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Correlation between Scanning Laser Polarimetry with and without Enhanced Corneal Compensation and High Definition Optical Coherence Tomography in Normal and Glaucomatous Eyes

Javier Benítez-del-Castillo (MD, PhD)[1], Antonio Martinez (MD)[2], Teresa Regi (MD) [1]

1.- Unidad de Glaucoma, Hospital General del S.A.S. de Jerez

2.- Clinical research department, Science research & Sports.

Correspondance: Javier Benítez-del-Castillo

Address: Plaza Monti, 7 Bajo

11403 Jerez (Cadiz)

Spain

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Abstract

Purpose: To assess the relationship between high-definition optical coherence tomography (HD-OCT) and scanning laser polarimetry (SLP) with variable (VCC) and enhance (ECC) corneal compensation in measuring peripapillary retinal nerve fiber layer (RNFL) thickness in healthy eyes and those with early-to-moderate glaucomatous VF loss.

Methods: Healthy volunteers and patients with glaucoma who met the eligibility criteria were enrolled in this prospective, cross-sectional, and observational study. Subjects underwent complete ophthalmologic examination, automated perimetry, SLP-ECC, SLP-VCC, and HD-OCT. SLP parameters were recalculated in 90 degrees segments (quadrants) in the calculation circle to be compared. Pearson correlation coefficients and Lin´s concordance correlation coefficients were calculated. P-values less than 0.05 were considered statistically significant. **Results:** Fifty-five normal volunteers (mean age 59.1 years) and 33 patients with glaucoma (mean age 63.8 years) were enrolled. In the glaucoma group, 18 patients (54.5 %) had MD ≥ -6.0 decibels (early glaucoma) and 15 patients (45.4%) had MD between -6.01 and -12.0 decibels (moderate glaucoma). The best correlation between HD-OCT and SLP was found in the superior quadrant thickness, r=0.74 (0.62 to 0.82) (p< 0.0001) with SLP-VCC and in the average thickness, r= 0.80 (0.71 to 0.86) (p< 0.0001) and the superior quadrant thickness r= 0.80 (0.71 to 0.87) (p< 0.0001) with SLP-ECC. Concordance correlation coefficients obtained for every parameter in our study between HD-OCT and SLP-VCC and between HD-OCT and SLP-ECC were poor. **Conclusions:** Our results suggest that HD-OCT parameters of

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RNFL thickness are significantly higher than SLP-VCC and SLP-ECC parameters, and therefore those thickness values are not interchangeable. HD-OCT and SLP methods are well correlated but concordance is poor. The difference plots show a lack of agreement that changes as a proportion of the mean.

What`s known?

Glaucoma is a progressive optic neuropathy that selectively affects retinal ganglion cells. Among most reliable imaging methods that have been developed to provide real-time, quantitative information of retinal nerve fiber layer thickness are scanning laser polarimetry (SLP) and optical coherence tomography (OCT).

Optical coherence tomography (OCT), is a high-resolution, cross-sectional imaging technique that allows in vivo measurements of the RNFL.

What`s new?

To the best of our knowledge, this is the first study to provide a comparison using the same population of the relationship between these three imaging modalities designed to analyze peripapillary RNFL thickness in glaucoma: the scanning laser polarimetry with VCC and ECC mode, and the high definition optical coherence tomography, which is a spectral-domain OCT.

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Introduction

Glaucoma is a progressive optic neuropathy that selectively affects retinal ganglion cells (RCG). Optic nerve head (ONH) and retinal nerve fiber layer (RNFL) damage often precedes the development of visual field (VF) loss in glaucoma [1-3].

Among the most reliable imaging methods that have been developed to provide real-time, quantitative information of RNFL thickness, are scanning laser polarimetry (SLP) [4] and optical coherence tomography (OCT) [5, 6].

SLP is a non-invasive imaging technique that uses scanning laser technology coupled with an integrated polarization modulator/detector to provide a retardation map of the peripapillary RNFL based on its birefringent properties [4]. The polarization state of light is modulated by retardation in one axis (slow axis) by its passage through the nerve fibers of the retina. This retardation is in proportion to the thickness of the RNFL [7].

