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The use of ocular coherence tomography in evaluating optic nerve health in eyes with large disc size

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Abstract

Large discs are often associated with large cups; in order to exclude glaucomatous cupping a good objective tool is needed. The purpose of this study is to evaluate ocular coherence tomography (OCT) optic nerve head (ONH) parameters as indicators of ocular health in subjects with large discs. Eighty-one eyes of 53 healthy patients were evaluated; 46 eyes had large discs (disc area ≥2.6 mm^2) and 35 eyes had regular size discs (disc area <2.6 mm^2). All subjects underwent OCT. All ONH parameters were documented, including vertical integrated rim area (VIRA), horizontal integrated rim width (HIRW), rim area, cup area, cup-to-disc (CD) area ratio, horizontal cup to disc ratio (HCDR), vertical cup to disc ratio (VCDR), cup area topography, and cup volume. In addition, OCT retinal nerve fiber layer (RNFL) global mean thickness and four quadrants mean thicknesses were analyzed. All cup parameters were significantly higher in the large disc group compared to the normal disc group. The parameters estimating the rim varied between the groups: in the large disc group VIRA was significantly lower while HIRW was significantly higher, compared to the control group. Rim area was the only parameter with similar values in both groups (1.52±0.24 mm^2 and 1.6±0.3 mm^2 in the large and regular disc groups, respectively). Correlation analysis revealed significant positive association between disc area and cup parameters in the large disc group. In contrast, in the regular disc group, disc area was positively associated with rim parameters. Rim area might serve as an indicator for ocular health in large discs with large cups.

Introduction

Ocular coherence tomography (OCT) is a reliable tool for diagnosing and following patients with glaucoma.[1-3] Glaucoma is characterized by a gradual loss of retinal ganglion cells and thinning of the retinal nerve fiber layer[4,5] leading to a typical increase in the cup-to-disc (CD) ratio. Peripapillary circumferential retinal nerve fiber layer (RNFL) scans and radial optic nerve head (ONH) scans have similar accuracy for glaucoma detection. The best ONH parameters for discriminating between healthy and glaucomatous discs in different studies were: rim area,[3] vertical cup to disc ratio (VCDR),[1] and CD area ratio (please see Appendix for definitions of cup and disc measurement terminology).[2] Unfortunately, there is no available normative database for the ONH scans in the commonly used StratusOCT instrument (Carl Zeiss Meditec, Inc. Dublin, CA, USA); therefore it is not possible to assess individual patients' values.

Large discs might have large cups and increased CD area ratio without an accompanying thinning in RNFL. Moreover, histological studies in primates and humans demonstrated an increase in the number of nerve fibers with the increase in disc area.[6,7] Yet in humans, the larger disc size was associated with a decrease in nerve fiber density per disc area, since the fibers have a larger area through which to cross.[7]

The effect of large ONH on RNFL thickness is controversial. It has been suggested that the peripapillary RNFL thickness is greater closer to the ONH.[8] When measuring RNFL around a large disc with fixed-diameter OCT protocol, the RNFL thickness is overestimated and pathological thinning might be overlooked. Savini, *et al.* demonstrated that an increase in disc size is associated with an increase in RNFL measurements using a fixed-diameter OCT protocol scan.[9] RNFL thickness decrease with increasing scan radii was also demonstrated by Carpineto, *et al.*[10] Another study using RNFL in a constant distance from the ONH rim, and not the standard fixed-diameter scan, found thinner RNFL in larger discs.[11] Other studies did not find such a correlation between the circumpapillary RNFL measurement placement and disc size.[12]

In this study we aim to evaluate OCT ONH parameters as indicators of eye health in subjects with large discs.

Materials and Methods

Eighty-one eyes of 54 healthy subjects were evaluated in this retrospective cross- sectional study in two separate cohorts. Forty-six eyes of consecutive eligible subjects with large discs imaged at the Edith Wolfson Medical Center (Holon, Israel) were recruited to the large disc size group. Thirty-five eyes of consecutive eligible subjects with normal disc size imaged at the University of Pittsburgh Medical Eye Center (Pittsburgh, PA, USA) were recruited to the control group. The definition of a large disc was established by the disc area measurement obtained by OCT according to previously published data in healthy subjects.[13-15] All discs with area larger than 2.6 mm^2 (mean area +1 standard deviation) were considered to be large discs, while the control group had disc areas under 2.6 mm^2 This study was approved by the Institutional Review Board (IRB) / Ethics Committee at both institutions and adhered to the Declaration of Helsinki and Health Insurance Portability and Accountability Act (HIPAA) regulations. Informed consent was obtained from all participants.

