Optical Coherence Tomographic Analysis of Eyes with Early Glaucomatous Visual Field Damage*

Erken Glokomatöz Görme Alanı Hasarı Olan Gözlerin Optik Koherens Tomografik Analizi

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ABSTRACT

Purpose: To evaluate retinal nerve fiber layer (RNFL) and optic nerve head characteristics of eyes with early visual field (VF) damage using spectral domain optical coherence tomography (SD-OCT) in primary open angle glaucoma (POAG).

Materials and Methods: Forty-five eyes with early glaucoma based on Hodapp-Parrish-Anderson classification (early glaucoma group) and 42 healthy eyes with normal SD-OCT and VF tests (control group) were retrospectively reviewed. The SD-OCT parameter values (average, superior, inferior, nasal and temporal RNFL thicknesses, RNFL symmetry, rim area, disc area, average cup/disc ratio [C/D], vertical C/D ratio and cup volume) were compared between the early glaucoma and control groups. Moreover, a receiver operating characteristic (ROC) analysis was performed and the area under the ROC curve (AUC) was calculated for the each OCT parameter to determine diagnostic cut points for early glaucoma.

Results: The average, superior, inferior, nasal and temporal RNFL thicknesses, RNFL symmetry and rim area values were decreased, and average C/D, vertical C/D and cup volume were increased in the early glaucoma group compared to those of the control group ($P<0.05$). Average, superior, and inferior RNFL thicknesses and rim area showed good diagnostic performance based on AUC values (AUCs>0.80). Values of 84, 110, 113 microns and 1.24 mm^2 (respectively) were found as the cut points for early glaucomatous VF defect.

Conclusions: The SD-OCT parameters appear to be diminished in eyes with early glaucomatous VF damage. Moreover, cut points regarding average, superior, inferior RNFL thicknesses and rim area might assist in discriminating early glaucoma from normal in clinical practice.

Key Words: Cut point; early glaucoma; optical coherence tomography; receiver operating characteristic; visual field.

ÖZ

Amaç: Primer açık açılı glokomda (PAAG), spektral domain optik koherens tomografi (SD-OKT) ile erken glokomatöz görme alanı hasarı olan gözlerin retina sinir lifi tabakası (RSLT) ve optik sinir başı (OSB) özelliklerinin incelenmesi.

Gereç ve Yöntem: Hodapp-Parrish-Anderson sınıflandırma sistemine göre erken glokomlu 45 göz (erken glokom grubu) ve normal GA ve SD-OKT testine sahip 42 sağlıklı göz (kontrol grubu) geriye yönelik olarak incelendi. Erken glokom ve kontrol grupları, SD-OKT parametreleri (ortalama, superior, inferior, nazal ve temporal RSLT kalınlıkları, RNFL simetrisi, rim alanı, disk alanı, ortalama çukur/disk oranı [C/D], vertikal C/D oranı ve çukur hacmi) bakımından karşılaştırıldı. Ayrıca, erken glokom tanısı için tanısal eşik noktalarını belirlemek üzere her OKT parametresi için "alıcı işletim karakteristiği (AİK)" analizi uygulandı ve "eğri altında kalan alan (EAA)" hesaplandı.

Bulgular: Kontrol grubu ile karşılaştırıldığında, erken glokom grubunda ortalama, superior, inferior, nazal ve temporal RSLT kalınlıkları, RNFL simetrisi ve rim alanı değerlerinde azalma, ortalama C/D, vertikal C/D ve çukur hacmi parametre değerlerinde artma saptandı ($P<0.05$). EAA değerlerine bakıldığında (EAA>0.80), ortalama, superior, inferior RSLT kalınlıkları ve rim alanı parametreleri iyi derecede tanısal performans gösterdi ve sırasıyla 84, 110, 113 mikron ve 1.24 mm^2 değerleri erken glokomatöz GA kaybı için eşik nokta olarak bulundu.

Sonuç: Erken glokomatöz GA hasarı olan gözlerde SD-OKT parametrelerinin de bozulmuş olduğu görülmektedir. Ayrıca, ortalama, superior ve inferior RSLT kalınlıkları ve rim alanı için saptanan eşik değerleri klinik uygulamada erken glokomu normalden ayırmada yardımcı olabilir.

Anahtar Kelimeler: Alıcı işletim karakteristiği; erken glokom; eşik noktası; görme alanı; optik koherens tomografi.

