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Evaluation of Retinal Nerve Fiber Layer Thickness with Spectral Domain Oct in Primary Open Angle Glaucoma and Ocular Hypertension

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Abstract

Purpose: To compare Primary Open Angle Glaucoma (POAG), Ocular Hypertension (OHT) and control groups by using Visual Field (VF) and Spectral Domain Optical Coherence Tomography (SD-OCT) and to investigate correlations between VF global indices and Retinal Nerve Fiber Layer (RNFL) thickness measurements.

Methods: Forty patients with POAG, 55 patients with OHT, and 40 normal subjects were included in the study. All subjects were evaluated by standard automated perimetry and Cirrus HD-OCT.

Results: RNFL global average thickness, average thicknesses in four quadrants and at 1 o'clock, 4 o'clock, 5 o'clock, 6 o'clock, 7 o'clock, 10 o'clock, 11 o'clock and 12 o'clock areas in POAG patients were significantly decreased compared with the OHT and the control groups. RNFL thicknesses at 2 o'clock, 8 o'clock and 9 o'clock areas in the POAG group were significantly lower than control subjects. There were statistically significant and a negative correlation between PSD and RNFL global average thickness, RNFL thicknesses in temporal quadrant and at 1 o'clock and 2 o'clock areas in the POAG group. According to the areas under the ROC curve, the parameter which has the best diagnostic ability was found as RNFL thickness in the superior quadrant. The sensitivity and specificity of Cirrus HD-OCT for RNFL thickness in superior quadrant were found 77% and 87%.

Conclusion: The correlations between MD, PSD and RNFL thickness parameters could represent the consistency of functional and structural tests. RNFL measurement with SD-OCT could provide important information for detection of early stages of glaucoma.

Keywords: Optic coherence tomography; Visual field, Primary open angle glaucoma

Introduction

Glaucoma is the leading cause of irreversible blindness in the world. Primary Open Angle Glaucoma (POAG) is the most common type of glaucoma. POAG can be considered chronic, progressive optic neuropathy that is accompanied by a characteristic cupping and atrophy of the optic disc, Visual Field (VF) loss, open angles, and no obvious ocular or systemic reason [1].

Glaucomatous optic neuropathy causes progressive death of retinal ganglion cells and their axons. These structural changes precede VF defects as measured by standard automated perimetry. The peripapillary Retinal Nerve Fiber Layer (RNFL) thickness evaluation is a useful method to detect the early structural damage of glaucoma [2]. Optical Coherence Tomography (OCT) provides an objective and quantitative measurement of RNFL thickness by measuring echo time delay and intensity of backscattered light from different retinal layers using a low coherence interferometry [2,3].

The OCT was first reported by Huang et al. in 1991 [4] and since then, this device has been evolving rapidly. The most recent technology, spectral domain or Fourier domain OCT uses a spectrometer as a detector of OCT signal [5,6]. Spectral domain OCT (SD-OCT) has benefits over the time domain OCT (TD-OCT) such as higher axial resolution (3 to 6 μm), up to 200 times faster scanning speed and better reproducibility [6-11]. Measurements of optic nerve head, RNFL and macular thicknesses by OCT are using for discrimination between the glaucomatous eyes and normal eyes [12].

The purpose of this study is to compare POAG, Ocular Hypertension (OHT) and control groups by using VF and SD-OCT; to investigate correlations between VF global indices and RNFL thickness measurements and to describe the best RNFL thickness parameter to discriminate glaucoma from normal's.

Materials and Methods

Forty patients with POAG, 55 patients with OHT, and 40 normal subjects seen in Ankara University, School of Medicine, Department of Ophthalmology between September 2007 and March 2010 were included in this prospective study. Informed consent was obtained from all patients and controls. The study was conducted in accordance with the principles of the Declaration of Helsinki.