In both groups, all subjects denied ocular complaints or diseases, had intraocular pressure of less than 22 mmHg, normal anterior segments on slit lamp exam, normal discs and maculae, reliable normal visual fields in both eyes, and normal mean RNFL thicknesses in both eyes. Exclusion criteria were refractive error > ± 6 D (spherical equivalent), peripapillary atrophy, and any eye pathology or previous eye surgery except for uncomplicated cataract extraction.

All subjects were scanned after pupillary dilatation with the time-domain OCT, the StratusOCT (software version 4.0; Carl Zeiss Meditec, Inc. Dublin, CA, USA), by experienced operators. OCT measurements of the ONH were generated with the fast optic disc acquisition protocol of six total radial scans 6 mm in length in a spoke pattern configuration cen-

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tered on the ONH, evenly spaced 30 degrees apart. Each radial scan included 128 A-scans. Qualified scans had signal strength of at least 6. The OCT defined the ONH margin automatically as the end of the retinal pigment epithelium. The generated image was manually corrected in case the OCT did not recognize accurately the ONH margin. The rate of images that were manually adjusted was not recorded; previous studies reported manual adjustment of disc margin in 50-60% of cases.[9,16] All ONH parameters were documented, including VIRA, HIRW, rim area, cup area, CD area ratio, HCDR, VCDR, cup area topography (using an offset of 150 microns), and cup volume (using an offset of 150 microns). In addition, OCT RNFL global mean thickness and four quadrant mean thicknesses were analyzed.

Statistical analysis was performed to determine the differences in mean values of ONH parameters between the two groups, using the general linear model (GLM). The number of eyes was included in the linear model in order to control for the use of both eyes in some patients. In each model, diagnosis and sex were included as fixed factors. Correlation analysis was used to determine the association between rim and cup parameters to disc area, in both groups. Significance was set as a P value of less than 0.05.

Results

The study population characteristics are summarized in Table 1. There were no age differences between the two study groups. All subjects were Caucasians. There were more female subjects in the large disc group than in the control group (P=0.03). The average disc area in the large disc group was 3.01 mm^2 (range 2.6-3.7) while the average disc area in the control group was 2.05 mm^2 (range 1.5-2.5, P<0.01).

The various average ONH parameters provided by the OCT in the two groups are shown in Table 2. All cup parameters were significantly higher in the large disc group compared to the control group. The parameters estimating the rim varied between the groups: in the large disc group, VIRA was significantly lower while HIRW was significantly higher, compared to the control group. The only parameter that did not vary between the groups was the rim area, with a value of 1.52 ± 0.24 mm^2 in the large disc group and 1.6 ± 0.3 mm^2 in the control group (P=0.15).

In the large disc group, a significant correlation was demonstrated between all cup parameters and disc area (cup area: r=0.75, P<0.01, CD area ratio: r=0.48, P=0.001, HCDR: r=0.34, P=0.02, VCDR: r=0.495, P<0.01, cup area topography: r=0.56, P<0.01, and cup volume: r=0.36, P=0.001, Figure 1). On the other hand, in this group, no significant correlation was demonstrated between any of the rim parameters and the disc area (Figure 2).

In the regular disc size group, a significant association with disc area was evident only in cup area (r=0.34, P=0.04) and cup volume (r=0.35, P=0.04) but not in the other cup parameters (Figure 3). In this group, 2 of 3 rim parameters were significantly correlated with disc area: HIRW (r=0.57, P<0.01) and rim area r=0.54, P=0.001 (Figure 4).

We found a trend of correlation (P=0.07, r=0.3) between the disc area and the mean RNFL in the control group but not in the large disc group or the two groups combined. The quadrant RNFL data did not correlate to the disc area in any of the groups.

