-coded image is projected onto a fundus photograph.

The CpRNFL thickness defects were compared with central RT and MTA in each group. The differences between the groups in the cpRNFL and macular thickness were compared using the Mann-Whitney U test. The correlation between the mean cpRNFL thickness and the RT was expressed as the Pearson’s correlation coefficient.

Results

Our clinical findings are summarized in Table I. The early glaucoma group consisted of 41 eyes of 5 male and 16 female patients at the mean age of 48.9 ± 17.9 years, while 106 eyes were enrolled in the glaucoma suspect group (44.3 ± 19.1 years, 15 males). The best-corrected visual acuity (BCVA) measured on Snellen’s chart ranged from 0.5 to 1.0 (mean ± SD: 0.94 ± 0.15 vs. 0.96 ± 0.11 vs. 0.97 ± 0.11 for the three study groups, respectively; P>0.05). Subjects in group B presented with significantly higher IOP (P<0.05).

	Group A/ Grupa A	Group B/ Grupa B	Group C/ Grupa C
Age (years)/ Wiek (lata)	48.9 ± 15.6	44.3 ± 19.1	39.3 ± 15.1
Sex (male : female)/ Płeć (mężczyźni : kobiety)	5 : 16	15 : 38	7 : 18
BCVA/ Najlepsza skorygowana ostrość wzroku (Snellen)	0.94 ± 0.15	0.96 ± 0.11	0.97 ± 0.11
IOP/ Ciśnienie wewnątrzgałkowe (mmHg)	15.37 ± 2.94	17.99 ± 4.51	14.53 ± 3.45

Tab. I. Patient characteristics (BCVA – best corrected visual acuity, IOP – Intraocular pressure).

Tab. I. Charakterystyka pacjentów (BCVA – najlepsza skorygowana ostrość wzroku, IOP – ciśnienie wewnątrzgałkowe).

cpRNFL (µm)	Group A/ Grupa A	Group B/ Grupa B	Group C/ Grupa C	P
Global/ Ogółem	92.15 ± 12.85	93.84 ± 11.45	97.82 ± 7.48	<0.05
Temporal superior/ Kwadrant skroniowy górny	120.80 ± 29.73	127.63 ± 21.20	133.38 ± 14.19	<0.05
Nasal superior/ Kwadrant nosowy górny	89.64 ± 21.38	96.75 ± 18.02	101.42 ± 16.50	<0.05
Nasal/ Kwadrant nosowy	66.90 ± 17.89	71.95 ± 16.28	68.18 ± 13.48	
Nasal inferior/ Kwadrant nosowy dolny	95.07 ± 23.54	108.42 ± 23.23	112.58 ± 19.71	<0.05
Temporal inferior/ Kwadrant skroniowy dolny	138.98 ± 23.12	138.93 ± 20.77	145.70 ± 19.62	<0.05
Temporal/ kwadrant skroniowy	78.44 ± 19.79	67.57 ± 10.90	75.65 ± 10.47	

Tab. II. The circumpapillary retinal nerve fibre layer (cpRNFL) thickness in individual quadrants measured using SD-OCT.

Tab. II. Grubości warstwy włókien nerwowych wokół tarczy nerwu wzrokowego (cpRNFL) w poszczególnych kwadrantach mierzone za pomocą spektralnej optycznej koherentnej tomografii.

The results of the SD-OCT cpRNFL measurements are shown in Table II. The global cpRNFL was significantly thinner in eyes with known and suspected glaucoma, as compared to controls (mean ± SD: 92.15 ± 12.85 µm and 93.84 ± 11.45 µm vs. 97.82 ± 7.48 µm for the three study groups, respectively; P<0.05). The measurement of the sectoral RNFL thickness demonstrated significant differences between groups A and B as compared to group C for all sectors, except for the nasal (N) and temporal (T) ones (P<0.05).

The results of macular RT measurements and asymmetry analysis are summarized in Table III. The obtained values were

Central retinal thickness (µm)/ Centralna grubość siatkówki (µm)	Group A/ Grupa A	Group B/ Grupa B	Group C/ Grupa C	P
Total/ Ogółem	291.05 ± 15.86	290.46 ± 13.60	293.94 ± 11.07	
Superior/ Półkula górna	291.71 ± 16.82	291.22 ± 13.82	294.12 ± 12.24	
Inferior/ Półkula dolna	290.29 ± 15.27	289.84 ± 14.22	293.58 ± 10.51	
Superior – inferior difference/ Różnica między półkulą górną a dolną	5.73 ± 4.76	5.21 ± 4.34	3.9 ± 2.27	<0.05
Macular thickness asymmetry/ Asymetria grubości plamki	31 eyes (76%)	70 eyes (66%)	16 eyes (32%)	<0.05

Tab. III. The central retinal thickness measured using SD-OCT. The percentage of patients with macular thickness asymmetry in each group.

Tab. III. Centralna grubość siatkówki mierzone za pomocą spektralnej optycznej koherentnej tomografii. Odsetek pozytywnych wyników asymetrii grubości plamki u badanych z poszczególnych grup.