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INTRODUCTION

Progressive retinal nerve fiber layer (RNFL) damage is the main mechanism in glaucoma pathogenesis, which leads typical optic nerve head (ONH) changes.[1,2] However, it was suggested that functional reflection of structural damage could be detected with a delay of several years with conventional visual field (VF) tests.[3] Hence, ocular diagnostic devices focused on uncovering RNFL abnormality, which was reported to precede glaucomatous VF damage.[4,5] There is growing evidence that spectral domain optical coherence tomography (SD-OCT) is an effective technology for detecting initial structural changes in preperimetric and early glaucoma.[4-8] On the other hand, only 10% of the total glaucoma patients can be diagnosed in an early stage using OCT and VF tests.[9,10]

Although standard automated perimetry (SAP) remains as the gold standard method for glaucoma diagnosis and follow-up, quantitative assessment of RNFL and ONH morphology provides an objective approach. Moreover, it can be valuable to determine alterations in SD-OCT parameters indicative of early glaucomatous damage.

In the present study, we investigated optical coherence tomographic hallmarks of early glaucoma in eyes with primary open angle glaucoma (POAG) and we sought for optical coherence tomographic cut points in discrimination of early glaucoma from normal.

MATERIALS AND METHODS

Study Cohort: Local ethics committee approved the study methodology and the tenets of the declaration of Helsinki were followed. The records of 45 patients with a confirmed diagnosis of early glaucoma (POAG, early glaucoma group) and 42 age-and-sex matched healthy subjects (control group) were retrospectively reviewed. The sample size in the present study was determined at 95% power and 0.05 significance level (95% confidence interval) from previous similar literature using a computer software (PASS version 11.0.1, NSCC, LLC, Kaysville, Utah, USA). One eye was selected randomly in bilateral cases (using random numbers table) for the statistical analysis.

All patients underwent ophthalmological examinations including corrected distance visual acuity (CDVA) measurement with Snellen charts, slit-lamp biomicroscopy, intraocular pressure (IOP) measurement (Goldmann applanation tonometer), gonioscopy and dilated fundoscopic examination (+90 diopters lens).

Inclusion And Exclusion Criteria: Eligibility criteria were; age between 40-80 years, confirmed diagnosis of early glaucoma (according to the Hodapp-Parrish-Anderson [HPA] classification of VF loss in glaucoma), normal anterior segment and gonioscopic examination.[11] Control group comprised healthy subjects with normal VF test and SD-OCT imaging.

Subjects with a CDVA less than 20/40 Snellen equivalent, refractive error over 5 diopters of sphere or 3 diopters of cylinder, unclear media and history of intraocular surgery (other than uncomplicated phaco surgery) or neuroretinal diseases were excluded.

Visual Field Testing and Optical Coherence Tomography Imaging: All subjects had at least two reliable and consecutive automated perimetry records (30-2 test pattern and Swedish interactive thresholding algorithm, Humphrey Visual Field Analyzer, Carl Zeiss Meditec, Inc., Dublin, CA, USA). Tests with artifacts, fixation losses >20% and false positive or negative responses >15% were excluded.

The glaucomatous VF defect was defined as follows ≥2 non-edge contiguous points with a sensitivity loss at P<0.01 level or ≥3 non-edge contiguous points with a sensitivity loss of at P<0.05 level in the superior or inferior arcuate areas or 10-dB difference across the nasal horizontal midline at two or more adjacent locations and abnormal result in glaucoma hemifield test (GHT). Early glaucomatous damage was based on the HPA classification of VF loss in glaucoma.[11]

A single experienced technician (MA) performed optical coherence tomography imaging (Zeiss Cirrus HD-OCT 400, Carl Zeiss Meditec, Dublin, CA, USA) and optic disc cube 200x200 scan protocol was used. The SD-OCT parameters included average, superior, inferior, nasal and temporal RNFL thicknesses, RNFL symmetry, rim area, disc area, average cup/disc (C/D) ratio, vertical C/D ratio and cup volume.

The control subjects had normal biomicroscopic and gonioscopic examination, IOP<20 mmHg (measured with Goldmann applanation tonometer), normal optic disc appearance (absence of neuroretinal rim thinning, notching and nerve fiber layer defect), a normal GHT report on SAP (with no signs of glaucomatous defect described by HPA classification system [above-mentioned]), normal ONH and RNFL report (defined as green or white shade) on SD-OCT imaging.

Statistical Analysis: The Statistical Package for Social Sciences software version 16.0 (SPSS Inc, Chicago, IL, USA) and MedCalc software version 12.6.1.0 (MedCalc Software bvba, Ostend, Belgium) were used for statistical analysis. Values were expressed as the mean±standard deviation (SD). Categorical variables were analyzed using the chi square test. The independent samples t test was used to determine differences between two groups in terms of quantitative variables. A receiver operating characteristic (ROC) curve and the area under the ROC curve (AUC) were assessed to determine diagnostic power of the SD-OCT (RNFL and ONH parameters) in distinguishing early glaucoma from normal. The performance of the each SD-OCT parameter was graded according to the AUC value as follows; excellent (0.90-1.00), good (0.80-0.89), fair (0.70-0.79), poor (0.60-0.69) and worthless (0.50-0.59). The ROC curve plots the true positives (sensitivity) against the false positives (100-specificity) for different threshold values. Values on the ROC curve, which indicated best sensitivity-specificity pair, were accepted as the cut points. At 95% confidence interval, a P value less than 0.05 was considered statistically significant.