Discussion

Disc size varies significantly in healthy subjects with ophthalmoscopically-measured disc area ranging between 0.8 and 6 mm^2.[17] Subjects with large discs and large cups are often referred to glaucoma clinics with suspected glaucoma by optic nerve appearance. It is known that in a large disc, a large cup is also expected.[6,18] Nevertheless, a good objective tool is needed to differentiate between physiological large cups in large discs and glaucomatous large optic nerves. Measuring circumferential RNFL with fixed-diameter OCT protocol may be misleading in these cases because of closer approximation to the ONH edge, which gives artificially higher values.[8] In this study we found that while all ONH parameters varied between subjects with regular disc size and those with large disc and large cups, rim area had similar values in both groups.

There are three different rim parameters derived from the ONH scan: VIRA, HIRW and rim area, each behaved differently when the two study groups were compared. VIRA estimates the total volume of rim tissue, as defined previously. In this study we found a significantly lower value in the large disc group, suggesting the discs in this group were shallower. HIRW estimates the total area of rim tissue, as defined previously. Interestingly, the value of HIRW was significantly higher in the large disc group compared to the controls, implying that the rim in this group is thicker, as was found in histology studies.[7,18] In contrast to the VIRA and HIRW, the rim area parameter, as defined previously, had similar values in both groups. We did find that in the large discs, all 6 parameters describing the cup and CD area ratio are larger, as described by previous histology studies that found larger

Table 1. Demographic and clinical characteristics of the study population.

	Large disc	Regular disc	P
N eyes (pts)	46 (25)	35 (28)	
Age (yrs)	55.1±12.6	54.4±19.4	0.86*
Female / Male	31/15	15/20	0.03°
Disc area (mm^2)	3.02±0.26	2.05±0.26	<0.0001*
RNFL (μm)	99.09±9.1	96.24±9.73	0.18*
Superior RNFL (μm)	121±11.8	117±17.3	0.26*
Nasal RNFL (μm)	80±13.2	79±14.5	0.89*
Inferior RNFL (μm)	126±16.8	120±16.1	0.11*
Temporal RNFL (μm)	70±12.3	69±11.5	0.62*

A comparison of patients' characteristics between the study groups. RNFL, retinal nerve fiber layer; *Independent-sample two-tailed *t-test*; °Chi-square tests.

Table 2. Optic nerve head mean parameters.

	Large disc (mean ± SD)	Regular disc (mean ± SD)	P*
Vertical integrated rim area (VIRA, mm^3)	0.25±0.01	0.41±0.18	<0.0001
Horizontal integrated rim width (HIRW, mm2)	1.76±0.16	1.64±0.19	0.003
Rim area (mm^2)	1.52±0.24	1.60±0.30	0.15
Cup area (mm^2)	1.49±0.37	0.45±0.27	<0.0001
CD area ratio	0.49±0.01	0.21±0.12	<0.0001
Horizontal CD ratio (HCDR)	0.72±0.008	0.46±0.14	<0.0001
Vertical CD ratio (VCDR)	0.66±0.01	0.43±0.13	<0.0001
Cup area topography (mm^2)	1.32±0.37	0.76±0.62	<0.0001
Cup volume (mm^3)	0.33±0.14	0.009±0.01	<0.0001

The mean value of the ONH parameters in each group and the P value of comparison. ONH, optic nerve head; CD, cup to disc; *Independent-sample two-tailed *t-test*.

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cup area in larger discs.[6,18]

Moreover, in large discs, we found a positive correlation between the cup parameters and disc area, while such association was not found with rim parameters. Thus, when passing a certain threshold of disc size, further enlargement of the disc directly influences the cup size while rim magnitude does not increase. On the other hand, in disc area range under 2.6 mm^2, as the disc is getting bigger, rim size increases while most cup dimensions are not influenced. Indeed, a recent large scale study with subjects who had a wide range of disc sizes (average 2.27 mm^2) found correlations between disc area and the same parameters as seen in the regular disc group in our study.[14]

Rim area was found to be similar in the entire cohort of healthy discs in our study, whether large or normal in size (1.52±0.24 mm^2 and 1.6±0.3 mm^2, respectively) as was previously demonstrated using the Heidelberg retinal tomography, HRT (Heidelberg Engineering, Inc., Carlsbad, CA, USA).[19] This parameter was also found to be a reliable indicator of glaucomatous optic neuropathy. The area under the receiver operating curve (AROC) for discrimination between healthy and glaucomatous eye in different publications was 0.92 to 0.97 with average values of 0.84±0.31 mm^2 in Wollstein, *et al.*[3] and 0.89±0.34 mm^2 in Naithani, *et al.*[13] in the glaucomatous population. This data from the literature further supports the role of rim area parameter as an important indicator for disc health.