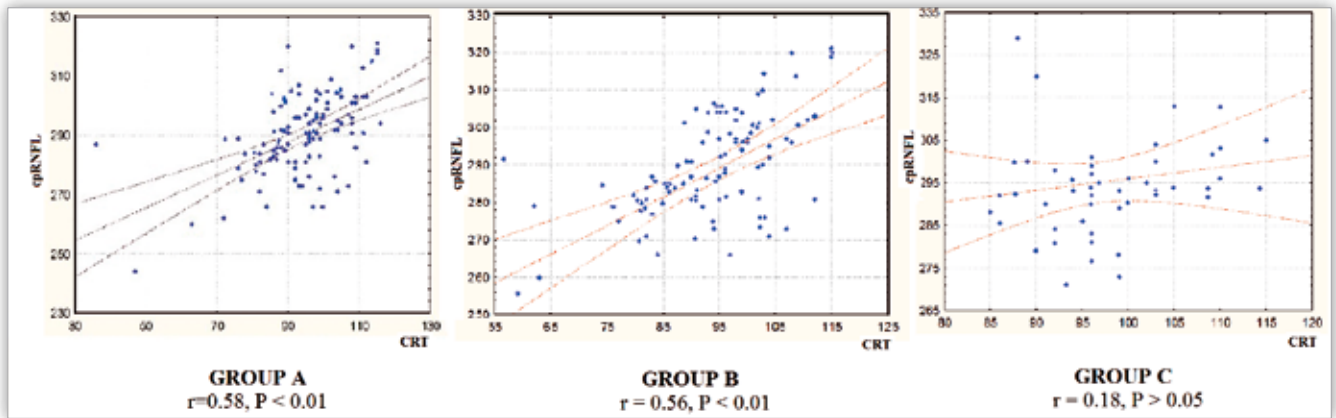


Fig. 3. The association between the circumpapillary retinal nerve fiber layer thickness and central retinal thickness expressed as the Pearson's correlation coefficient.

Ryc. 3. Zależność między grubością warstwy włókien nerwowych wokół tarczy nerwu wzrokowego a centralną grubością siatkówki wyrażona jako współczynnik korelacji Pearsona.

similar in all the groups ($291.05 \pm 15.86 \mu\text{m}$ vs. $290.46 \pm 13.60 \mu\text{m}$ vs. $293.94 \pm 11.07 \mu\text{m}$; $P > 0.05$). The mean difference between the two hemispheres was significantly higher in groups A and B with MTA observed significantly more frequently in these groups (76% vs. 66% vs. 32% for groups A, B and C, respectively; $P < 0.05$).

The association between the cpRNFL thickness (global and sectoral) and the central RT (total, superior and inferior) was investigated. The highest correlation coefficients for the global cpRNFL ($r = 0.58$, $P < 0.01$) and for the TI region ($r = 0.69$, $P < 0.01$) were observed in glaucoma group. Furthermore, in eyes with suspected glaucoma, there was a statistically significant correlation between the circumpapillary retinal thinning and the reduction of central RT in all units ($P < 0.05$). No such association was found in the control group, where the cpRNFL thinning was not followed by the macular thickness reduction, and the correlation coefficients were: $r = 0.18$ globally, $r = 0.16$ for the upper and $r = 0.21$ for the lower hemisphere ($P > 0.05$). The association between the global cpRNFL thickness and the central RT for all groups is shown in Figure 3.

Macular thickness asymmetry analysis

Group A

Macular thickness asymmetry (MTA) was shown in 31 eyes (76%) in group A. In most cases, central retinal thinning involved either an inferior nasal quadrant (IN) only (29.3%) or the IN along with the inferior temporal (IT) quadrant (9.8%). In 7 eyes (17.1%) the MTA was confirmed in the superior nasal (SN) quadrant and in another 2 eyes in SN along with 1 other quadrant. The asymmetry in the temporal portion of the macula was identified less frequently and if confirmed, it was mainly limited to the lower hemisphere (19.5%). 10 eyes had no macular thickness asymmetry and in 6 other eyes the asymmetry was shown without any cpRNFL defects. Finally, in 3 eyes the asymmetry was concomitant with abnormal cpRNFL thickness in the corresponding inferior and superior fibre bundles.

Group B

34% of eyes had no macular thickness asymmetry. In another 34%, the analysis revealed a reduction of central

RT in the inferior nasal (IN) quadrant: isolated RT reduction in the IN quadrant in 22 eyes (20.7%) and in the IN along with 1 other quadrant (14 eyes). In 16 eyes (26.6%) the MTA was confirmed in the superior nasal (SN) quadrant and in another 8 eyes (13.3%) in SN along with 1 other quadrant, without any concomitant cpRNFL defects in all these cases.

The cpRNFL defects were observed in 38 eyes (35.8%) and the initial RT reduction in the corresponding hemisphere was confirmed in 22 of these eyes.