The POAG patients were included if all the following criteria were met: (1) elevated intraocular pressure (IOP) (greater than 21mm Hg) without treatment on at least two separate visits; (2) glaucomatous optic disc appearance; (3) VF damage (two or more contiguous points with a pattern deviation sensitivity loss of $P<0.01$, or three or more contiguous points with a sensitivity loss of $P<0.05$ in the superior or inferior arcuate areas, or a 10 dB difference across the nasal horizontal midline at two or more adjacent locations and an abnormal result in glaucoma hemifield test); (4) wide and open angle on gonioscopy; (5)

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no other obvious causes for these changes. Glaucomatous optic disc appearance was defined as vertical cup disc ratio >0.5, focal or diffuse thinning of the neuroretinal rim and asymmetry of the cup disc ratio ≥ 0.2 between two eyes without asymmetric refraction.

Ocular hypertensive eyes were defined as an IOP reading greater than 21mm Hg on at least two separate occasions 1-3 months apart, normal optic disc, VF and normal open angle. The control group was selected from the general ophthalmology polyclinic (Department of Ophthalmology, Ankara University School of Medicine, Ankara, Turkey). Control subjects were included if they had IOP measurements less than 21smm Hg on at least two separate occasions, absence of glaucomatous optic nerve head, a normal visual field and no family history of glaucoma. Each subject underwent a complete ophthalmologic examination including best corrected visual acuity, IOP measurements with Goldmann applanation tonometry, slit lamp biomicroscopy, gonioscopy, and fundus evaluation after pupil dilatation on the slit lamp using a 90.0 D lens. Optic discs of all patients were evaluated by both an experienced glaucoma specialist (OT) and an ophthalmologist (ES) and classified POAG, OHT, or normal. All patients and controls had no ocular surgery, history of retinal disease, and refractive error > 5 diopters of sphere or 3 diopters of cylinder. Some patients had mild cataract which did not affect examination or prevent to perform visual field test. The best corrected visual acuities of all patients were 20/40 or better and of control subjects 1.0.

All subjects underwent Standard Achromatic Perimetry on the Humphrey's Field Analyzer 750i (Model 4000 Carl Zeiss- Humphrey Systems, Dublin, CA) using the 30-2 testing protocol by SITA-FAST strategy. Visual field reliability criteria included fixation losses of less than 20% and false-positive and false-negative rates of less than 33%. Patients with no reliable VF test results obtained at two separate times were excluded. In the control group, to minimize the learning effect, the second reliable VF result obtained was included. We used two of VF global indices, Mean Deviation (MD) and Pattern Standard Deviation (PSD), in this study. The VF test indices obtained within 4 weeks before OCT scans, were included the study.

Visual field global indices and RNFL thickness measurements (global average and four quadrant average thicknesses) obtained by Cirrus HD-OCT were compared statistically for right and left eyes in all groups. There was no statistically significant difference between pairs of eyes of individuals in each of the 3 groups. The measurements obtained from the left eye were included in the study.

All included subjects were scanned with the Cirrus HD-OCT (software version 4.0) Carl-Zeiss Meditec Inc., Dublin, CA) by a single operator (ES). Scan protocol of Cirrus HD-OCT called 'optic disc cube 200 x 200' which consists of 1024 (depth) × 200 (vertical) × 200 (horizontal) data points is used for measurement of RNFL thickness. It was excluded that an image with a minimum signal strength 7/10 and below. One of the 3 scans, obtained the same day, with maximum signal strength was included. For this study, we analyzed the global average RNFL thickness, average RNFL thickness in the superior, inferior, nasal and temporal quadrants and average RNFL thickness in 12 clock hours in the 3 groups of subjects.

The results were analyzed using the SPSS for Windows software, Version 11.5 (SPSS, Chicago, II, USA) and relationships were considered significant if P<0.05. Data were reported as mean ± standard deviation (SD). The intergroup differences in sex were analyzed by the chi-square test statistics. The difference between groups in age was defined by one-way ANOVA. Pairs were compared with Bonferroni test statistics. We used an Analysis of Covariance (ANCOVA) with age as continuous covariate, because our patient groups (POAG patients, OHT patients and normal subjects) did not represent age-matched groups. We also used ANCOVA with VF and OCT parameters as the covariate to test differences between the 3 groups. The Pearson correlation coefficient was used to estimate correlations between the thickness of RNFL and global indices of VF. Visual field global indices and RNFL thickness measurements obtained by right and left eye compared with 'paired t test'.