The lack of correlation between RNFL measurements and disc size in the large disc group may have resulted from inhomogeneity of the discs characteristics. Two possible and contradicting factors may influence the RNFL thickness measurement with a fixed-diameter scan circle in large discs. The first factor is the shorter distance from the ONH rim which increases the thickness,[9,10] and the second factor is the thinner overall RNFL thickness in these discs.[7,11] As these factors are opposed, the net correlation in a group may vary.

One potential limitation of this study is the exclusive inclusion of Caucasian subjects. Subjects from African ancestry present higher prevalence of large discs, when compared with Caucasian patients,[14] therefore further investigation is warranted in this population. Another possible limitation results from a higher prevalence of female participants in the large disc group, although we controlled for sex bias in the statistical analysis we conducted. We did not perform sample size calculations, thus the lack of difference in rim area could result from insufficient study cohort, although differences in other ONH parameters were highly significant. Another limitation is the lack of axial length comparison between the groups,

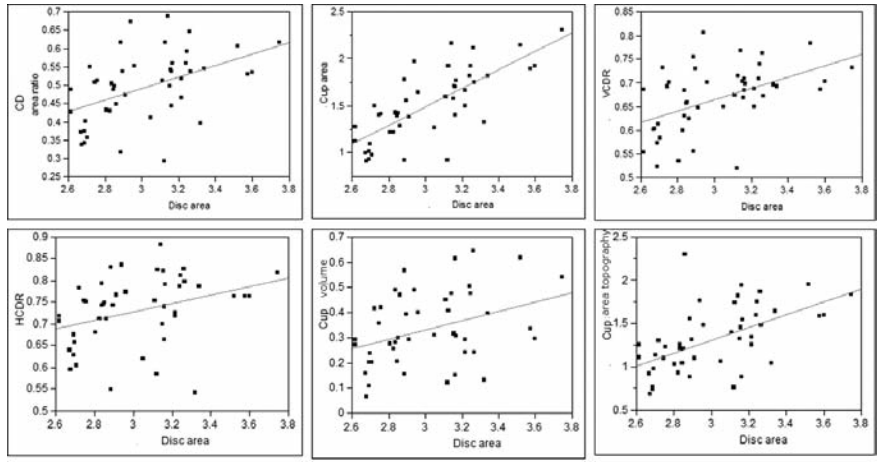

Figure 1. Correlation of cup parameters with disc area in the large disc group. In the large disc group, a significant correlation was demonstrated between all cup parameters and disc area.

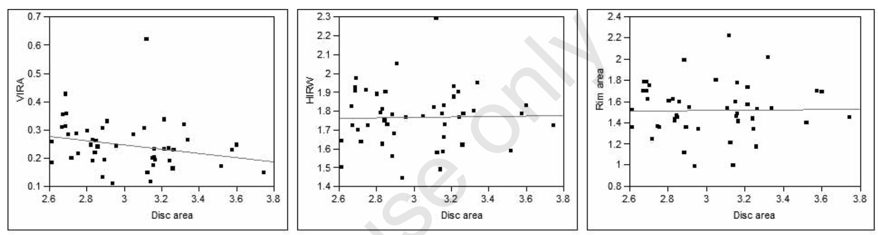

Figure 2. Correlation of rim parameters with disc area in the large disc group. In the large disc group, no significant correlation was demonstrated between any of the rim parameters and the disc area.

