• Clinical Research •

The assessment of structural changes on optic nerve head and macula in primary open angle glaucoma and ocular hypertension

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Abstract
● AIM: To assess morphological changes in macula, retinal nerve fiber layer (RNFL) and optic nevre head (ONH) of cases with primary open angle glaucoma (POAG) and ocular hypertension (OH) with spectral domain optic coherence tomography (OCT).

● METHODS: This study included 109 eyes from 62 POAG patients, 50 eyes from 30 OH patients, and 101 eyes from 53 healthy volunteers. Data gained by OCT were compared with perimetry indexes. ONH, RNFL and macula analysis were performed for all subjects. Rim area, disc area, average cup/disc (C/D) ratio, vertical C/D ratio, cup volume data were recorded during ONH analysis. Average RNFL thickness and the thickness of four quadrants (superior, inferior, nasal and temporal) was established in microns. In total, nine macular quadrants involving the foveal region mentioned in the Early Treatment Diabetic Treatment Study (ETDRS) template were measured, and average macular thickness and macular volume data were recorded during macula analysis. Differences between groups were evaluated with the one-way ANOVA test. Tukey's multiple comparison test was performed to detect difference between groups. Receiver-operating characteristic (ROC) analysis was done for early stage POAG patients to establish sensitivity and specificity of chosen parameters in early stage POAG. Area under the receiver operating characteristic (AUROC) values were calculated to compare ROC areas.

● RESULTS: Statistically significant differences were found in all ONH parameters, except optic disc area. Neuroretinal rim area was identified as the parameter with the highest difference between groups (F=21.72, P<0.05). The highest correlation between ONH parameters and perimetry was observed at neuroretinal rim region (r=0.487). Inferior RNFL thickness was established as the parameter with the highest difference between groups among RNFL parameters. In the mean of all glaucoma patients, the highest correlation between data handled with OCT and mean deviation was observed in RNFL thickness. Average macular thickness was detected as the parameter with the highest difference between groups among macular parameters. The highest correlation between macula parameters and perimetry indexes was observed between average macular thickness and perimetry indexes (r=0.514).

● CONCLUSION: Although the assessment of ONH and the analysis of macular thickness are important in diagnosis and treatment, RNFL assessment is the most valuable parameter.

● KEYWORDS: glaucoma; ocular hypertension; optic coherence tomography
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INTRODUCTION
Glaucoma is a chronic optic neuropathy characterized by progressive atrophy in optic nerve head (ONH), degenerations in retinal ganglion cells and visual field defects in perimetry; and it can cause important visual loss if it is not treated[1]. This is an important public health problem because of its high frequency in the general population, and although the blindness it causes is irreversible, it is possibly preventable.

Half of all glaucoma cases are composed of primary open angle glaucoma (POAG) patients, although there are differences between studies. POAG is creeping disease, generally seen bilaterally. The disease progresses from early to late stages in months, even years, and it is asymptomatic until it causes severe visual loss. Ocular hypertension (OH) is a clinical condition with no glaucomatous changes and findings, despite high intraocular pressure (IOP).

Functional visual loss occuring during the course of POAG can be detected with perimetry. But there is significant ganglion cell loss before the appearence of detectable visual field loss, and this impels the doctors to research new methods that could provide early diagnosis of glaucoma.

It is obvious that methods providing objective and reliable data about ONH and retinal nerve fiber layer (RNFL) damage can be of great help to doctors when diagnosing and treating glaucoma. Imaging technologies, used in parallel with other emerging technologies, may provide this opportunity. One of these emerging technologies is optic coherence tomography (OCT), which handles high resolution tomographic section images of ONH, RNFL and retina *via* using 800-840 nm wavelength light in a non-contact, non-invasive fashion. This imaging method provides reliable quantitative data about RNFL and ONH morphology.

The aim of this study is to detect morphological changes in macula and RNFL, ONH of cases with POAG, and OH with spectral domain OCT (SD-OCT); to compare existing structural changes with functional loss by the aid of standard perimetry; and to establish the most valuable diagnostic parameters at early stages of POAG. It is hoped that this study can light the way for clinical assessments.

