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ORIGINAL RESEARCH

Optic nerve head topography and retinal structural changes in eyes with macrodisks: a comparative study with spectral domain optical coherence tomography

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Purpose: To compare optic nerve head parameters, the thicknesses of the peripapillary retinal nerve fiber layer (pRNFL), the macular retinal nerve fiber layer (mRNFL), the ganglion cell complex (GCC), and the ganglion cell–inner plexiform layer (GCIPL) in macrodisks and normal-sized healthy disks using spectral domain optical coherence tomography.

Patients and methods: A total of 88 healthy eyes (42 macrodisks and 46 normal-sized disks) were prospectively enrolled in the study. Optic nerve head parameters as well as pRNFL, mRNFL, GCC, and GCIPL thicknesses were measured in all subjects. Optic disk areas (ODAs) >2.70 mm^2 were defined as macrodisks. All spectral domain optical coherence tomography parameters were compared between normal-sized disks and macrodisks.

Results: The mean age of the participants was 49.4±5.7 years in the normal size group and 51.55±6.3 years in the macrodisk group (P=0.65). The average ODAs were 2.23±0.29 mm^2 and 3.30±0.59 mm^2 in the normal size and the macrodisk groups, respectively. ODA (P<0.001), cup area (P<0.001), cup disk area ratio (P<0.001), horizontal cup disk ratio (P<0.001), vertical cup disk ratio (P<0.001), horizontal disk diameter (P<0.001), vertical disk diameter (P<0.001), and cup volume (P<0.001) were significantly higher in the macrodisk group. The inferior mRNFL thickness was significantly lower (P=0.042), and the GCC inferior and GCIPL inferior thicknesses were found to be lower with low significance (P=0.052, P=0.059, respectively) in the macrodisk group. Rim volume (P=0.622), total pRNFL (P=0.201), superior pRNFL (P=0.123), inferior pRNFL (P=0.168), average macular thickness (P=0.162), total mRNFL (P=0.171), superior mRNFL (P=0.356), total GCC (P=0.080), superior GCC (P=0.261), total GCIPL (P=0.214), and superior GCIPL (P=0.515) thicknesses were similar in both groups.

Conclusion: Optic disk topography and retinal structures show different characteristics in healthy eyes with macrodisks. These disk size-dependent variations suggest that large optic disks may be more susceptible to glaucomatous damage.

Keywords: macrodisk, optic nerve head, nerve fiber layer, ganglion cell complex

Introduction

The capacity of optical coherence tomography (OCT) to differentiate glaucomatous and healthy eyes by measurements of the optic nerve head (ONH), the retinal nerve fiber layer (RNFL), and macular thickness has been shown in various studies.[1–4] The advent of spectral domain optical coherence tomography (SD-OCT) allows visualization of the segments of the macular region with improved imaging resolution.[5,6] The Topcon three-dimensional (3D) OCT 2000 is an SD-OCT device that procures a detailed

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assessment of the inner layers of the macula.[7,8] This is called ganglion cell complex (GCC) analysis and consists of the scan of the macular RNFL (mRNFL) and the ganglion cell–inner plexiform layer (GCIPL). These layers contain the axons, cell bodies, and dendrites of the ganglion cells, respectively.[9] Macrodisks exhibit more nerve fibers and a larger area of neuroretinal tissue than do regular disks.[10] This appearance can sometimes lead to a misdiagnosis of glaucoma. Recognizing the progression of the loss of neuroretinal rim tissue is challenging in eyes with a slim neuroretinal rim. As the Heidelberg retina tomography and scanning laser polarimetry (GDx) databases do not include macrodisks in the diagnosis of glaucoma, their results will be influenced by the size of the optic disk leading to artificial high results. A visual field test is necessary to diagnose glaucoma in these patients.

A macrodisk is a large optic disk with an increased cupping, a normal rim volume, a normal visual field, and normal intraocular pressure.[11,12] However, it remains necessary to understand whether these disks are vulnerable to nerve fiber loss. The aim of this study was to evaluate optic disk and macular characteristics of eyes with macrodisks.