The polarimeter has an integrated variable corneal compensator (VCC) that determines and neutralizes the eye-specific corneal polarization axis and magnitude by using the concept of the macula as an intraocular polarimeter [8-12]. It has been reported that in a subset of eyes, SLP-VCC scans with atypical birefringence patterns (ABPs), where the brightest areas of the retardation maps are not consistent with the histologically thickest portions of the peripapillary RNFL along the superior and inferior arcuate bundles [13]**.** An enhanced compensator module (enhanced corneal compensation, ECC) has recently been launched and is currently used to reduce artifacts associated with ABP by removing the noise and enhancing the signal [13-15].

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OCT is another non-invasive optical signal acquisition and processing method based on an interferometric technique, which allows for extreme high-quality and micrometer-resolution on three-dimensional images, as well as providing measurements of the RNFL. Traditional OCT is time domain OCT (TD-OCT). The mechanism of scanning largely limits the acquisition speed and makes real-time imaging impossible. In recent years a new model OCT based on Fourier domain interferometry has emerged. It´s called spectral OCT (SD-OCT). SD-OCT can reach very high acquisition speed and increased depth resolution compared to previous technology [16]. This latest OCT technology currently used, named High Definition OCT (HD-OCT) by Zeiss (Carl-Zeiss Meditec, Inc., Dublin, CA), allows in-vivo quantification of RNFL thickness and the optic disc. The purpose of this study is to assess the concordance between the retinal nerve fiber layer thickness parameters using SLP with both VCC and ECC mode, and HD-OCT in normal subjects, and in patients with early to moderate open-angle glaucoma.

Methods

Subjects and measurement protocol

Healthy volunteers and patients with glaucoma who met the eligibility criteria according to the same study observer (JB-C) were consecutively enrolled in this prospective, cross-sectional, and observational study run at Glaucoma Unit from Hospital General del S.A.S. de Jerez. All participants signed an informed

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written consent form approved by the ethics committee of Hospital General del S.A.S. de Jerez, which was in agreement with the provisions of the Declaration of Helsinki for biomedical research.

All subjects underwent a complete ophthalmic examination, including slit lamp biomicroscopy, dilated stereoscopic examination, gonioscopy, Goldmann applanation tonometry, ultrasound pachymetry, and photography of the optic disc. Two reliable visual field (VF) examinations were obtained with standard automated perimetry (SAP; Humphrey Field Analyzer; Carl-Zeiss Meditec, Inc., Dublin, CA), by using the SITA (Swedish Interactive Threshold Algorithm) standard strategy program 24-2.

All participants were required to meet the following inclusion criteria: refractive error between -7.00 and +3.00 D (spherical equivalent), best corrected visual acuity equal or better than 20/40, age range between 40 and 79 years, reliable SAP (< 33% rate of fixation losses, false positives, and false negatives), and no prior history of intraocular surgery except for uncomplicated cataract extraction. Exclusion criteria were any ocular disease other than glaucoma or cataract, neurological disorders or medications that can cause visual field defects, visual acuity < 20/40, peripapillary atrophy extending to 1.7 mm from the disc's centre, retinal disease, or unreliable SAP.

The control group consisted of healthy individuals who were recruited consecutively among volunteers such as office employees, friends or family members of patients with glaucoma. Normal subjects had no history of ocular disease except cataract, their intraocular pressure (IOP) was less than or equal to 21 mm Hg by Goldmann applanation tonometry, and had a normal optic disc appearance based on both clinical stereoscopic examination and review of

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stereo disc photography. All normal eyes had two SAP examinations with normal findings, defined as glaucoma hemifield test results within normal limits, and mean and pattern standard deviation (SD) of P > 5%. A normal optic disc was defined as having a cup/disc area ratio less than or equal to 0.4, a neuroretinal rim with no glaucomatous changes such as localized rim loss or slimmining of the rim or peripapillary hemorrhages seen ophthalmoscopically. Glaucomatous optic neuropathy was defined as either cup-to-disc asymmetry between fellow eyes of greater than 0.2, rim thinning, notching, excavation, and/or RNFL defect. Patients with glaucoma had glaucomatous optic nerve damage and corresponding abnormal SAP defined as an abnormal glaucoma hemifield test results and pattern SD outside 95% of normal limits. Patients with SAP abnormalities had at least one confirmatory visual field examination.