SUBJECTS AND METHODS

This study involves 109 eyes from 62 POAG patients, 50 eyes from 30 OH patients, and 101 eyes from 53 healthy volunteers. Some subjects were patients followed in Opthalmology Department of Medical Faculty of Ufuk University, Unit of Glaucoma follow-up between January 2010 and January 2015 included to the study. Detailed opthalmologic examination was done on all subjects by same doctor. Perimetry was with an automatic perimetry machine (Humphrey Systems Field Analyzer Model II 750, Zeiss, USA) using 24-2 mode, and mean deviation (MD) and patern standard deviation (PSD) values on perimetry were recorded. POAG was diagnosed by glaucomatous optic nerve cupping, glaucomatous visual field loss, open anterior chamber angle, and IOP measured at 21 mm Hg without medication. Also patients with normal eye examinations, including visual field, but with an IOP applanation tonometer above 21 mm Hg on two or more measurements were taken into the OH group. POAG patients were divided into groups according to MD values, with early stage as MD smaller than -6 dB (n=65 eyes), intermediate stage as MD between -6 dB and -12 dB (n=32 eyes), and late stage being MD higher than -12 dB (n=3 eyes).

The assessment with OCT was done by an opthalmologist by the use of Cirrius SD-OCT (Carl Zeiss OPthalmic System Inc, Model 400, Dublin, USA, Software 5) without the need of pupil dilatation. ONH, RNFL and macula analysis were performed for all subjects. Rim area (mm^2), disc area (mm^2), average cup/disc (C/D) ratio, vertical C/D ratio, cup volume (mm^3) data were recorded during ONH analysis. Average RNFL thickness and the thickness of four quadrants (superior, inferior, nasal and temporal) was established in microns. In total, nine macular quadrants (micron) involving the foveal region mentioned in the Early Treatment Diabetic Treatment Study (ETDRS) template were measured, and average macular thickness (micron) and macular volume (mm^3) data were recorded during macula analysis.

The study received Institutional Review Board approval from the Ethical Committee of Medical Faculty of Ufuk University, and was conducted according to the ethical standards set in the 1964 Declaration of Helsinki, as received in 2000. All patients and healthy volunteers were informed about the study and all of them provided informed consent.

Statistical Analysis Statistical analysis was performed using the SPSS (Statistical Package for Social Science, Chicago, II, USA) 19.0 Windows programme. Differences between groups were evaluated with the one-way ANOVA test. Tukey's multiple comparison Test was performed to detect difference between groups. Receiver-operating characteristic (ROC) analysis was done for early stage POAG patients to establish sensitivity and specificity of chosen parameters in early stage POAG, and ROC curves was drawn. Area under the receiver operating characteristic (AUROC) values were calculated to compare ROC areas. This AUROC value shows excellent discrepancy when it is equal to one, and a lack of discrepancy when it is equal to 0.5. A correlation analysis was performed to observe the relationship between compared parameters, and the level of significance was set at 0.05 with a 95% confidence interval.

RESULTS

This study involved 109 eyes from 62 (42.76%) POAG patients, 50 eyes from 30 (20.69%) OH patients and 101 eyes from 53 (36.55%) healthy volunteers; totalling 260 eyes from 145 subjects. The general characteristics of these subjects is shown in Table 1 and findings from the ONH analysis are shown in Table 2.

Statistically significant diferences were established in all parameters, except optic nerve area. The neuroretinal rim area was established as ONH parameter with the highest difference between groups (F=21.72, P<0.05). The correlation values between perimetry indexes and ONH parameters in POAG patients is shown in Table 3. While the highest correlation was seen in rim area, the lowest correlation was seen in cup volume (r=-0.202).

Measurement values of RNFL thickness between groups is shown in Table 4. Inferior RNFL thickness was found to be the parameter with the highest difference between groups among all RNFL data (F=35.68, P<0.05). The correlation values between perimetry indexes and RNFL thickness parameters in POAG patients is shown in Table 5. While the

Table 1 Distribution of general characteristics of groups

Measurements	POAG (*n*=109)	OH (*n*=50)	Normal (*n*=101)	*F*	*P*
Age	59.31±9.962	55.58±7.551	59.10±10.415	2.906	0.057
Central corneal thickness (μm)	553.28±34.574	578.66±36.022	539.39±36.602	20.312	0.000[a]
Spheric refraction (D)	-0.19±1.418	-0.39±1.945	0.48±1.233	7.912	0.000[a]
IOP (mm Hg)	19.85±4.190	22.92±2.709	15.73±2.315	88.368	0.000[a]

[a]$P<0.05$ statistically significant difference.