Receiver Operating Characteristic (ROC) curves was used to describe the accuracy of each OCT parameter to differentiate glaucoma from normal controls. The diagnostic sensitivity and specificity was examined with the area under ROC curve (AUC).

Results

Forty patients (19 men, 21 women) with POAG, 55 patients (26 men, 29 women) with OHT and 40 healthy subjects (19 men, 21 women) were included in the study. There was no difference in sex between three groups. The mean age in the POAG group was 65.18 ± 10.38 years, compared with 55.87 ± 11.03 years in the OHT group and 54.58 ± 14.78 years in the control group. There was no statistically significant difference in mean age between the OHT and the control groups. The mean age of POAG group was significantly higher than that of the control group. Analysis of covariance with age was performed for adjusting the groups for age difference.

The average MD on VF in the POAG group, OHT group and normal controls was -5.81 ± 7.80, -2.12 ± 1.97, and -1.60 ± 4.25 dB respectively. The average PSD on VF in the POAG group, OHT group and normal controls was 4.55 ± 3.58, 2.30 ± 1.02, and 3.40 ± 2.24 dB respectively. Statistically significant differences between the POAG and the OHT groups, and the POAG and the control groups in MD were observed (p=0.03, and p=0.02 respectively). There was statistically significant difference between POAG and OHT groups in PSD (p<0.001).

The global average RNFL thicknesses, average RNFL thicknesses in four quadrants and in 12 clock hours measured by OCT were compared in all groups. Table 1 summarized RNFL thickness values

OCT Parameters	POAG	OHT	Control
Average	70,48 ± 21, 84	88, 62 ± 9, 98	84, 69 ± 18, 45
Quadrants	87, 43 ± 32, 01	112, 18 ± 20, 78	121, 74 ± 24, 93
Superior			
Temporal	54, 68 ± 16, 50	65, 36 ± 15, 19	63, 92 ± 15, 11
Inferior	81,93 ± 38, 01	108, 78 ± 20, 22	119, 76 ± 21, 23
Nasal	56, 40 ± 17, 45	67, 73 ± 19, 34	71, 18 ± 13,31
Clock hours	91, 79 ± 35, 68	112,43 ± 28, 02	122, 16 ± 8, 96
1			
2	63, 87 ± 21, 99	72, 13 ± 14, 27	75, 16 ± 17, 71
3	47, 49 ± 14, 27	49, 02± 8, 64	50, 47 ± 10, 52
4	58, 13 ± 17, 42	69, 69 ± 17, 85	67, 26 ± 11, 84
5	93, 64 ± 46, 87	130, 35 ± 21, 063	135, 53 ± 28, 01
6	88, 38 ± 44, 71	117, 93 ± 26, 08	128, 11 ± 27, 48
7	64, 51 ± 31, 18	88, 35 ± 17, 19	96, 47 ± 21, 74
8	54, 90 ± 20, 72	59, 31 ± 12, 95	65, 21 ± 12, 43
9	48, 85 ± 16, 36	55, 35 ± 14, 14	58, 26 ± 14, 13
10	67, 03 ± 24, 47	77, 89 ± 16, 06	85, 63 ± 22, 12
11	83, 85 ± 30, 92	107, 59 ± 17, 07	115, 84 ± 23, 50
12	92, 62 ± 37, 91	121, 57 ± 24, 57	129, 24 ± 30, 28

Table 1: The mean and standard deviation values of RNFL thicknesses in four quadrants, 12 hour quadrants and average thickness measured by SD-OCT in POAG, OHT and control groups.

in all parameters measured by OCT. RNFL global average thickness, average thicknesses in four quadrants and at 1 o'clock, 4 o'clock, 5 o'clock, 6 o'clock, 7 o'clock, 10 o'clock, 11 o'clock and 12 o'clock areas in POAG patients were significantly decreased compared with the OHT and the control groups. RNFL thicknesses at 2 o'clock, 8 o'clock and 9 o'clock areas in the POAG group were significantly lower than control subjects. There was no difference between the OHT group and the control group in any OCT parameter.