Patients and methods

All subjects were examined between February and May 2014 at Istanbul Research and Training Hospital according to the principles of the Declaration of Helsinki. The study was approved by Istanbul Research and Training Hospital Ethics Committee and signed informed consent was obtained from each patient. Prospective evaluation of 88 eyes (42 with macrodisks and 46 with normal-sized disks) subjected to Topcon 3D SD-OCT was performed.

All participants underwent slit-lamp examination, dilated fundus examination with a 90 D fundus lens, applanation tonometry, measurement of the central corneal thickness with a corneal ultrasound pachymeter (Nidek UP-1000), axial length measurement (IOL Master), visual field testing, and the measurement of ONH, RNFL, and GCC with a Topcon 3D SD-OCT 2000 (Topcon Corporation, Tokyo, Japan). Visual field was tested using the 30-2 Swedish interactive threshold algorithm standard strategy of the Humphrey Field Analyzer (Carl Zeiss Meditec AG, Jena, Germany).

All subjects had a best corrected visual acuity of 20/60 or better, refraction error $\leq \pm 3.0$ D sphere and $\leq \pm 1.5$ D cylinder, intraocular pressure <21 mmHg, an open angle on gonioscopy, clear media, and vital optic disks. The exclusion criteria for both groups were a family history of glaucoma, having systemic diseases such as diabetes mellitus and hypertension, opaque media, macular disease, abnormal visual field testing, previous intraocular surgery, and a neurological disease.

All subjects had to have a reliable and normal Humphrey 30-2 Swedish interactive threshold algorithm standard test result.

Eyes were dilated with 0.5% tropicamide, and OCT images were obtained by the same technician. Images with signal strength >40 were used for analyses.

For each eye, total, superior, and inferior peripapillary retinal nerve fiber layer (pRNFL) thicknesses were evaluated by ONH and automatically calculated by OCT using existing software. The 3D OCT 2000 (software Version 8.00; Topcon Corporation) automatically detects the disk center by referring to the infrared reflectance image. Based on the inputted refractive information, the software adjusts the circle diameter for the circle scan and corrects papillary diameter, area, and volume, while also calculating magnification compensation, which enables accurate scanning. The machine automatically detects the edge of the optic disk as the end of the retinal pigment epithelium/choriocapillaris.

Among the measurements provided by ONH analysis, the following were examined: disk area, cup area, rim area, cup disk area ratio (CDAR), horizontal cup disk ratio (HCDR), vertical cup disk ratio (VCDR), vertical and horizontal disk diameters, cup volume, and rim volume.

OCT macular scans were segmented into the average macular thickness, mRNFL, GCC, and GCIPL. GCC thickness was measured from the internal limiting membrane to the outer inner plexiform layer boundary. The average macular thickness and superior and inferior hemi-retina thicknesses of mRNFL, GCC, and GCIPL were calculated.

The average optic disk area (ODA) of the normal population ranges from 2.10 mm^2 to 2.45 mm^2 when evaluated by OCT.[2,13] Macrodisks can be defined as disks larger than the mean + 2SD on the basis of the Gaussian-like distribution curve of the ODA.[14] According to this, we defined macrodisks as disks >2.70 mm^2, and they were studied separately from the normal size group.

All OCT parameters were compared between normal disks and macrodisks. Nonparametric analysis between the two groups was evaluated with independent-samples *T*-tests and Mann–Whitney *U*-tests. Spearman's test was used for nonparametric correlations between the ODA and other OCT variables. The Kolmogorov–Smirnov and Shapiro–Wilk nonparametric tests were used to evaluate the normal distribution of numerical data. A *P*-value <0.05 was considered statistically significant.