Table 2 The assessment of differences in ONH measurements between groups

Measurements	Early stage POAG	Intermediate stage POAG	Late stage POAG	OH	Normal	*F*	*P*
Disc area (mm^2)	1.99±0.37	2.02±0.43	1.85±0.36	1.96±0.41	1.98±0.33	0.47	0.753
Rim area (mm^2)	1.20±0.27	1.05±0.28	0.76±0.17	1.27±0.26	1.40±0.28	21.72	0.000[a]
Average C/D	0.58±0.17	0.65±0.14	0.73±0.10	0.55±0.16	0.50±0.15	9.62	0.000[a]
Vertical C/D	0.56±0.15	0.63±0.14	0.71±0.10	0.51±0.16	0.47±0.15	10.90	0.000[a]
Cup volume (mm^3)	0.27±0.25	0.34±0.28	0.39±0.29	0.24±0.22	0.15±0.14	7.42	0.000[a]

[a]$P<0.05$ statistically significant difference.

Table 3 The assessment of correlation between perimetry indexes and ONH parameters in POAG patients

Perimetry index		Rim area	Disc area	Average C/D	Vertical C/D	Cup volume
MD	*r*	0.487	0.056	-0.345	-0.366	-0.202
	P	0.000[b]	0.562[a]	0.000[b]	0.000[b]	0.035[a]
	n	109	109	109	109	109
PSD	*r*	-0.443	-0.020	0.310	0.320	0.235
	P	0.000[b]	0.838	0.001[a]	0.001[a]	0.014[a]
	n	109	109	109	109	109

[a]$P<0.05$ statistically significant difference; [b]$P<0.01$ statistically highly significant difference.

highest correlation was observed with average RNFL thickness (r=0.538), the lowest correlation was observed with temporal RNFL thickness (r=-0.206).

The findings of macular thickness analysis between groups is shown in Table 6. Statistically significant differences between groups were found in all parameters, except foveal thickness ($P<0.05$).The parameter with the highest difference between groups was established to be average macular thickness (F=34.34, $P<0.05$). A ROC analysis was performed to compare sensitivity and specificity of data handled with OCT in diagnosis of early stage POAG. Inferior RNFL thickness was established as the parameter with the highest diagnostic value (AUROC: 0.771), as shown in Table 7.

DISCUSSION

It is known that there are serious losses in nerve fiber layer when functional loss in perimetry is diagnosed. It is obvious that perimetry alone is not enough to diagnose and treat glaucoma. Together with diurnal variation in IOP, the sensitivity of the optic nerve to increase in IOP shows important differences between individuals. Therefore, the importance of IOP in diagnosis of glaucoma becomes controversial with developing technologies[2]. Another important point in diagnosis of glaucoma is that clinical examination of ONH and RNFL is subjective and causes different comments between doctors[3]. Because of these reasons, objective and quantitative assessment of ONH and RNFL is critically important. Diagnostic imaging machines (including OCT) are used to develop to achieve this.

OCT is beneficial in topographic assessment of ONH and in acquisition of quantitative measurements of RNFL and macular thickness in glaucoma patients. There are some advantages of every region assessed theoratically. For this reason, morphological changes on ONH, RNFL and macula in POAG and OH patients were assessed and researched to establish their importance in glaucoma by comparing with a control group. The existence of significant differences in ONH parameters between normal group and early stage POAG patients is important for differentiating glaucoma patients at early stage by the use of OCT. In our study, significant differences between groups are set in all ONH parameters, except optic disc area. Rim area was established as the ONH parameter with the highest differences between groups and it was observed as the only ONH parameter with a significant difference between late stage POAG group and other groups. This finding shows that rim area decreases to an important degree in late stage glaucoma patients. Wollstein *et al*[4] report that the most valuable ONH parameter in differentiating POAG patients from normal group handled with OCT is rim area. Correspondingly, Sung *et al*[5] and Aydogan *et al*[6] recognize rim area as the ONH parameter showing the highest correlation with RNFL thickness in their study with SD-OCT (Cirrius), and emphasize that rim area is the most valuable parameter among ONH data in diagnosis. Recent studies show important developments include appreciation of