The relationships between VF global indices and OCT RNFL thickness parameters were evaluated by Pearson correlation analysis in all groups. There were statistically significant and positive correlation between MD and RNFL global average thickness, RNFL thicknesses in superior, inferior, and temporal quadrants and at 1 o'clock, 2 o'clock, 5 o'clock and 6 o'clock areas; negative correlation between PSD and RNFL global average thickness, RNFL thicknesses in temporal quadrant and at 1 o'clock and 2 o'clock areas in the POAG group (Table 2). There were statistically significant and positive correlation between MD and RNFL thicknesses at 5 o'clock and 10 o'clock areas; PSD and RNFL thicknesses at 10 o'clock area in the OHT group. There was no correlation between MD or PSD and OCT parameters in the control group.

The ROC curve area was calculated to discriminate normal eyes from glaucomatous eyes. According to the areas under the ROC curve, the parameter which has the best diagnostic ability was found as RNFL thickness in the superior quadrant (AUC=0.83, p<0.001). The following parameters were RNFL global average thickness and RNFL thickness in the inferior quadrant (AUC=0.824, p<0.001; AUC=0.822, p<0.001). Using the RNFL thickness in superior quadrant, Cirrus HD-OCT had a sensitivity of 77% and a specificity of 87% (cut-off point: 109) (Figure 1).

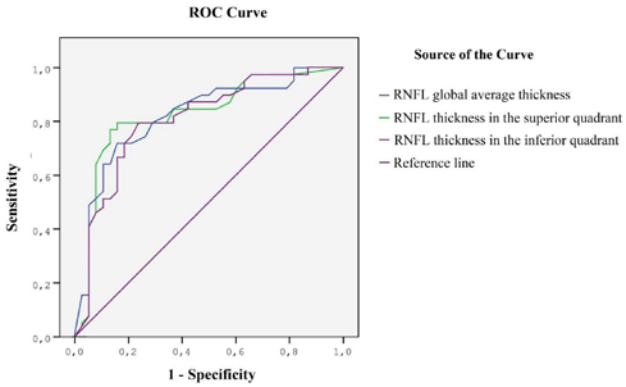

Figure 1: Calculation of the sensitivity and specificity of SD-OCT by ROC curve for RNFL thickness in superior quadrant, RNFL thickness in inferior quadrant and global average thickness. According to the areas under the ROC curve, the superior quadrant RNFL thickness was found as the best diagnostic parameter in SD-OCT RNFL thickness parameters (AUC=0.83 p<0.001). The sensitivity and specificity of Cirrus HD-OCT for RNFL thickness in superior quadrant were 77% and 87% (cut-off point: 109). AUC for RNFL global average thickness and the inferior quadrant RNFL thickness were 0,824 (sensitivity: 72%, specificity: 84%, cut-off: 87) and 0,822 (sensitivity: 80%, specificity: 76%, cut-off:111, 5) respectively.

Discussion

Because of the glaucoma is the second leading cause of blindness in the world, the main goal of glaucoma management is to diagnose this disease when it is asymptomatic. Visual field testing is essential in the diagnosis and monitoring of glaucoma. However it is known that standard perimetry can not detect VF defects until 20% - 40% of ganglion cells have been lost [13,14]. Nowadays RNFL defects have been objectively demonstrated earlier than VF defects with new investigative technologies. Measuring RNFL thickness by OCT enables an objective and quantitative assessment of glaucomatous structural loss[7]. It has been shown that all generations of OCT provide reproducible measurements of RNFL thickness in many previous studies [15-21]. Mwanza et al. [22] showed that Cirrus OCT had an excellent intravisit and intervisit reproducibility of RNFL thickness and ONH parameters. Hong et al. also reported reproducibility of Cirrus HD-OCT to analyze peripapillary RNFL thickness was excellent in healthy eyes [11].