Results

The mean age of the patients in the control and macrodisk group were 49.44±5.71 years and 51.55±6.32 years, respectively. There were no significant differences in age (P=0.65), sex ratio

Table 1 Demographic and clinical characteristics of the study

Variables	Macrodisk (n=42)	Normal disk (n=46)	*P*-value
Age (years) (mean ± SD)	51.55±6.32	49.44±5.71	0.65
Sex (female/male) (n)	15/12	14/14	0.12
Intraocular pressure (mean ± SD) (mmHg)	16.31±2.01	15.28±2.70	0.52
MD (dB)	–0.69±1.01	–0.60±1.22	0.15
Central corneal thickness (mean ± SD) (μm)	551.43±31.2	547.72±33.2	0.07
Axial length (mean ± SD) (mm)	23.12±0.70	23.25±0.83	0.65

Abbreviations: MD, mean deviation; SD, standard deviation.

(*P*=0.12), intraocular pressure (*P*=0.52), mean deviation in visual field testing (*P*=0.15), central corneal thickness (*P*=0.07), or axial length (*P*=0.65) between patients with normal and large disks (Table 1).

The average ODAs were 2.23±0.29 mm^2 (1.56–2.68 mm^2) in the control group and 3.30±0.59 mm^2 (2.73–4.92 mm^2) in the macrodisk group ($P<0.001$). When the two groups were compared, cup area ($P<0.001$), CDAR ($P<0.001$), HCDR ($P<0.001$), VCDR ($P<0.001$), horizontal disk diameter ($P<0.001$), vertical disk diameter ($P<0.001$), and cup volume ($P<0.001$) were larger, and inferior mRNFL thickness was significantly smaller (*P*=0.042) in the macrodisk group. GCC inferior and GCIPL inferior were also thinner in the macrodisk group with low significance (*P*=0.052 and *P*=0.059, respectively). The rim area (*P*=0.109), rim volume (*P*=0.622), total RNFL thickness (*P*=0.201), superior RNFL thickness (*P*=0.123), inferior pRNFL thickness (*P*=0.168), average macular thickness (*P*=0.162), total mRNFL thickness (*P*=0.171), superior mRNFL thickness (*P*=0.356), total GCC thickness (*P*=0.080), superior GCC thickness (*P*=0.261), total GCIPL thickness (*P*=0.214), and superior GCIPL thickness (*P*=0.515) were similar in both groups (Table 2).

In multiple linear regression analyses, cup area ($r=0.659$, $P<0.001$), rim area ($r=0.430$, $P<0.001$), CDAR ($r=0.436$, $P<0.001$), HCDR ($r=0.437$, $P<0.001$), VCDR ($r=0.439$, $P<0.001$), cup volume ($r=0.532$, $P<0.001$), horizontal disk diameter ($r=0.920$, $P<0.001$), and vertical disk diameter ($r=0.864$, $P<0.001$) were significantly related to the ODA (Table 3).

Table 2 A comparison of OCT parameters between macrodisks and normal disks

Variables	ODA <2.70 mm²		ODA ≥2.70 mm²		*P*-value
	Mean	SD	Mean	SD	
ODA (mm²)	2.23	0.29	3.30	0.59	**<0.001**
Cup area (mm²)	0.63	0.34	1.49	0.53	**<0.001**
Rim area (mm²)	1.51	0.44	1.82	0.57	0.109
CDAR	0.28	0.14	0.45	0.14	**<0.001**
HCDR	0.50	0.17	0.66	0.10	**<0.001**
VCDR	0.50	0.16	0.65	0.07	**<0.001**
Horizontal disk diameter (mm)	1.59	0.15	1.98	0.18	**<0.001**
Vertical disk diameter (mm)	1.79	0.12	2.10	0.18	**<0.001**
Cup volume (mm³)	0.11	0.09	0.32	0.21	**<0.001**
Rim volume (mm³)	0.47	0.21	0.51	0.29	0.622
pRNFL total (μm)	102.94	7.05	105.85	9.49	0.201
pRNFL superior (μm)	120.24	9.19	123.46	10.72	0.123
pRNFL inferior (μm)	127.14	11.84	132.46	16.82	0.168
Average macular thickness (μm)	261.01	10.37	256.39	13.34	0.162
mRNFL total (μm)	36.48	3.88	34.85	2.15	0.171
mRNFL superior (μm)	35.07	3.70	34.08	2.47	0.356
mRNFL inferior (μm)	37.73	4.61	35.69	2.81	**0.042**
GCC total (μm)	106.32	7.13	102.62	5.68	0.080
GCC superior (μm)	104.96	6.98	102.62	6.14	0.261
GCC inferior (μm)	107.70	7.64	102.69	5.78	0.052
GCIPL total (μm)	69.83	4.06	67.85	4.67	0.214
GCIPL superior (μm)	69.79	4.04	69.46	4.74	0.515
GCIPL inferior (μm)	69.94	4.39	67.00	4.80	0.059