Table 4 The assessment of differences in RNFL measurements between groups mean±SD, μm

Measurements	Early stage POAG	Intermediate stage POAG	Late stage POAG	OH	Normal	F	P
Average RNFL thickness	86.21±9.71	78.12±15.48	61.15±11.81	88.76±14.87	94.52±9.31	31.09	0.000[a]
Superior quadrant	106.39±14.69	96.48±23.98	70.85±16.39	112.28±12.46	119.49±19.11	29.04	0.000[a]
Temporal quadrant	61.39±10.82	58.84±11.42	49.92±5.54	65.12±10.52	64.92±9.42	8.34	0.000[a]
Inferior quadrant	109.82±16.05	97.44±28.18	70.23±23.97	118.76±16.87	124.00±14.51	35.68	0.000[a]
Nasal quadrant	67.23±10.83	60.12±10.47	53.77±9.57	66.52±9.53	69.90±8.52	11.61	0.000[a]

[a]P<0.05 statistically significant difference.

Table 5 The assessment of correlation between perimetry indexes and RNFL thickness in POAG patients

Perimetry index		RNFL thickness				
		Average RNFL thickness	Superior quadrant	Temporal quadrant	Inferior quadrant	Nasal quadrant
MD	r	0.538	0.492	0.311	0.512	0.372
	P	0.000[b]	0.000[b]	0.001[b]	0.000[b]	0.000[b]
	n	109	109	109	109	109
PSD	r	-0.429	-0.386	-0.206	-0.444	-0.265
	P	0.000[b]	0.000[b]	0.031[a]	0.000	0.005[a]
	n	109	109	109	109	109

[a]P<0.05 statistically significant difference; [b]P<0.01 statistically highly significant difference.

Table 6 The assessment of differences in macular thickness measurements between groups mean±SD

Measurements	Early stage POAG	Intermediate stage POAG	Late stage POAG	OH	Normal	F	P
Fovea (μm)	248.33±17.13	250.80±22.45	240.42±7.14	256.06±19.54	250.31±17.88	2.34	0.055
Average macular thickness (μm)	273.19±10.74	267.08±13.16	248.00±15.39	283.46±10.18	282.62±12.18	34.34	0.000[a]
Cup volume (mm^3)	9.84±0.38	9.61±0.48	8.94±0.55	10.21±0.36	10.17±0.43	33.59	0.000[a]

[a]P<0.05 statistically significant difference.

Table 7 AUROC values for general OCT datas in early stage POAG patients

Measurements	AUROC	Border value	Sensitivity (%)	Specificity (%)	P
Inferior RNLF thickness	0.771	112.5	58.6	83.0	0.000[b]
Average RNFL thickness	0.732	95.5	88.6	45.0	0.000[b]
Average macular thickness	0.722	278.5	72.9	67.0	0.000[b]
Cup volume	0.720	10.05	72.9	64.0	0.000[b]
Average outer quadrant macular thickness	0.714	276.8	74.3	63.0	0.000[b]
Rim area	0.712	1.185	61.4	77.0	0.000[b]
Superior RNFL thickness	0.690	108.5	54.9	70.3	0.000[b]
Average inner quadrant macular thickness	0.664	319.6	71.4	57.0	0.000[b]

[b]P<0.01 statistically highly significant difference.

the need to use a consistent point of reference for structural measurements, leading to the introduction of Bruch's membrane opening (BMO)-based measurements, including BMO-minimum rim width and BMO-minimum rim area[7-11].

In glaucoma pathophysiology, an increase in cupping from tissue loss at the neuroretinal rim, and non-consantric, vertical progression of this cupping are very well-known conditions. In our results, showing the differences between groups that had already expected with OCT could be important to attract attention to this new imaging method in glaucoma. Fan *et al*[12] reported 3D neuroretinal rim parameters demonstrated better diagnostic capability for primary and secondary open-angle glaucomas compared with 2D neuroretinal parameters (rim area, rim thickness).