Early and moderate glaucoma were defined according to the criteria described by Hodapp et al. [17]. Early glaucoma requires the mean deviation (MD) to be less than – 6 dB, with < 18 points depressed below p < 0.05, < 10 points depressed below p < 0.001, and no point in the central 5 º with a sensitivity of< 15 dB. Moderate glaucoma requires a mean deviation between – 6.01 and –12 dB, on the pattern deviation plot, fewer than 50% (37) of the points are depressed below the 5% level and fewer than 20 points are depressed below the 1% level; no points in the central 5º has a sensitivity of 0 dB, and only one hemifield may have a point with sensitivity of < 15 dB within 5º of fixation.

SLP imaging (GDx SLP, software version 5.5.0; Carl Zeiss Meditec, Inc. Dublin, CA) was performed through undilated pupils. Three consecutive scans were obtained with VCC and ECC on the same day by the same examiner. An average of the three measurements was used for the analysis. A primary scan

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was obtained before each measurement, to compensate for the corneal birefringence. Images that were obtained during eye movement were excluded, as well as unfocused, poorly centred images or images with a quality scan score of less than 8. A fixed concentric measurement band centred on the optic disc with a 3.2-mm outer and a 2.4-mm inner diameter was used to generate the peripapillary retardation measurements. SLP parameters used as outcome measures for this investigation included: TSNIT (temporal, superior, nasal, inferior, temporal) average, superior average, inferior average, nasal average, temporal average, and the typical scan score (TSS). The 64 segments in the calculation circle of RNFL thickness values were extracted by means of an electronic data export and recalculated in 90 degrees segments (quadrants) in order to be compared.

HD-OCT imaging (Cirrus OCT, software ver. 3.0; Carl Zeiss Meditec, Inc. Dublin, CA) was performed through undilated pupils using the Optic Disk cube scan 2000x200 pixels protocol on the same day by the same examiner. The average of two measurements was used for the analysis. Images that were obtained during eye movement or were unfocused, were poorly centred, or with signal strength of less than 7 were excluded. OCT parameters in the TSNIT calculation circle (3.46 mm diameter) used as outcome measures for this investigation included average TSNIT RNFL thickness and superior, inferior, temporal and nasal quadrants RNFL thicknesses.

Statistical analysis

Sample size calculation was based on the assumption that a correlation coefficient of 0.4 is statistically significant. Approximately 45 patients were

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required given an α of 0.05 and a 1 – β of 0.8 was chosen to decrease the risk of a false negative result. A minimum recruitment of 50 patients in each group was planned to allow for patient exclusions.

Only one eye per subject was enrolled. If both eyes met eligibility criteria, one eye was selected randomly.

Data were tested for normal distribution using a Kolmogorov-Smirnov test. If data were normally distributed, a two-tailed unpaired Student's t test or Chi-square test were used to compared clinical and demographic characteristics between glaucoma and healthy subjects.

We compared the retinal nerve fiber layer thickness parameters of the HD-OCT with those of the SLP-VCC and SLP-ECC and analyzed the difference. We also compared the difference between SLP-VCC and SLP-ECC.

To analyze the correlation between HD-OCT and SLP, with VCC and ECC mode, Pearson correlation coefficients were calculated for every parameter.

To evaluate agreement between HD-OCT and SLP, with VCC and ECC mode, we calculated Lin's concordance correlation coefficient (CCC) for every parameters [18, 19] then Bland & Altman difference plots were designed and analyzed [20].

Statistical analysis was performed using MedCalc11.1.0 (MedCalc software, Mariakerke, Belgium and Stata 9.0 (StataCorp LP, College Station, TX, USA).

A probability value of $p<0.05$ was considered indicative of statistical significance.

Results

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One hundred and seventeen eyes from 64 normal volunteers and 53 patients with glaucoma were enrolled.

9 subjects were not included in the control group: 4 for quality SLP-VCC scan < 8; 3 for OCT signal strength < 7, and two for unreliable visual field.

Twenty glaucoma patients were not included: 9 for quality SLP-VCC scan < 8; 6 for OCT signal strength < 7, and five for unreliable visual field.

After exclusions, overall study population (88 eyes of 88 patients) included 55 eyes of 55 patients in the control group and 33 eyes of 33 patients in the glaucoma group. The analyses had a statistical power of the 68.7% to detect a correlation coefficient statistically significant between the two groups, at a significance level of 0.05. Table I demonstrates the clinical characteristics of the study population.