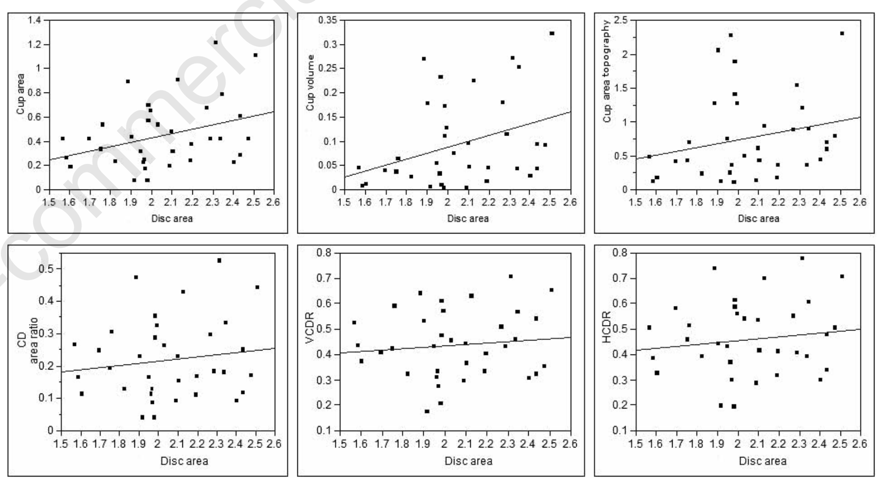

Figure 3. Correlation of cup parameters with disc area in the control group. In the regular disc group, a significant association with disc area was not evident in most cup parameters except for the cup area and cup volume.

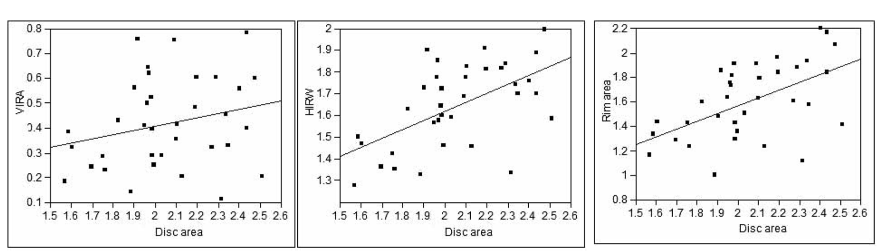

Figure 4. Correlation of rim parameters with disc area in the control group. In the regular disc group, 2 of 3 rim parameters were significantly correlated with disc area (HIRW and rim area).

despite exclusion of subjects with high refractive errors. The axial length was found to be inversely correlated to the disc size[20] and should be included in future studies. A possible bias is a selection bias of large cups among the large disc cohort, since these subjects were referred to the clinic with suspicious discs, yet this served to answer the clinical question.

Our findings may have significant implications on the clinical use of OCT. Rim area might serve as an indicator for disc health in large discs. These findings need to be further explored in subjects with large discs who have glaucoma.

Appendix

The StratusOCT provides several calculated values. The vertical integrated rim area (VIRA) is a measure of the total volume of the retinal nerve fiber layer within the rim that is calculated by the StratusOCT using the product of the disc circumference and average of 6 individually-calculated sectional rim areas (in each of the 6 spokes). The horizontal integrated rim width (HIRW) is a measure of the total rim area that is calculated by the StratusOCT using the product of the disc circumference and average of 6 individually-calculated sectional rim widths (in each of the 6 spokes) rather than rim areas. The rim area is the area of the cup subtracted from the area of the disc, calculated from a flattened planimetric image of the disc in axis with the pupil. The cup area also is calculated from a flattened planimetric image of the disc in axis with the pupil. The horizontal cup to disc ratio (HCDR) is the ratio of longest horizontal line across the flattened planimetric ring image of the cup calculated from cross-sectional 3-dimentional data along 6 axes (in each of the 6 spokes) to the longest horizontal line across the flattened planimetric image of the disc calculated from cross-sectional 3-dimentional data along 6 axes (in each of the 6 spokes), whether or not these two horizontal lines overlap. The vertical cup to disc ratio (VCDR) is the ratio of longest vertical line across the flattened planimetric image of the cup calculated from cross-sectional 3-dimentional data along 6 axes (in each of the 6 spokes) to the longest vertical line across the flattened planimetric image of the disc calculated from cross-sectional 3-dimentional data along 6 axes (in each of the 6 spokes), whether or not these two vertical lines overlap. The cup area topography is the calculated cup area based on the 3-dimentional topography of the cup obtained along 6 axes (in each of the 6 spokes) using a fixed standard offset which is often 150 microns. The cup volume is the calculated cup area based on the 3-dimentional topography of the cup obtained along 6 axes (in each of the 6 spokes) using a fixed standard offset, which is often 150 microns.

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