It is important to know the structural relation between perimetry losses and glaucomatous ONH parameters. In our study, the highest correlation with the perimetry index showed average and superior RNFL thickness values, respectively. Knowing which data handled with OCT is related to functional loss could guide the clinician. In the present study, a significant correlation between RFNL thickness abnormalities and glaucomatous functional defects was confirmed. Nakatsue *et al*[13] showed a significant correlation between perimetry and cup area, C/D ratio, rim area and rim volume in POAG and normotensive glaucoma patients. López-Peña *et al*[14] showed a weak correlation between perimetry indexes and cup area and horizontal C/D ratio, but a strong correlation between perimetry indexes and rim area and vertical C/D ratio in glaucoma group. In our results, a linear correlation in intermediate strength was established between perimetry indexes and ONH OCT data, except optic disc area in POAG patients. This correlation demonstrates a parallel functional loss and structural damage. Also, the parameter with the highest correlation coefficient was determined to be rim area. Lee *et al*[15] reported macular OCT-visual field relationships have localised arcuate characteristics in the central region of the macula. Given the overlapping nature of structure-function relationships, a smaller number of visual field test locations may be used to summarise macular functional damage. Zhang *et al*[16] reported OCT is more sensitive than visual field for the detection of progression in early glaucoma.

RNFL damage is important in early diagnosis and treatment of glaucomatous optic neuropathy because it can lead to functional losses later detected with perimetry. Thanks to this, it will be possible to detect functional failure of axons before permanent cell loss happens. Schuman *et al*[17] found RNFL thickness in their study with stratus OCT as 95.9±10.09 μm in the normal group, 80.3±18.4 μm in early stage glaucoma patients, and 50.7±13.6 μm in late stage glaucoma patients respectively. They reported that RNFL thickness measured *via* OCT showed significant difference between healthy and glaucoma eyes. In our study, average RNFL thicknesses handled with SD-OCT were found as 94.52±9.31 μm in the normal group, 88.76±14.87 μm in the OH group, 86.21±9.71 μm in early stage glaucoma patients, and 61.15±11.81 μm in late stage glaucoma patients, respectively.

To assess RNFL thickness of quadrants handled with OCT is also important. Guedes *et al*[18] ascertained that all RNFL parameters decrease significantly in glaucoma group, and only inferior RNFL thickness decreases in glaucoma suspected group in their study. Leung *et al*[19] reported that RNFL thickness, especially in the inferior quadrant, showed significant difference between glaucoma suspected group and normal group in their study. They also showed that there were significant differences in all quadrants, except temporal quadrant in normal and glaucoma eyes. Differences in RNFL thickness determined in our study are similar to results of previous studies. The most evident slimming is observed in the inferior quadrant, in accordance with the rule described as ISNT rule by some researchers, and shows the sequence of RNFL loss. Superior, nasal and temporal quadrants follow this. It has been determined that changes in inferior quadrant RNFL thickness is more important than other RNFL thickness data involving average RNFL thickness in the assessment and following of glaucoma patients. In our study, a statistically significant difference is found only in average RNFL thickness between normal group and OH patients; and in inferior quadrant RNFL thickness between normal group and early stage POAG group.

The association between RNFL measurements handled with OCT and standard perimetry test was shown in several studies. Kanamori *et al*[20] report the existence of a correlation between RNFL thickness data handled with OCT and MD in all quadrants, except the nasal quadrant, in their study with OCT. Similar to our study, they establish average RNFL thickness as the parameter with the highest correlation coefficient. In their study, Utine *et al*[21] show a weak correlation between average RNFL thickness and MD. We obtained similar results to these studies, but have established a generally intermediate level correlation. Lederer *et al*[22] detected that macular thickness was thinner in a statistically significantly way in early stage glaucoma cases than in normal cases. Also, they found macular thickness in late stage galucoma cases as normal, but significantly thinner than early stage galucoma group and glaucoma suspected cases. No difference in foveal thickness was seen in any group, and morphological changes in foveal region do not seem to be beneficial in the diagnosis and treatment of glaucoma patients. Conversely, a change was observed in macular volume, and especially in average macular thickness, even at early stages of glaucoma, and these changes increased compared to staging done according to standard perimetry. Another noteworthy point from our results is that there was no significant difference in any macular parameter detected *via* OCT between OH and healthy groups. Conversely, significant difference in all macular thickness data, except fovea, was observed between OH patients and POAG groups involving early stage glaucoma.

