Using Enhanced Depth Imaging Optical Coherence Tomography-Derived Parameters to Discriminate between Eyes with and without Glaucoma: A Cross-Sectional Comparative Study

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Keywords

Glaucoma · Tomography · Optical coherence tomography · Optic nerve diseases

Abstract

Introduction: New technologies have been developed in order to decrease interpersonal influence and subjectivity during the glaucoma diagnosis process. Enhanced depth imaging spectral-domain OCT (EDI OCT) has turned up as a favorable tool for deep optic nerve head (ONH) structures assessment. **Objective:** A prospective cross-sectional study was conducted to compare the diagnostic performance of different EDI OCT-derived parameters to discriminate between eyes with and without glaucoma. **Material and Methods:** The following ONH parameters were measured: lamina cribrosa (LC) thickness and area; prelaminar neural tissue (PLNT) thickness and area; average Bruch's membrane opening – minimum rim width (BMO-MRW), superior BMO-MRW, and inferior BMO-MRW. Peripapillary retinal nerve fiber layer (pRNFL) thickness was also obtained. **Results:** Seventy-three participants were included. There were no significant differences between AUCs for average BMO-MRW (0.995), PLNT

area (0.968), and average pRNFL thickness (0.975; $p \geq 0.089$). However, AUCs for each of these 3 parameters were significantly larger than LC area AUC (0.701; $p \leq 0.001$). Sensitivities at 80% specificity were: PLNT area = 92.3%, average BMO-MRW = 97.4%, and average pRNFL thickness = 94.9%. **Conclusions:** Comparing the diagnostic performance of different EDI OCT ONH parameters to discriminate between eyes with and without glaucoma, we found better results for neural tissue-based indexes (BMO-MRW and PLNT area) compared to laminar parameters. In this specific population, these neural tissue-based parameters (including PLNT area, which was investigated by the first time in the present study) had a diagnostic performance comparable to that of the conventional pRNFL thickness protocol.

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Introduction

Glaucoma is a multivariable optic neuropathy, characterized by distinctive findings of the optic nerve head (ONH), retinal nerve fiber layer (RNFL) thinning, and visual field (VF) defects, which can ultimately lead to

progressive and irreversible vision loss [1, 2]. Early diagnosis and proper treatment continue to be the most important cornerstone for controlling and avoiding blindness due to glaucoma. According to present guidelines for glaucoma diagnosis and monitoring, functional evaluation is usually performed with VF testing through standard automated perimetry, whereas structural documentation is based on retinography/disc photographs and optical coherence tomography (OCT) exams [3–5].

Evaluation of ONH structures has always taken much attention in glaucoma research. Although clinical examination and documentation of ONH characteristics through disc photos is recommended and usually available in daily practice, it requires specific training (diagnostic performance varies among physicians) and has significant reproducibility issues [6, 7]. In the past decades, new technologies have been developed in order to decrease interpersonal influence and subjectivity during the glaucoma diagnosis process. In this scenario, enhanced depth imaging spectral-domain OCT (EDI OCT) has turned up as a favorable tool for the assessment of deep ONH structures [8–10]. By means of advancement in OCT technology and software improvements, new anatomic parameters and landmarks such as Bruch's membrane opening (BMO) and BMO-minimum rim width (BMO-MRW) have been identified, adding to the early diagnosis of glaucoma [11–13].

When it comes to using ONH parameters for glaucoma diagnosis and monitoring (besides the well-established BMO-MRW analysis), more recently, researchers have been investigating new metrics based both on prelaminar neural tissue (PLNT) and laminar analyses [14–16]. In previous studies from our group in this research line [17], we reported on glaucoma-related features within the ONH and on structure-function relationships in glaucoma (considering both laminar and prelaminar parameters) using EDI OCT quantitative analysis. Even though some interesting data about these new EDI OCT-based parameters have been emerging, their usefulness as an additional tool for glaucoma diagnosis is still unclear. Therefore, in the present study, we sought to compare the diagnostic performance of different EDI OCT-derived parameters to discriminate between eyes with and without glaucoma. In addition, the diagnostic ability of these parameters were compared with the conventional peripapillary RNFL (pRNFL) protocol.