Group C

Out of 50 eyes of 25 healthy volunteers in a control group, 44 eyes (88%) presented with a normal cpRNFL thickness in all analyzed segments. In the majority of cases (31 eyes, 62%) no asymmetry was observed. Another 9 eyes showed a significant central reinal thinning in the temporal quadrants of the upper (14%) or lower (4%) hemispheres. 6 eyes (12%) in the control group had a confirmed cpRNFL defect in a single quadrant. In 3 eyes, this reduction was not associated with any macular thickness asymmetry. We observed no correlation between the quadrant with a confirmed cpRNFL defect and the hemisphere with macular thickness reduction and asymmetry.

Discussion

Retinal thickness mapping was first proposed for quantitative detection of glaucomatous damage at the posterior pole by Zeimer (9). Other reports confirmed this hypothesis, nevertheless the discrimination power of macular thickness measurements was lower than the one of cpRNFL thickness measurements using a time domain optical coherence tomography (TD-OCT) (10–12). A significant structural relationship between macular thickness measured with TD-OCT and visual field (VF) defects in glaucoma was also confirmed (13, 14). The VF defects limited to one hemisphere only were usually associated with macular thickness asymmetry (14).

Due to higher resolution and improved scanning speed of SD-OCT, high density scanning over a large macular region with less motion artifacts has become possible (15). Spectralis HRA + OCT device has an in-built 3-dimensional eye-tracking system, which enables obtaining up to 100 B-scans of exactly the same location. It yields an improved accuracy and repe-

atability of macular imaging, increasing its diagnostic potential in glaucoma (16). Nakatani et al. reported high discriminating power of such macular parameters as thickness and volume measured using the SD-OCT, comparable with the one of peripapillary RNFL measurements in early glaucoma. Their reproducibility did not differ significantly, either (17).

However, our study shows that despite confirmed macular thinning globally and separately in the upper and lower hemispheres across the study groups, the differences between the three groups were not statistically significant.

Lee et al. suggested that total macular thickness measured using Cirrus SD-OCT may offer higher efficacy in detecting progressive VF loss in patients with early glaucoma, as compared to cpRNFL thickness measurements (18).

In 2011 Asrani et al. presented a novel software strategy for glaucoma diagnosis using SD-OCT (8). Macular thickness is presented as an 8x8 colour-coded grid with the fovea in the centre of the grid, symmetrically in two eyes. The protocol uses a compressed colour scale to highlight the differences in macular thickness in corresponding areas of both eyes, and two hemispheres of the same eye (Fig. 1).

Rolle et al., who evaluated the correlation between the visual field sensitivity and macular thickness, also used Spectralis posterior pole analysis. They reported statistically significant correlations between the structure and function for the quadrant mean RT values, suggesting that these measurements may provide additional data in glaucoma detection (19).

To the best of our knowledge, our study is the first to assess the concomitance and correlation between macular asymmetry seen in SD-OCT and the RNFL loss in glaucoma. Recent studies have shown that the macular asymmetry analysis may offer higher sensitivity than the mean cpRNFL thickness measurements in eyes with early-stage glaucoma, with a similar specificity (20).

Currently, there are no clear guidelines on glaucoma diagnosis based on the assessment of macular thickness asymmetry. Further population studies are needed. First published reports showed statistically significant physiological asymmetry of inter- and intraocular central retinal thickness in young, healthy Caucasians (21).

However, the criteria we propose in this research are in line with Seo's results, who suggested that the sensitivity and specificity of macular asymmetry analysis are comparable to these of cpRNFL thickness measurements, when two adjacent black areas sized $3^\circ \times 3^\circ$ are assumed to be glaucoma-related (22).

In our study MTA was significantly more common in eyes with known or suspected glaucoma than in healthy subjects. Retinal thinning involving the IN quadrant was shown in all groups and, interestingly, it was never present in patients with symmetrical cpRNFL defects in the upper and lower hemispheres. This study suggests that a slight retinal depression, manifested as reduced RT, may be caused by the normal retinal vessels captured in SD-OCT; therefore, it may not always be conclusive for glaucoma diagnosis. Nevertheless, as the asymmetry in the IN quadrant was detected significantly more often in groups A and B, it should be considered as glaucomatous change, especially at the presence of the cpRNFL defect in the corresponding region.

Another interesting issue is that all eyes in group A had the cpRNFL thinning in the SN quadrant concomitant with macular asymmetry in the same region. Moreover, 26.6% of patients with suspected glaucoma with the normal circumpapillary findings, presented with retinal thickness reduction in the SN quadrant of the examined area. This may indicate that the nasal part of the superior hemisphere is more susceptible to glaucomatous damage than the remaining portion of the posterior pole.

The most recent developments in posterior pole imaging make it easy to distinguish individual retinal layers. As a result it is possible to determine an asymmetry index of the macular ganglion cell-inner plexiform layer (23). Some promising data to support diagnostic utility of these findings has been reported for early stage glaucoma but not for moderate to advance stages.

Conclusions

The reduced macular thickness is associated with circumpapillary RNFL thinning. The SD-OCT of the macula and thickness asymmetry analysis may be sufficient for early glaucoma diagnosis, nevertheless further studies are needed to investigate into the character of macular changes and their association with optic nerve degeneration.

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