In the glaucoma group, 18 patients (54.5%) had MD ≥ -6.0 decibels (early glaucoma) and 15 patients (45.4%) had MD between -6.01 and -12.0 decibels (moderate glaucoma).

Table 2 shows important and statistically significant differences (all with $p<0.002$) that were found between the HD-OCT and the SLP-VCC and ECC parameters, in total average and in each quadrant RNFL thickness. These differences were found in the overall population of the study and also in the normal and the glaucoma group.

Additionally, statistically significant differences were found between SLP-VCC and ECC in the overall population of the study and in both the normal and the glaucoma group, in: average thickness ($p=0.0034$ in overall population, $p=0.0200$ in control group and $p=0.0275$ in glaucoma group), temporal quadrant thickness ($p<0.0001$ in overall population, in control and in glaucoma group),

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and nasal quadrant thickness (p=0.0003 in overall population, p=0.0022 in control group and p=0.0224 in glaucoma group). There were no statistically significant differences between SLP-VCC and ECC in superior quadrant thickness (p=0.9385 in overall population, p=0.5960 in control group and p=0.8289 in glaucoma group) nor in inferior quadrant thickness (p=0.1716 in overall population, p=0.1483 in control group and p=0.2521 in glaucoma group) (Table 2).

Our study showed significant correlations (r) between HD-OCT and SLP-VCC or ECC, for most RNFL parameters (Table 3) except for the temporal RNFL quadrant between HD-OCT and SLP-VCC, in the overall study population (r=0.08, 95% CI= -0.13 to 0.29, p= 0.4479), in the control group (r=0.20, 95% CI= -0.06 to 0.44, p= 0.1367) and in the glaucoma group (r=0.35, 95% CI= -0.01 to 0.63, p= 0.0579), and except for the nasal RNFL quadrant between HD-OCT and SLP-ECC in the glaucoma group (r=0.26, 95% CI= -0.10 to 0.57, p= 0.1536). Correlation coefficients between HD-OCT and SLP-VCC in the overall study population ranged from r= 0.08 (95% CI= -0.13 to 0.29, p= 0.4479) for temporal quadrant RNFL thickness, to r=0.74 (95% CI= 0.62 to 0.82, p< 0.0001) for superior quadrant RNFL thickness. Correlation coefficients between HD-OCT and SLP-VCC in the control group ranged from r= 0.20 (95% CI= -0.06 to 0.44, p= 0.1367) for temporal quadrant RNFL thickness, to r=0.62 (95% CI= 0.42 to 0.76, p< 0.0001) for superior quadrant RNFL thickness. Correlation coefficients between HD-OCT and SLP-VCC in the glaucoma group ranged from r= 0.35 (95% CI= -0.01 to 0.63, p= 0.0579) for temporal quadrant RNFL thickness, to r=0.70 (95% CI= 0.45 to 0.85, p< 0.0001) for superior quadrant RNFL thickness. Correlation coefficients between HD-OCT and SLP-ECC in the

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overall study population ranged from r= 0.40 (95% CI= 0.21 to 0.58, p= 0.0001) for nasal quadrant RNFL thickness, to r=0.80 (95% CI= 0.71 to 0.87, p< 0.0001) for superior quadrant RNFL thickness. Correlation coefficients between HD-OCT and SLP-ECC in the control group ranged from r= 0.30 (95% CI= 0.03 to 0.53, p= 0.0301) for nasal quadrant RNFL thickness, to r=0.67 (95% CI= 0.49 to 0.80, p< 0.0001) for superior quadrant RNFL thickness. Correlation coefficients between HD-OCT and SLP-ECC in the glaucoma group ranged from r= 0.26 (95% CI= -0.10 to 0.57, p= 0.1536) for nasal quadrant RNFL thickness, to r=0.77 (95% CI= 0.56 to 0.88, p< 0.0001) for average RNFL thickness. Comparison of correlation coefficients between HD-OCT and SLP-VCC versus HD-OCT and SLP-ECC shows only statistically significant differences in average RNFL thickness (Diff Z statistics= -3.22, p=0.0013) and in temporal quadrant RNFL thickness (Diff Z statistics= -2.31, p= 0.0205) within the overall population of the study.