Materials and Methods

The Department of Ophthalmology of the Federal University of São Paulo conducted this observational cross-sectional study. The Institutional Review Board of the Federal University of São Paulo approved the study protocol and it complied to the tenets of the Declaration of Helsinki. Preceding enrollment and examination, written informed consent was obtained from all subjects.

Participants

We prospectively enrolled consecutive glaucomatous patients (glaucomatous optic neuropathy and reproducible VF defect) with a wide range of disease stages and healthy individuals between January 2016 and March 2017. Initially, all participants underwent a complete ophthalmologic examination. Exclusion criteria for both groups were age under 18 years old, earlier posterior segment intraocular surgery, ocular trauma, significant media opacity, ineptitude to perform the examinations, and diseases affecting the eye and/or eye diseases, apart from glaucoma (e.g., diabetic retinopathy, macular edema, hypertensive retinopathy, or macular degeneration).

We adopted the same glaucoma definition that we used in our previously published studies [16, 17]. In short, characteristic glaucomatous optic neuropathy was defined as a vertical cup-to-disc ratio (VCDR) ≥ 0.6 , asymmetry of VCDR ≥ 0.2 between eyes, presence of localized or diffuse pRNFL defects and/or neuroretinal rim defects in the absence of any other abnormalities, which could explain such findings [16, 18, 19]. Glaucomatous VF defect in the standard automated perimetry (Humphrey SITA – Standard 24-2, Carl Zeiss Meditec, Dublin, CA, USA) was defined as 3 or more points in clusters with a probability of $<5\%$ (excluding those on the edge of the field or directly above and below the blind spot) on the pattern deviation plot, a pattern SD index with a probability of $<5\%$, or a glaucoma hemifield test with results outside the normal limits. Even though all glaucomatous eyes had to have structural damage associated with functional loss, a topographical correspondence between the disc damage location and the VF defect was not required.

Included controls were healthy individuals with normal VF testing and normal appearance of the optic disc, defined as a VCDR <0.6 , without localized or diffuse pRNFL defects and/or neuroretinal rim thinning, and untreated intraocular pressure lower than 21 mm Hg [18].

Imaging and Data Collection

Imaging acquisition has been described in detail in a previous study from our group [16]. In a few words, EDI OCT imaging (SD-OCT; Spectralis, wavelength: 870 nm; Heidelberg Engineering Co., Heidelberg, Germany) was carried out for both eyes of each participant and a sequence of vertical B-scan images of the ONH was achieved [20, 21]. Of note, EDI OCT was only used for optic disc analysis, and not for RNFL data acquisition. The OCT device was set to image a 15° (vertically) $\times$ 10° (horizontally) rectangle (vertical scans) centered on the optic disc with a 30° retinal window. The EDI mode of the Spectralis SD-OCT automatically positions the OCT reference plane toward the bottom of the OCT acquisition screen, shifting the zero delay to the bottom of the OCT screen, with no need of image inversion. This permits an enhancement of the image of deeper layers of ONH. This rectangle was scanned with 97 sections, with an interval between adjacent sections of ap-

proximately 30 μm and each section had an average of 100 OCT frames.

The following ONH parameters were evaluated in EDI OCT vertical B-scans by the examiners F.S.S.L. and I.A. without access to patients clinical data (Fig. 1): lamina cribrosa (LC) thickness and area, PLNT thickness and area, anterior LC depth, BMO, and average BMO-MRW, superior BMO-MRW, and inferior BMO-MRW. The average of 2 measurements was considered for analysis for each examiner and only good-quality images were considered for analysis, showing at least a signal-to-noise ratio >25 dB as suggested by the OCT device manufacturer. To enhance LC visibility at the EDI OCT scans, image contrast was increased to the maximum level and image colors were switched (black or white) as needed using the device software. The line connecting Bruch's membrane edges was used as a reference plane for all depth measurements [22]. The chosen parameters were measured in the B-scans based on the horizontal center of the ONH using the built-in software calipers (linear measurements; unit: μm). Area measurements were also taken (manually measured) using the built-in software calipers (unit of measurement: mm^2).