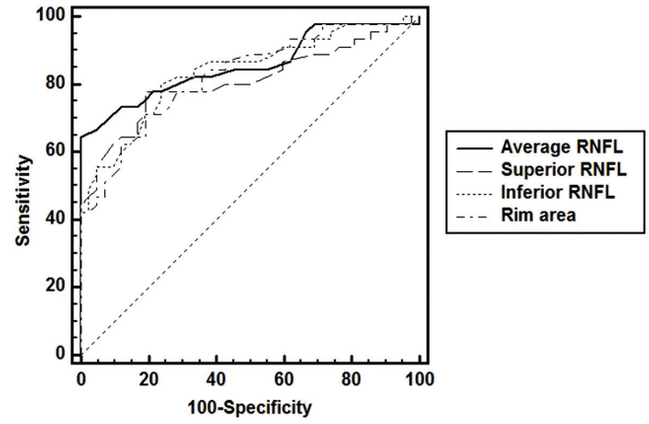
RESULTS

Forty-five eyes had early visual field damage with a mean deviation (MD) of -3.6±1.6 dB and the MD value was -0.50±0.19 dB in the control group (n=42) based on Humphrey automated perimetry records (P<0.001). Table 1 demonstrates the comparison of age, gender distribution and means for SD-OCT parameters (RNFL thicknesses [average, superior, inferior, nasal and temporal], RNFL symmetry, rim area, disc area, average C/D ratio, vertical C/D ratio and cup volume) between the early glaucoma and control groups. All SD-OCT parameters except the disc area were worse in the early glaucoma group than in the healthy controls (Table 1).

The ROC analysis and AUC values revealed that average, superior and inferior RNFL thicknesses and rim area showed good diagnostic performance in detecting early damage in POAG patients, whereas nasal RNFL thickness, RNFL symmetry, C/D ratios and cup volume failed to reach a clinically significant level (ranged from poor to fair). The graphic and Table 2 demonstrate the ROC curves, AUCs, sensitivity and specificity values for the SD-OCT parameters. On the ROC curve, threshold values with a better sensitivity and 100-specificity pair were accepted as the cut points for the each OCT parameter (Table 2).

DISCUSSION

The relation between structural and functional glaucomatous damage is one of the popular research issues, and studies suggested that early structural damage could be detected prior to the VF deterioration in glaucoma patients.[3,6,12,13] Although SAP, as a patient-dependent test, is the reference method for diagnosis and management of glaucoma, SD-OCT allows quantification of structural alterations in glaucoma patients.[5-8]



Graphic: *The ROC curves for average, superior and inferior retinal nerve fiber layer (RNFL) thicknesses and rim area.*

Furthermore, researchers demonstrated that optical coherence tomographic measurement of RNFL thickness is effective in discriminating glaucomatous eyes from normals, whereas a number of studies investigated the diagnostic ability of RNFL and ONH parameters in detecting early glaucoma.[14-18]

The main objective of the current study was to reveal optic coherence tomographic characteristics of eyes with early glaucoma and to determine cut points indicative of early damage in POAG patients. In our study, all SD-OCT parameter values (except disc area) were found worsened in the eyes with early glaucoma compared to those of the healthy subjects. However, the ROC analysis revealed that average, superior and inferior RNFL thicknesses and rim area had good diagnostic ability in discriminating early glaucoma from normal. Mwanza et al.,[19] performed a similar analysis using Cirrus HD-OCT. They found that average RNFL thickness, RNFL thickness at clock-hour 7/5 sector, inferior RNFL thickness, vertical rim thickness, rim area and vertical C/D ratio were able to discriminate

Table 1: *Comparison of age, gender distribution and OCT parameter values between the early glaucoma and control groups.*