Table 4 shows Concordance Correlation Coefficient (CCC, r_c) for retinal nerve fiber layer thickness parameters between HD-OCT and SLP in the overall population, control and glaucoma group. Concordance correlation coefficients between HD-OCT and SLP-VCC in the overall study population ranged from r_c= 0.03 (95% CI= -0.04 to 0.11) for temporal quadrant RNFL thickness, to r_c= 0.22 (95% CI= 0.15 to 0.28) for inferior quadrant RNFL thickness. Concordance correlation coefficients between HD-OCT and SLP-VCC in the control group ranged from r_c= 0.03 (95% CI= -0.01 to 0.07) for temporal quadrant RNFL thickness, to r_c= 0.08 (95% CI= 0.04 to 0.12) for superior quadrant RNFL thickness. Concordance correlation coefficients between HD-OCT and SLP-VCC in the glaucoma group ranged from r_c= 0.23 (95% CI= 0.06 to 0.38) for

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average RNFL thickness, to r_c= 0.32 (95% CI= 0.14 to 0.48) for inferior quadrant RNFL thicknes. Concordance correlation coefficients between HD-OCT and SLP-ECC in the overall study population ranged from r_c= 0.03 (95% CI= 0.01 to 0.05) for temporal quadrant RNFL thickness, to r_c= 0.22 (95% CI= 0.15 to 0.29) for inferior quadrant RNFL thickness. Concordance correlation coefficients between HD-OCT and SLP-ECC in the control group ranged from r_c= 0.02 (95% CI= 0.00 to 0.04) for temporal quadrant RNFL thickness, to r_c= 0.08 (95% CI= 0.04 to 0.12) for superior quadrant RNFL thickness. Concordance correlation coefficients between HD-OCT and SLP-ECC in the glaucoma group ranged from r_c= 0.04 (95% CI= -0.01 to 0.09) for nasal quadrant RNFL thickness, to r_c= 0.36 (95% CI= 0.18 to 0.53) for inferior quadrant RNFL thickness.

Agreement between HD-OCT versus SLP-VCC and HD-OCT versus SLP-ECC, were also evaluated with Bland and Altman plots. We obtained similar results for every parameter in the study. Figure 1 shows the difference plots for average thickness HD-OCT and SLP-VCC (regression equation: $y = 25{,}0974 + -0{,}8502\ x$; coefficient of determination R^2 : 0.4557; p< 0.0001) and for average thickness HD-OCT and SLP-ECC (regression equation: $y = 21{,}2377 + -0{,}8769\ x$; coefficient of determination R^2 : 0.7226; p< 0.0001), respectively. As it is shown in the graphics, agreement level between methods is low because of a proportional error that increases as the mean values of average thickness increase.

Discussion

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To the best of our knowledge, this is the first study to provide a comparison within the same population of these three imaging modalities designed to analyze peripapillary RNFL thickness in glaucoma: the scanning laser polarimetry (SLP) with both VCC and ECC mode, and the high definition optical coherence tomography (HD-OCT), which is a spectral-domain OCT.

We have found important and statistically significant differences (all with $p<0.002$) in every thickness parameters between HD-OCT and SLP-VCC and between HD-OCT and SLP-ECC, in the overall study population and in the control and glaucoma group. HD-OCT parameters show higher values than SLP parameters. This, even though the standard set in the calculation circle for conventional SLP measurements is smaller than the OCT circle, and the RNFL thickness becomes thinner along the distance from the optic disc [21], and that SLP parameters in our study were converted into quadrants in order to be compared. Similar differences between OCT and SLP were found by others, Leung et al [22], Kanamori et al [23] and Chung & Sohn [24] but comparing time-domain OCT and SLP-VCC, by Sehi et al [25] comparing also time-domain OCT with SLP-VCC and ECC, and finally by Horn et al [26] comparing spectral-domain OCT but only with SLP-VCC. Most simple explanation for this finding could be that although both instruments express RNFL thickness in micrometers, they are using different scales as some author pointed out [27]. But, it should also be noted that targets of measurements by SLP and OCT are different [23]. OCT analyzes a retinal section from the inner retinal membrane to the posterior NFL boundary, which is automatically calculated. Hence, RNFL thickness measured by OCT presumably includes not only ganglion cell axons, but also Müller cell processes and astrocytes. In contrast, SLP measures the

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RNFL thickness based on analysis of retardations developed by only retinal nerve fibers.