In any occasion that the chosen image presented vascular shadows which compromised LC or prelaminar tissue visualization, we used the closest temporal B-scan which did not present such artifacts (approximately 30 μm apart). Therefore, LC and PLNT were measured as close to the horizontal center of the ONH as possible. The LC thickness was defined as the distance between the anterior and posterior borders of the highly reflective region at the vertical center of the ONH in the vertical EDI OCT cross-sectional B-scans [23]. The PLNT was defined as the perpendicular distance between the anterior PLNT surface and the anterior surface of the LC. Cup depth was defined as the perpendicular distance from the reference line to the anterior PLNT surface. BMO-MRW was defined as the minimal distance from the inner opening of the BMO to the internal limiting membrane. PLNT area is an area of soft tissue located between the optic cup surface and the anterior LC surface [24]. It was defined as the area comprised between the superior and inferior BMO-MRW and the anterior portion of the LC (please refer to Fig. 1) [25–27]. We used the average of 2 measurements for each parameter. Whenever both eyes were eligible, one was randomly selected for analysis.

Statistical Analysis

Descriptive analysis was used to present demographic and clinical data. D'Agostino-Pearson's test was performed to determine whether the data had a normal distribution or not. Descriptive statistics included mean and SD for normally distributed variables and median, quartiles for those non-normally distributed. Independent samples *t* test was used to compare continuous normally distributed variables between groups, while the Mann-Whitney test was used to compare those non-normally distributed. Categorical data were compared using chi-square test. We analyzed the structure-functional relationships between different OCT parameters and patient's VF status. In order to do that, scatter plots were constructed, and regression analysis was used to investigate the correlations between each anatomic parameter and patient's VF mean deviation (VFMD) index. Receiver operating characteristic (ROC) curves and sensitivities at fixed specificities were generated for different parameters. The areas under the ROC curve (AUCs) of each parameter were compared using the Delong test.

Fig. 1. Optic nerve head EDI OCT B-scan. A, Bruch's membrane opening (BMO); B, cup depth; C, prelaminar neural tissue (PLNT) thickness; D, lamina cribrosa (LC) thickness; E, BMO-minimum rim width; F, PLNT area; G, LC area.

Sample Size Calculation

For a power of 80% (type I α error of 0.05 and type II β error of 0.20), the minimal required sample size would be 33 subjects in each group, considering the hypothesized differences between the AUCs to be 0.1 (e.g., 0.9 vs. 0.8) and assuming a high correlation between the 2 tests in normal and abnormal cases. Computerized analysis was performed using MedCalc software (MedCalc Inc., Mariakerke, Belgium).

Results

Among the 81 participants enrolled for the study, 73 eyes of 73 participants (39 with glaucoma and 34 controls) were included in the analysis, as 8 eyes were excluded due to poor-quality images and/or impossibility to define the posterior limits of the LC. Most glaucoma patients had primary open-angle glaucoma (69%). Other diagnoses included primary angle-closure glaucoma (20%), secondary glaucoma (8%), and pigmentary glaucoma (3%). Mean age, intraocular pressure, and axial length did not differ significantly between glaucomatous eyes and controls ($p \geq 0.122$ for these 3 comparisons). Demographic and clinical characteristics of included patients are provided in Table 1. The average VFMD index for glaucomatous eyes was -9.4 ± 7.4 dB. Stratifying the glaucomatous eyes according to VFMD index values into 3 groups (mild >-6 dB, moderate -6 to -12 dB, and advanced <-12 dB), we found the following results: 14 patients with mild glaucoma (VFMD: -3.98 dB and visual field index [VFI]: 89%), 13 patients with moderate glaucoma (VFMD: -8.11 dB and VFI: 80%), and 12 patients with advanced glaucoma (VFMD: -17.01 dB and VFI:

Fig. 2. Scatter plots depicting the association between VFMD index and different EDI OCT parameters (**a** PLNT area; **b** pRNFL thickness; **c** average BMO-MRW). BMO-MRW, Bruch's membrane opening-minimum rim width; PLNT, prelaminar neural tissue; pRNFL, peripapillary retinal nerve fiber layer; VFMD, visual field mean deviation.