Note: As *P*-value <0.05 was considered statistically significant, the entries in bold define that there was a statistically significant difference between both groups.
Abbreviations: OCT, optical coherence tomography; ODA, optic disk area; CDAR, cup disk area ratio; HCDR, horizontal cup disk ratio; VCDR, vertical cup disk ratio; pRNFL, peripapillary retinal nerve fiber layer; mRNFL, macular retinal nerve fiber layer; GCC, ganglion cell complex; GCIPL, ganglion cell–inner plexiform layer; SD, standard deviation.

Discussion

Our study demonstrated the relationships between disk size, the nerve fiber layer, and the GCC, and eyes with large disk areas have a significantly greater incidence of inferior nerve fiber layer loss. This finding suggests that large disks within the normal range of IOP may be susceptible to glaucomatous damage.

Burgoyne et al[15] showed that the ONH is a biomechanical structure, and the mechanical failure of the connective tissue of the lamina cribrosa underlies glaucomatous cupping. The normal ONH is arranged with more and larger pores at the inferior and superior poles that have less connective tissue, indicating less structural support for the nerve fibers passing through the optic disk.[16–18] Preferential nerve fiber loss observed in the superior and inferior pole region in glaucoma may be due to these structural properties of the optic nerve.

There is a high prevalence of glaucoma in African and African-Caribbean populations that have larger optic disks compared with the Caucasian population.[19–24] This finding has led to the hypothesis that large optic disks may be more vulnerable to glaucomatous damage.[25] Zangwill et al[26] determined that large disks might be an important predictor of primary open-angle glaucoma in ocular hypertensive patients. There is also a relationship between disk size and CDR as a large CDR

Table 3 Linear regression analysis: the association between ODA and other OCT parameters

Variables	ODA	
	R	*P*-value
Cup area, mm^2	0.659	**<0.001**
Rim area, mm^2	0.430	**<0.001**
CDR	0.436	**<0.001**
HCDR	0.437	**<0.001**
VCDR	0.439	**<0.001**
Cup volume, mm^3	0.532	**<0.001**
Horizontal disk diameter, mm	0.920	**<0.001**
Vertical disk diameter, mm	0.864	**<0.001**
Rim volume, mm^3	0.115	0.296
pRNFL total, μ	−0.050	0.652
pRNFL superior, μ	0.042	0.703
Average macular thickness, μ	−0.039	0.728
pRNFL inferior, μ	−0.093	0.399
mRNFL total, μ	−0.050	0.652
mRNFL superior, μ	0.042	0.703
mRNFL inferior, μ	−0.093	0.399
GCIPL total, μ	−0.044	0.688
GCIPL superior, μ	0.005	0.964
GCIPL inferior, μ	−0.105	0.343
GCC total, μ	−0.067	0.547
GCC superior, μ	0.017	0.877
GCC inferior, μ	−0.119	0.281

Note: As *P*-value <0.05 was considered statistically significant, the entries in bold define that there was a statistically significant difference between both groups.
Abbreviations: ODA, optic disk area; OCT, optical coherence tomography; CDR, cup disk ratio; HCDR, horizontal cup disk ratio; VCDR, vertical cup disk ratio; pRNFL, peripapillary retinal nerve fiber layer; mRNFL, macular retinal nerve fiber layer; GCIPL, ganglion cell–inner plexiform layer; GCC, ganglion cell complex.

can be physiologic in a large disk. The Blue Mountains Eye Study showed that the CDR linearly increased for increasing disk diameters.[27] Therefore, it is important to make a differential diagnosis of a healthy macrodisk from glaucoma.