Ojima *et al*[23] reported a significant decrease in six of nine macula segments at early stage of glaucoma and normal foveal thickness even at late stages. Guedes *et al*[18] stated significant slimming of RNFL and macular thickness in glaucomatous eyes. Significant differences in thickness were found only in outer segment macula measurements between early stage glaucoma and the normal group in their study. They also stated that changes in macular thickness showed a correlation with changes in RNFL thickness. Similar to their study, our study shows that outer segment macular thickness is affected more than inner segment thickness. When POAG patients are compared with the normal group, an increase in the difference between foveal thickness and peripheral macular thickness going away from center of macula is evident. Choi *et al*[24] reported foveal avascular zone circularity index may be a novel biomarker representing disruption of the parafoveal capillary network in glaucoma, as supported by its association with structural parameters. Greenfield *et al*[25] reported a significant correlation between macular thickness and MD, PSD among perimetry parameters, and average RNFL thickness in glaucoma patients. A high correlation between thickness values of the inferior outer segment and MD, as well as PSD, in comparison with other segments is one of important results of this study.

Fifty percent of retinal ganglion cells are localized in the perimacular region, which includes ganglion cells and a nerve fiber layer related to the central 20 degree visual function in standard perimetry tests. This region was assessed because it is an ideal region for early changes and progression in glaucoma. Chen *et al*[26] showed the measurement of the macular superficial vessel density had similar diagnostic accuracy to peripapillary RNFL and macular ganglion cell complex thickness for differentiating between glaucomatous and healthy eyes. Macular ganglion cell asymmetry analysis showed good glaucoma diagnostic ability, especially in early-stage glaucoma[27]. Kim and Park[28] Showed macular ganglion cell thickness parameters recently have been considered to be an effective glaucoma-diagnostic tool comparable to RNFL thickness parameters. The other study, Pazos *et al*[29] reported macular intraretinal measurements still have not overcome standard peripapillary RNFL parameters.

In our study, the macular segment that has the highest correlation with perimetry is the inferior outer segment, which is consistent with their study, and we think that this condition could be related to changes in inferior RNFL thickness. Additionally, the correlation of average macular thicknesses belong to outer segments with perimetry is observed to be better when compared with thicknesses belong to inner segments. Khanal *et al*[30] informed average RNFL thickness, total macular volume and inferior outer macular thickness were the best SD-OCT parameters with superior discriminating capabilities. Additionally, some studies show choroidal thickness of the macular and peripapillary regions is not decreased in glaucoma[31-32].

Early diagnosis of glaucoma and a correct assessment during the initial stage of disease is so important, which is why our research focuses on these analyses in early stage glaucoma patients. The OCT parameter with the highest diagnostic value in POAG is the inferior RNFL thickness. Also, the parameter with the highest diagnostic value among ONH data is the rim region. Sacconi *et al*[33] also reported patients affected by advanced POAG damage have a thinner choroidal thickness compared with normal subjects, using SD-OCT.

In conclusion, OCT presents valuable information that could direct doctors when diagnosing and treating glaucoma, by providing objective and reliable data regarding peripapiler nerve fibar layer thickness, macular thickness measurement and optic disc parameters. Although assessment of ONH and the analysis of macular thickness (a relatively new method) are important in the diagnosis and treatment of glaucoma, the assessment of RNFL still seems to be the most valuable parameter. The diagnostic value of macular thickness analysis following RNFL assessment is noteworthy, but the assessment of OCT data, together with clinical findings, is of critical importance in the assessment of glaucoma patients. In addition, a high intervisit reproducibility of the SD-OCT parameters, which is very useful in monitoring disease progression and the course of treatment. The present study showed a structure and function relationship in patients with glaucoma using SD-OCT determined parameters including macula thickness, RFNL thickness and ONH parameters compared with visual field index. This association may help glaucoma specialists use SD-OCT thickness measurements for accurate and diagnosis of glaucoma in suspected cases.

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