The measured retardation maps in SLP are converted into RNFL thickness maps by using a constant birefringence value (conversion factor 0.67 nm/mm), and under the assumptions that (i) the RNFL is the only birefringent structure in the area, and (ii) the light is backscattered by a polarization-preserving layer. But previous works already have indicated that the RNFL birefringence is not constant across the whole nerve head region [28-29] and more importantly, the RNFL birefringence observed in the healthy eye differed from that of the glaucomatous eye [30]. The conversion factor of the RNFL retardation, as measured by SLP, to RNFL thickness by a constant factor throughout the retina could be too simple and even provides inaccurate thickness readings. The conversion would have to be done by locally varying birefringence values that are, however, not accessible by SLP. Therefore, it is suggested by some authors that SLP results should be displayed as retardation values (instead of thickness) since this is the quantity actually measured [30]. Theses are in fact the new measuring units incorporated for GDxPRO, new model of SLP by Zeiss (Carl-Zeiss Meditec, Inc., Dublin, CA): Polarimetric-microns (P-microns) of RNFL “Integrity” to be distinguished from “thickness” microns of the OCT.

Differences between SLP-VCC and SLP-ECC were statistically significant in the overall population of the study and in both the normal and the glaucoma group, in several parameters: average thickness ($p=0.0034$ in overall population, $p=0.0200$ in control group and $p=0.0275$ in glaucoma group), temporal quadrant thickness ($p<0.0001$ in overall population, in control and in glaucoma group), and nasal quadrant thickness ($p=0.0003$ in overall population, $p=0.0022$ in

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control group and p=0.0224 in glaucoma group). These differences were not found in the superior and inferior quadrants, in concordance with Reus et al. [31]. ECC method improves the signal-to-noise ratio of RNFL retardation measurements with SLP by shifting the measurements to a more sensitive detection range of the instrument. The shift is made possible by introducing a preset measurement bias that is mathematically removed from the measurements afterward. ECC method improves SLP images by showing the expected RNFL appearance better than in those obtained with VCC. In addition, the typical scan score, which quantifies inversely the amount of atypia, is higher with ECC than with VCC [31- 32], as we have confirmed in our study (Table 1). Diagnostic accuracy in glaucoma is also better with ECC than with VCC [25, 33]. We mentioned before how previous works have indicated that RNFL birefringence is not constant across the whole nervehead region being highest in the superior and inferior quadrants and lowest in the temporal and nasal quadrants [29]. We also mentioned that RNFL birefringence measurements were most reliable in those thicker areas of RNFL [28]. We should expect from ECC mode an eventual improvement in SLP images representing the expected RNFL morphology, especially in the temporal and nasal quadrants, so that differences between SLP-VCC and ECC mode in temporal and nasal quadrants and in average RNFL thickness are explained.

Important and statistically significant differences found in thickness parameters between OCT and SLP reveal that those values are not interchangeable. It´s worth mentioning that those differences of SLP and OCT, providing RNFL thickness measures, does not invalidate their usefulness as glaucoma-detection tools. For glaucoma-detection purposes, results in individual patients are

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compared with a normative data base that was acquired under similar assumptions, therefore conclusions concerning the diagnosis and/or the stage of glaucoma are still valid.

Results of this study suggest that the high-definition OCT retinal nerve fibre layer thickness parameters were significantly correlated with those of the SLP-VCC and SLP-ECC, except in the temporal RNFL quadrant between HD-OCT and SLP-VCC and except in the nasal RNFL quadrant between HD-OCT and SLP-ECC in the glaucoma group.

The real point is that the significant correlations found between OCT and SLP are not really unexpected findings because with all 3 technologies we try to measure the same biological feature. Similar correlations between OCT and SLP were found by others, Leung et al [22] and Chung & Sohn [24] but comparing time-domain OCT and SLP-VCC, and by Sehi et al [25] comparing also time-domain OCT with SLP-VCC and ECC.