Jonas et al[28] reported that the vertical CDR measurement is more valuable compared with other optic disk parameters for distinguishing normal subjects from glaucoma patients.[29] Some other studies have also showed that the rim area increases as disk size increases.[30–33] Our study found that there were positive correlations between the optic disk size and VCDR and HCDR, and there was no significant correlation between disk size and rim area. This result might be due to use of a different diagnostic instrument and the different optic disk sizes evaluated in the study.

Furthermore, Quigley et al[34] reported that the number of nerve fibers increased linearly with increasing disk sizes in monkey eyes. In contrast, Yucel et al[35] found no correlation between the number of nerve fibers and the disk area in monkey eyes with laser-induced glaucoma. Mikelberg et al[36] also found no correlation between the nerve fiber layer and disk size in humans. These different results may be explained by different methodologies used to estimate disk size, species, and the number of eyes examined.

With the introduction of OCT, several studies focused on the optic disks with different characteristics; however, there were still conflicting results, most of them showing positive correlation between optic disk size and nerve fiber layer thickness.[37–39] Gabriele et al[40] supported the idea that macrodisks with optic neuropathy may be missed by OCT assessment. They explained that if a fixed area scan protocol is used, the distance between the scan and the optic disk margin will be reduced in the presence of a large optic disk. This may lead to an overestimation of nerve fiber layer thickness in large optic disks, as the measurements are made closer to the optic disk edge.[40] Therefore, if a fixed 3.4 mm diameter scan is applied, pRNFL thickness tends to be larger in eyes with larger optic disks.

Also, Huang et al[41] reported that magnification correction factor is the link for the true analysis of the optic disk and nerve fiber layer. They suggested that different results in other studies are due to magnification variation related to axial length variation. Onmez et al[42] found similar RNFL thicknesses between macrodisks and normal disks using Litmann formula for the correction of axial length-related ocular magnification. In our study, despite the inclusion of only the subjects with proper refraction error and axial length, software adjusted the circle diameter for the scan and corrected the papillary diameter, area, and volume while calculating magnification compensation, which enabled accurate scanning. We found no correlation between the average total, superior, or inferior pRNFL and ONH size, which is consistent with the previous literature.

Some studies indicated that GCC and peripapillary nerve fiber layer thicknesses show similar performance for the detection of early glaucoma.[7,43–47] In general, pRNFL values are superior to mRNFL thickness in the diagnosis of glaucoma. However, in a group of glaucomatous eyes having larger disk diameters, macular thickness assessment was superior to pRNFL measurement.[48,49] According to these studies, glaucomatous eyes with macrodisks may be missed by pRNFL assessment.

There is only one study published in the literature that obtained the diagnostic ability of macular parameters using 3D OCT.[50] Measurements of the inner retinal layers in the macular region were used as additional parameters for glaucoma detection.[7,43–46] Several studies have proposed that retinal ganglion cells with large axons are more vulnerable than ganglion cells with small axons in the macular area, and large axons were observed in the inferior retina in particular.[51,52]

This morphology may contribute to earlier nerve fiber layer loss in the inferior retina in glaucoma.

In our study, the inferior mRNFL thickness was significantly lower in the macrodisk group, whereas we found no correlation between the optic disk size and total macular thickness. The inferior GCIPL thickness was also thinner in the macrodisk group, but this result was not statistically significant.

Conclusion

The assessment of optic disk size is important in the diagnostic evaluation of glaucoma. In addition to ONH parameters and peripapillary nerve fiber layer thickness, mRNFL and inner retinal layer analyses should also be considered whether large disks may be more prone to pressure damage.[15,53] To understand the relationship between ganglion cell loss and macrodisk morphology, longer follow-up with larger sample sizes is necessary.

Disclosure

The authors report no conflicts of interest in this work.

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