Table 1. Characteristics of the control and glaucoma groups

Variables ^a	Control group (<i>n</i> = 34)	Glaucoma group (<i>n</i> = 39)	<i>p</i> value
Age, years	60.7±10.7	64.9±11.9	0.122
Gender (W/M)	22/12	13/26	0.014
Race (Wh/AD/O), %	52/11/37	47/25/28	0.582
IOP, mm Hg	14.2±2.5	14.1±3.2	0.882
CCT, μm	547±31.0	511±38.1	<0.01
Axial length, mm	23.1±0.9	23.1±0.8	0.794
VFMD, dB	-1±0.9	-9.4±7.4	<0.01
VFI, %	99 (98, 100)	83 (62.2, 91.2)	<0.01

^a Data are given as mean ± SD whenever indicated; non-normally distributed variables are represented by median (first quartile, third quartile). W, women; M, men; Wh, White; AD, African descendants; O, others; IOP, intraocular pressure; CCT, central corneal thickness; VFMD, visual field mean deviation; VFI, visual field index.

48%). All evaluated OCT parameters differed significantly between eyes with and without glaucoma ($p < 0.01$). More specifically, average pRNFL thickness for glaucomatous eyes and controls was $65.2 \mu\text{m} \pm 12.4$ and $101.1 \mu\text{m} \pm 14.3$, respectively. Average BMO-MRW for glaucomatous eyes and controls was $328.6 \pm 55.2 \mu\text{m}$ and $153.7 \pm 50.7 \mu\text{m}$, respectively. PLNT area for glaucomatous eyes and controls was $0.65 \pm 0.17 \text{ mm}^2$ and $0.33 \pm 0.09 \text{ mm}^2$, respectively. Finally, LC area for glaucomatous eyes and controls was $0.24 \pm 0.04 \text{ mm}^2$ and $0.20 \pm 0.05 \text{ mm}^2$, respectively.

The investigation of structure-function relationships in our glaucoma population (control eyes were not included in the regression analysis) revealed significant non-linear correlations between the 3 OCT parameters – PLNT area ($R^2 = 0.20$), average pRNFL thickness ($R^2 = 0.32$), and average BMO-MRW ($R^2 = 0.38$) – and VFMD values ($p < 0.01$). Scatter plots depicting the association between VFMD index and each different OCT parameter are provided in Figure 2.

Regarding the diagnostic performance of the different OCT parameters, AUCs for average PLNT thickness and PLNT area were 0.837 (95% CI 0.732–0.913) and 0.968 (95% CI 0.898–0.995), respectively. The AUCs for average LC thickness and LC area were 0.696 (95% CI 0.577–0.798) and 0.701 (95% CI 0.582–0.802), respectively. AUCs for average, superior, and inferior BMO-MRW were 0.995 (95% CI 0.942–1.000), 0.975 (95% CI 0.908–0.997), and 0.988 (95% CI 0.929–1.000), respectively. Finally, the AUC for average pRNFL thickness was 0.975 (95% CI 0.906–0.997).

Regarding the comparison of AUC values within each type of ONH parameter, PLNT area had a larger AUC when compared to PLNT thickness measurements ($p < 0.001$). No statistic difference was found between LC parameters ($p = 0.935$). Although average BMO-MRW AUC values were higher than inferior and superior values, the differences were not statistically significant ($p \leq 0.086$).

Concerning the comparison of AUC values between each type of ONH parameter (the one with larger AUC was considered for analysis, and average pRNFL thick-

Fig. 3. ROC curves for different OCT parameters. AUCs for average BMO-MRW (0.995), PLNT area (0.968), and average pRNFL thickness (0.975) were similar ($p \geq 0.089$). However, AUCs of each of these 3 parameters were significantly larger when compared to the AUC of LC area (0.701; $p \leq 0.001$).

ness was also included in this comparison; Fig. 3), there was no significant difference among average BMO-MRW, PLNT area, and average pRNFL thickness ($p \geq 0.089$). However, AUCs of each of these 3 parameters were significantly larger when compared to the AUC of LC area ($p \leq 0.001$).