Variables (mean ± SD)	Early glaucoma group (n= 45)	Control group (n= 42)	P
Age (years)	58.5±7.7	55.7±6.9	0.075*
Gender (M/F)	16/29	14/28	0.827†
RNFL thicknesses (microns)			
Average	81.3±12.1	96.1±6.9	<0.001†
Superior	99.8±18.2	119.3±11.7	<0.001†
Inferior	100.5±19.9	123.5±11.4	<0.001†
Nasal	64.7±10.8	74.7±11.2	<0.001†
Temporal	59.7±11.6	66.2±7.2	0.003†
RNFL symmetry (%)	80.4±15.7	86.1±8.4	0.036†
Rim area (mm^2)	1.15±0.21	1.41±0.19	<0.001†
Disc area (mm^2)	1.86±0.36	1.88±0.38	0.807†
Average C/D ratio	0.57±0.15	0.45±0.16	0.011†
Vertical C/D ratio	0.55±0.14	0.41±0.14	<0.001†
Cup volume (mm^3)	0.23±0.17	0.12±0.12	0.001†

*Independent samples t test, † Chi square test, P<0.05 indicates statistical significance between two groups, bold and italic values emphasize statistical significance. C/D; Cup/Disc, OCT; Optical Coherence Tomography, RNFL; Retinal Nerve Fiber Layer, SD; Standard Deviation.

Table 2: The AUC values and cut points for OCT parameters in discrimination of early glaucoma from normal.

OCT parameters (mean ± SD)	AUC value (at 95% CI lower-upper bounds)	P	Cut points (sensitivity–specificity)
RNFL thicknesses (microns)			
Average	0.856 (0.764-0.922)	<0.001	≤84 (64.4%-100%)
Superior	0.808 (0.709-0.884)	<0.001	≤110 (77.8%-81%)
Inferior	0.835 (0.741-0.906)	<0.001	≤113 (80%-76.2%)
Nasal	0.736 (0.631-0.825)	<0.001	≤65 (57.8%-78.6%)
Temporal	0.690 (0.582-0.785)	0.001	≤55 (42.2%-92.9%)
RNFL symmetry (%)	0.620 (0.509-0.723)	0.047	≤89 (79.5%-45.2%)
Rim area (mm^2)	0.825 (0.728-0.898)	<0.001	≤1.24 (71.1%-81%)
Disc area (mm^2)	Worthless	0.884	Worthless
Average C/D ratio	0.653 (0.543-0.752)	0.011	>0.61 (42.2%-88.1%)
Vertical C/D ratio	0.749 (0.645-0.836)	<0.001	>0.52 (64.4%-85.7%)
Cup volume (mm^3)	0.686 (0.578-0.781)	0.001	≥0.143 (62.2%-71.4%)

P<0.05 indicates statistical significance, bold and italic values emphasize "good" diagnostic ability. AUC; Area under the curve,; C/D; Cup/disc, CI; Confidence interval, OCT; Optical coherence tomography, RNFL; Retinal nerve fiber layer, SD; Standard deviation. AUC values are graded as follows; excellent (0.90-1.00), good (0.80-0.89), fair (0.70-0.79), poor (0.60-0.69) and worthless (0.50-0.59).

eyes with mild glaucoma from normal (AUCs between 0.890-0.918). A study by Elbendary et al.,[20] evaluated the diagnostic ability of RNFL parameters in eyes with different stages of glaucoma (using VFI based grading system). They suggested that average, inferior and superior RNFL thickness were the best parameters to discriminate normal from early glaucoma (AUC: 0.91–0.86), early from moderate (AUC: 0.77–0.70) and moderate from severe (AUC: 0.85–0.83). Moreover, they reported cut off values for average RNFL thickness in mild (≥97.5 microns), moderate (between 72.5-97.5 microns) and severe (<72.5 microns) glaucoma.[20] Another study by Alasil et al.,[21] demonstrated that average, superior and inferior RNFL thicknesses of 89, 100 and 73 microns (respectively) were tipping points for initial VF loss in eyes with open angle glaucoma when compared with healthy controls. Similarly, Yüksel et al.,[22] reported that inferior (0.74 microns), average (0.74 microns) and superior (0.68 microns) RNFL thicknesses, cup area (0.83 mm^2), C/D area ratio (0.82), and vertical integrated rim area (VIRA) (0.82) parameters had the best AUC values for discriminating between early glaucomatous and healthy eyes. In our study, 84, 110, 113 microns for average, superior and inferior RNFL thicknesses (respectively), and a rim area value of 1.24 mm^2 were found as the cut points for distinguishing early glaucomatous eyes from normals. Our study and above-mentioned studies conclude that decreased average, superior and inferior RNFL thicknesses might indicate the early glaucomatous damage.

In conclusion, we suggest that RNFL and ONH morphology appears to be deteriorated in eyes with early glaucoma when compared with those of the healthy controls. Furthermore, assessment of average, superior and inferior RNFL thicknesses and rim area on SD-OCT seem to have good diagnostic ability and optical coherence tomographic cut points might guide for OCT-assisted diagnosis of early glaucomatous damage in POAG patients. However, further studies in a larger population should be conducted to determine novel diagnostic parameters with better sensitivity and specificity values.

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