OCT Parameters	VF-MD		VF-PSD	
	r	p	r	p
Average	0, 433**	0, 005	-0, 316	0, 047
Quadrants	0, 410**	0, 009	-0, 308	0, 054
Superior				
Temporal	0, 440**	0, 005	-0, 326*	0, 040
Inferior	0, 372*	0, 018	-0, 286	0, 074
Nasal	0, 097	0, 551	-0, 069	0, 673
Clock hours	0, 318*	0, 049	-0, 390*	0, 014
1				
2	0, 406*	0, 010	-0, 506**	0, 001
3	0, 281	0, 083	-0, 308	0, 056
4	0, 215	0, 188	-0, 107	0, 516
5	0, 368*	0, 021	-0, 293	0, 070
6	0, 339*	0, 034	-0, 294	0, 070
7	0, 291	0, 073	-0, 161	0, 328
8	0, 007	0, 968	-0, 014	0, 935
9	-0, 014	0, 935	0, 000	0, 999
10	0, 128	0, 438	-0, 127	0, 441
11	0, 250	0, 125	-0, 256	0, 116
12	0, 214	0, 192	-0, 181	0, 271

Table 2: r and p values of correlations between VF global indices (MD and PSD) and RNFL thicknesses in four quadrants, 12 hour quadrants and average thickness measured by SD-OCT in the POAG group (The Pearson correlation coefficient was used to evaluate correlations).

Mwanza et al. [22] reported that, in the mild POAG patients, focal RNFL thickness loss was found in the inferior area. In the moderately advanced disease subgroups, RNFL defects were in sectors 1, 6, and 7. RNFL defect extended through almost all sectors in the advanced disease subgroups [23]. Analysis of the pattern of RNFL defects with SD-OCT imaging demonstrated that the most frequently RNFL defects have been at the inferotemporal meridian followed by the superotemporal meridian [24]. Previous reports showed that both the measurement and classification agreements between the consecutive scans were lower in the nasal quadrant than in the other quadrants [8,20,21].

In our study, we found that RNFL global average thickness, average thicknesses in four quadrants and at 1 o'clock, 4 o'clock, 5 o'clock, 6 o'clock, 7 o'clock, 8 o'clock, 9 o'clock, 10 o'clock, 11 o'clock and 12 o'clock areas were significantly lower in POAG patients. These clock hour areas are matched with the superior, inferior and temporal quadrants for the left eye. No difference was found between the OHT group and the control group in any OCT parameter.

Norvi-Mahdavi et al. [25] reported that superior and inferior RNFL thicknesses had the highest performance for discrimination of normal controls from early glaucoma by using TD-OCT [25]. Naithani et al.

[26] compared the performance of optic nerve head and RNFL thickness parameters obtained by TD-OCT and HRT II for the detection of early to moderate glaucoma from control eyes. In differentiating early and moderate glaucoma from normal controls, the average RNFL thickness was the best parameter among the RNFL parameters [26]. Badala et al. [27] compared the ability of the four methods used imaging of optic disc and RNFL (Stratus OCT, scanning laser polarimetry, VCC, HRT III, and disc photograph). Combination of Stratus OCT average RNFL thickness and HRT III cup-disc area ratio was shown to provide a high diagnostic precision [27]. Pablo et al. [28] found similar diagnostic accuracy of OCT and scanning laser polarimetry with AUC of 0.785 and 0.758 respectively in OHT patients [28]. Yalvac et al. [29] suggested that the best parameters for distinguishing the high risk OHT group from the moderate and low risk groups, defined according to Scoring Tool for Assessing Risk (STAR) score, were inferior average and 6 o'clock area in Stratus OCT RNFL thickness parameters [29].

Huang et al. [30] compared the capability of the optic disc, peripapillary RNFL thickness, macular inner retinal layer thickness and their combinations in differentiating a glaucoma suspect from perimetric glaucoma by using SD-OCT and found that average RNFL thickness is the optimal parameter to detect perimetric glaucoma [30].