Regarding the above-mentioned parameters, we found the following sensitivity values at 80% specificity: LC area = 53.8% (cut-off value, $\leq 0.195 \text{ mm}^2$), PLNT area = 92.3% (cut-off value, $\leq 0.47 \text{ mm}^2$), average BMO-MRW = 97.4% (cut off value, $\leq 244 \text{ }\mu\text{m}$), and average pRNFL thickness = 94.9% (cut-off value, $\leq 86 \text{ }\mu\text{m}$).

When considering the ability to identify glaucomatous eyes based on the abovementioned cut-off values, the average BMO-MRW protocol identified 38 of the 39 patients, the average pRNFL thickness protocol identified 37 of the 39 patients, and the PLNT area protocol identified 36 of the 39 patients. The combination of these 3 OCT parameters (average BMO-MRW, average pRNFL thickness, and PLNT area) was able to identify all the 39 patients. Finally, regarding the agreement between ob-

servers (measurements) for various OCT parameters, we found the following interobserver intraclass correlation coefficient values (ranging from 0.69 to 0.99): LC thickness = 0.69, LC area = 0.73, PLNT thickness = 0.99, PLNT area = 0.96, anterior LC depth = 0.99, BMO = 0.98, average BMO-MRW = 0.99, superior BMO-MRW = 0.97, and inferior BMO-MRW = 0.98.

Discussion

Even though some interesting new strategies for glaucoma diagnosis and monitoring are currently under investigation [28–30], physicians still rely on objective structural analysis (ONH, macula, and pRNFL parameters) and functional evaluation. Although the well-established conventional pRNFL analysis has a good diagnostic ability, it is not adequate for every eye. Its use is limited depending on optic disc characteristics (e.g., disc tilt), magnitude of myopia, amount of peripapillary atrophy, and other ocular conditions such as ONH drusen and

congenital disc abnormalities [31–34]. In addition, its cross-sectional use for glaucoma diagnosis has a relatively modest performance in cases of mild and pre-perimetric glaucoma [19, 35–37]. Therefore, in the past years, researchers have been focusing on both segmented macular evaluation and on topographic characteristics of the ONH, searching for new anatomic parameters for glaucoma diagnosis and follow-up. It is well-known that a large proportion of total macular thickness is composed of RNFL and ganglion cell bodies; this region is an attractive area for identifying structural damage from glaucoma [38]. In the present study, comparing the diagnostic performance of different EDI OCT ONH parameters to discriminate between eyes with and without glaucoma, we found better results for neural tissue-based indexes (such as BMO-MRW and PLNT area) compared to laminar parameters (such as LC area). Moreover, these neural tissue-based parameters had a diagnostic performance comparable to that of the conventional pRNFL thickness protocol (in this specific study population).

In order to put our findings in perspective and to better compare our results to those previously published, we will address each type of OCT parameter separately. Initially, regarding the BMO-MRW (a relatively new OCT parameter in comparison with pRNFL thickness), one can note that its clinical investigation and applicability in daily practice has significantly grown in the past 5 years [11–13, 26, 39]. Some studies have shown that the diagnostic performance of BMO-MRW is comparable to that of conventional pRNFL thickness in cases of pre-perimetric and early glaucoma [11, 12]. In addition, more recently, Reis et al. [39] demonstrated that BMO-MRW measurements have a good reproducibility, which is comparable to that of pRNFL thickness. It is of note that while in some studies, BMO-MRW measurements were taken in an automated manner, in others, they were manually obtained [11, 13, 26, 39]. In our study, in which all EDI OCT parameters were manually obtained, BMO-MRW had an excellent diagnostic performance (comparable to that of pRNFL thickness), corroborating these previously published data [39]. Moreover, while investigating another prelaminar EDI OCT-derived parameter, we found that the ability of PLNT area (which represents a different way to quantify prelaminar tissue loss in glaucoma) to discriminate between eyes with and without glaucoma seems to be comparable to that of other more established parameters (pRNFL thickness and BMO-MRW). The comparison between this specific finding (PLNT area diagnostic performance) with similar previously published data is difficult due to the lack of studies assessing this