In agreement with Leung et al [22] and Sehi et al [25], we found lower correlation in temporal RNFL quadrant with SLP-VCC and in nasal RNFL quadrant with SLP-ECC. It would be possible that the regional variability in the RNFL measurements and the variation of the optic nerve head birefringence around the optic nerve head are responsible for the observation. Being the thinnest portions in the RNFL profile, the nasal and temporal sectors have been reported to have higher variability in the OCT [34] and in SLP RNFL measurements [28-29]. Curiously, the average values in the temporal RNFL quadrant in images obtained with VCC, were significantly higher in glaucomatous eyes (40.36 microns) than in healthy eyes (29.70 microns) (p= 0.0016). In images obtained with ECC, this difference was not statistically

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significant (glaucomatous eyes and healthy eyes: 21.54 microns and 20.74 microns, respectively) (p= 0.4802). Similar results were obtained by Reus et al [31]. They found that the amount of retardation in the temporal region, in healthy and ocular hypertensive eyes, measured with VCC, significantly correlated with the amount of residual anterior segment birefringence, and in the nasal region, this correlation was of borderline significance. With ECC, no relationship was apparent between measured peripapillary retardation and residual anterior segment birefringence. These data suggested to the authors [31] that some of the differences between VCC and ECC were due most likely due to measurement artifacts affecting nasal and especially temporal sectors in the RNFL peripapillary area. This would explain the low and not statistically significant correlation coefficient between SLP-VCC and OCT in the temporal RNFL quadrant that we found in our study. Improving residual anterior compensation with ECC mode reduces retardation magnitude and also induces changes in polarization axis. We speculate that rotation in retardation axis could be related with our finding of a low and not significant correlation between OCT and SLP-ECC in the nasal RNFL quadrant of the glaucoma group. Anyway, we should say that in our study, compared with SLP-VCC, SLP-ECC has stronger correlations with HD-OCT, especially when measuring the whole calculation circle in RNFL average thickness (p= 0.0013), and in superior and inferior RNFL quadrants. Others have shown this but with td-OCT [25].

Correlation and agreement are not always the same thing. Therefore, a high correlation does not automatically imply that there is good agreement between the two methods. Correlation essentially assesses the linear relationship between the two sets of measurements. It is directly related with the precision of

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the data measuring the tightness of the data about its reduced major axis. Precision is inversely related to random analytical errors. Agreement (concordance) assesses about reliability and consistency between the two sets of measurements. Agreement is inversely related to systematic analytical errors, constant or proportional errors. So the Pearson correlation coefficient (r) is not a good agreement measure. In fact, the 'r' implies that data from two variables (x, y) with perfect correlation (r=1) lie on a straight line which, however, may not pass through the origin or may not have a slope equal to unity, which would provide information about a low agreement between the data.

Lin's [18-19] concordance correlation coefficient (CCC or "r_c") computes agreement on a continuous measure obtained by two methods. The CCC combines measures of both precision and accuracy to determine how far the observed data deviate from the line of perfect concordance (that is, the line at 45 degrees on a square scatter plot). Lin's coefficient increases in value as a function of the nearness of the data's reduced major axis to the line of perfect concordance (the accuracy of the data) and of the tightness of the data about its reduced major axis (the precision of the data). CCC values obtained for every parameter in our study between HD-OCT and SLP-VCC and between HD-OCT and SLP-ECC were poor.

Agreement between methods, HD- OCT versus SLP (VCC or ECC mode) were also evaluated with Bland & Altman plots. The Lin and Bland & Altman approaches are complementary, indicating agreement (or lack of) on two different scales. Analyzing Bland & Altman plots we obtained similar trend results for every parameter in our study [20, 35].

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Difference plots as we see in Fig 1 show that agreement level between methods is low because of a proportional error that increases as the mean values of average thickness increase. We already mentioned the reasons that could explain different values between methods and in this context, we theorize that this proportional error could also be explained taking into account that SLP will measure only axons (and neural microstructures) while OCT will measure axons and glia, support tissue, that could be lost in a parallel manner with the ganglion cells axons in the disease process of glaucoma [21].

Our study has several limitations that should be taken into account. This study was conducted in a Caucasian population with early to moderate stage POAG. Appropriate caution is therefore recommended when extending the results to other populations.

Another limitation might be the high rate of patient exclusions, mainly due to the inadequate quality imaging and unreliability of visual field exams. Finally, the small number of cases with glaucoma that did not allow for the possibility of doing subanalysis in our study population.

In conclusion, our results suggest that HD-OCT parameters of RNFL thickness are significantly higher than SLP-VCC and SLP-ECC parameters, therefore those thickness values are not interchangeable. HD-OCT and SLP methods are well correlated but concordance is poor. The difference plots show a lack of agreement that changes as a proportion of the mean.