Li et al. [31] suggested that the best parameters of SD-OCT technique for discriminating normal from early glaucoma were average thickness for RNFL thickness parameters. Leite et al. [32] reported that the largest pooled AUCs were average thickness, inferior quadrant thickness and superior quadrant thickness. Disease severity was found a significant effecting factor in the detection of glaucoma [32]. Jeoung et al. [33] found no significant difference between the AUROCs for the best parameters of the Cirrus OCT (inferior thickness) and Stratus OCT (7 o'clock sector). Previous studies have mostly reported that RNFL thickness in inferior quadrant and RNFL average thickness have the best performance to discriminate healthy eyes from glaucomatous eyes [12,25,26,29-31,33]. In our study, we found RNFL thickness in superior quadrant as the best parameter to distinguish glaucomatous eyes. Lee et al. [34] determined the rate of RNFL thinning in affected clock hour sectors had the highest ability to discriminate stable RNFL thinning than progressive RNFL thinning (sensitivity of 62%, specificity ≥ 80%). Schulze et al. [12] evaluated the diagnostic ability of retinal ganglion cell complex, macular thickness, peripapillary RNFL thickness and optic nerve head parameters with SD-OCT in open angle glaucoma patients, patients with OHT and normal subjects. The parameters who have best diagnostic ability in the comparison between glaucoma patients and normal subjects was reported cup disc ratio, RNFL average thickness, and ganglion cell complex global loss volume, respectively. There were no differences between patients with OHT and normal subjects in optic nerve head, RNFL and ganglion cell complex [12].

We assessed the diagnostic ability of SD-OCT to distinguish between glaucomatous eyes from normal eyes. In our study, the best parameter to differentiate glaucoma from healthy controls was found as RNFL thickness in the superior quadrant. Our AUC results suggest that the RNFL thickness in the superior quadrant was the most useful parameter for detecting changes in RNFL thickness in glaucomatous eyes. The following parameters were RNFL global average thickness and RNFL thickness in inferior quadrant. In this study, according to the RNFL thickness in superior quadrant, which has the largest pooled AUC, we found that Cirrus HD-OCT had a sensitivity of 77% and a specificity of 87%.

Taliantzis et al. [35] found a moderate correlation between RNFL thickness measured by Stratus OCT and VF indices (mean sensitivity, mean defect, loss variance). The correlation became stronger when the structural alterations became deeper in OCT. They suggested that segmental RNFL thickness was more reliable index than average thickness for early diagnosis of glaucoma and for follow-up of patients with OHT.

Although SITA-Standard is more commonly used strategy for glaucoma patients, we used SITA-Fast strategy which provides faster assessment. It's known that, SITA test strategies are faster than older strategies. SITA-Standard takes 50% less time and SITA-Fast takes 70% less time compared with Full-Threshold test [36]. Even though more variability is allowed between repeated measurements in SITA-Fast strategy, the sensitivity and specificity of SITA-Fast and SITA-Standard in detecting glaucomatous defects were found similar [37]. We wanted to evaluate the correlation between VF indices obtained with SITA-Fast strategy and RNFL thicknesses to see SITA-Fast test is adequate for crowded polyclinic conditions. We found a moderate correlation between VF global indices and OCT RNFL thickness parameters in the POAG group and a weak correlation in the OHT group. Statistically significant and positive correlation between MD and RNFL global average thickness, RNFL thicknesses in superior, inferior, and temporal quadrants and at 1 o'clock, 2 o'clock, 5 o'clock and 6 o'clock areas; negative correlation between PSD and RNFL global average thickness, RNFL thicknesses in temporal quadrant and at 1 o'clock and 2 o'clock areas were defined in the POAG group. These correlations between MD, PSD and RNFL thicknesses are clinically important. Determination of the correlations between MD and global average thickness, superior, inferior, and temporal quadrant thicknesses made us think that we can use and evaluate these tests together. There was statistically significant and positive correlation between MD and RNFL thicknesses at 5 o'clock and 10 o'clock areas in the OHT group. There was no correlation between MD or PSD and OCT parameters in the control group.

The positive correlation defined in this study between MD and RNFL thicknesses in super temporal and infer temporal hour quadrants and the negative correlation between PSD and RNFL thickness in super temporal hour quadrants may represent the consistency of functional and structural tests. But further studies are needed on this subject.

Early diagnosis of glaucoma and early initiation of treatment is so important, therefore further vision loss can be stopped or slowed down. RNFL measurement with SD-OCT could provide important information for detection and evaluation of glaucoma. Our patients in the POAG group were patients with early glaucoma and SD-OCT could determine significant differences between these patients and healthy subjects and these patients and patients with OHT in RNFL thickness measurements.

The evaluation by SD-OCT is not superior to ophthalmologist. SD-OCT is not the end point of technology. Because of this data acquired from SD-OCT, which can be a guide for us, must be evaluated with the clinical findings of glaucoma patients together.

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