type of EDI OCT measurement. Finally, regarding the investigation of laminar parameters for glaucoma diagnosis in our study, LC thickness and LC area had the worst performance among all the OCT parameters we evaluated. We believe this can be explained in part by the difficulty that examiners usually face to determine the posterior limits of the LC, and the resulting poor reproducibility of LC measurements [16]. There are scant data in the literature about the diagnostic ability of LC thickness measurements. Evaluating a distinct glaucoma population and using a different method of data acquisition from EDI OCT images, Park and Park [40] reported a better diagnostic performance of LC thickness when compared to our findings. Probably these conflicting results can be explained in part by the fact that many patients in the abovementioned study had normal-tension glaucoma diagnosis, in which LC thickness measurements had a better diagnostic performance when compared to the general glaucoma population [35]. In addition, manual delimitation of LC parameters may also bring subjective bias. Although automated segmentation methods have been described before, until nowadays, there is no commercially available software for this purpose [41]. Moreover, the lack of a normative database for LC parameters means one is unable to determine whether an individual exam is within normal limits.

At this point, we believe it is important to discuss the main clinical implications of our findings. As previously discussed, although being well established and having a good diagnostic performance, conventional pRNFL analysis does not apply for all types of eyes. Many ocular conditions may preclude proper pRNFL scanning [31–34]. Moreover, accuracy issues (false positive and false negative cases) have been reported even in eyes with favorable anatomy [42]. Therefore, we believe that other structural parameters should be constantly investigated in order to improve imaging devices' diagnostic performance. In this context, our findings not only highlight the use of neural tissue-based indexes for glaucoma diagnosis, but also suggest that their combined use along conventional pRNFL analysis might help clinicians to discriminate between eyes with and without glaucoma in daily practice.

Some specific characteristics and limitations of our study should be considered. First, this was a cross-sectional study and certainly, some of these structural parameters we investigated need to be longitudinally evaluated. Second, as there is no normative database for most of the OCT parameters we evaluated, our results should be confirmed in other populations with distinct characteristics. Third, as some of the structural parameters we

investigated in this study had their diagnostic performance evaluated for the first time, we opted for a proof-of-concept design. As a result, our study group consisted of glaucomatous patients with a wide range of disease stage (including eyes with moderate and advanced disease). This fact should be taken into consideration while interpreting our results. Finally, despite some technical limitations, BMO-MRW values can now be automatically acquired (currently). In our study, BMO-MRW measurements (along with other structural parameters) were manually obtained, as reported in some other previous studies [11, 13, 26, 39]. Even though it could have influenced our findings, we believe it was not in a significant manner, as all BMO-MRW parameters had an excellent diagnostic ability in our study, corroborating the previously published data [11, 12, 39].

Conclusions

Comparing the diagnostic performance of different EDI OCT ONH parameters to discriminate between eyes with and without glaucoma, we found better results for neural tissue-based indexes (BMO-MRW and PLNT area) compared to laminar parameters. In this specific population, these neural tissue-based parameters (including PLNT area – which was investigated for the first time in the present study) had a diagnostic performance comparable to that of the conventional pRNFL thickness protocol, which provides the basis for further research focusing on how the combination of these two analyses would perform. Further diagnostic studies comprised by patients with early glaucomatous damage are warranted in order to confirm the clinical utility of some of our findings.

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Statement of Ethics

The Department of Ophthalmology of the Federal University of São Paulo conducted this observational cross-sectional study. The Institutional Review Board of the Federal University of São Paulo approved the study protocol and it complied to the tenets of the Declaration of Helsinki. Preceding enrollment and examination, written informed consent was obtained from all subjects.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

F.S.S.L.: study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript. I.M.: acquisition of data. I.A.: acquisition of data, study conception and design. C.P.B.G.: study conception and design, critical revision. S.K.D., R.M.V., and A.P. Jr.: study conception and design. T.S.P.: study conception and design, analysis and interpretation of data, drafting of manuscript, critical revision.

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