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Table 1. Clinical characteristics of the study population.

	Overall study population (n=88)		
	Control group (n= 55)	**Glaucoma group (n= 33)**	**P value**
Age (mean ± SD, years)	59.1 ± 7.5	63.8 ± 13.3	0.0364
Gender:			
Male	22	23	
Female	33	10	0.0132
TSS with SLP-VCC (mean ± SD)	87.50 ± 15.97	78.93 ± 28.2	0.0719
TSS with SLP-ECC (mean ± SD)	98.83 ± 2.36	96.78 ± 7.9	0.0773
SAP MD (mean) (95% CI) (dB)	-1.02 (-1.45 to -0.58)	-6.69 (-8.07 to -5.31)	< 0.0001
SAP PSD (mean) (95% CI) (dB)	2.03 (1.72 to 2.34)	6.22 (4.80 to 7.65)	< 0.001

Abbreviations: HD-OCT= High Definition Optical Coherence Tomography; TSS= Typical Scan Score; SLP-VCC= Scanning Laser Polarimetry with VCC mode; SLP-ECC= Scanning Laser Polarimetry with ECC mode; SAP= Standard Achromatic Perimetry; MD= Mean Deviation (decibels); PSD= Pattern Standard Deviation (decibels)

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Table 2. Retinal nerve fiber layer thickness parameters using high-definition optical coherence tomography and scanning laser polarimetry with variable and enhance corneal compensation in the study overall population, control and glaucoma group.

Overall population	***HD-OCT (95% CI)***	***SLP-VCC (95% CI)***	***P value****	***SLP-ECC (95% CI)***	***P value*****	***P value******
Avg Thick +	82.4 (78.8 to 86.1)	50.4 (48.5 to 52.2)	<0.0001	46.7 (45.1 to 48.3)	<0.0001	0.0034
SupQ Thick	99.4 (94.1 to 104.7)	59.9 (57.1 to 62.6)	<0.0001	60.0 (57.3 to 62.7)	<0.0001	0.9385
InfQ Thick	101.3 (94.8 to 107.8)	62.5 (59.6 to 65.3)	<0.0001	65.2 (62.5 to 67.9)	<0.0001	0.1716
TemQ Thick	61.2 (58.1 to 64.3)	33.5 (30.2 to 36.8)	<0.0001	21.4 (19.1 to 22.1)	<0.0001	<0.0001
NasQ Thick	67.7 (64.9 to 70.4)	42.6 (40.3 to 44.8)	<0.0001	37.5 (35.9to 39.0)	<0.0001	0.0003
Control group	***HD-OCT (95% CI)***	***SLP-VCC (95% CI)***	***P value****	***SLP-ECC (95% CI)***	***P value*****	***P value******
Avg Thick +	91.1 (87.6 to 94.5)	52.5 (51.0 to 54.0)	<0.0001	50.1 (48.7 to 51.5)	<0.0001	0.0200
SupQ Thick	111.7 (106.6 to 116.7)	64.5 (61.8 to 67.2)	<0.0001	65.5 (62.9 to 68.0)	<0.0001	0.5960
InfQ Thick	116.3 (109.9 to 122.7)	68.3 (65.7 to 70.9)	<0.0001	70.9 (68.5 to 73.3)	<0.0001	0.1483
TemQ Thick	65.1 (61.4 to 68.8)	29.7 (27.2 to 32.1)	<0.0001	20.7 (19.4 to 22.0)	<0.0001	<0.0001
NasQ Thick	71.0 (67.8 to 74.3)	44.5 (42.4 to 46.7)	<0.0001	40.3 (38.7 to 41.9)	<0.0001	0.0022
Glaucoma group	***HD-OCT (95% CI)***	***SLP-VCC (95% CI)***	***P value****	***SLP-ECC (95% CI)***	***P value*****	***P value******
Avg Thick +	67.3 (62.9 to 71.8)	46.5 (42.2 to 50.8)	<0.0001	41.1 (38.5 to 43.6)	<0.0001	0.0275
SupQ Thick	78.0 (71.5 to 84.5)	51.6 (46.9 to 56.4)	<0.0001	51.0 (46.6 to 55.3)	<0.0001	0.8289
InfQ Thick	75.1 (67.2 to 83.1)	52.1 (47.5 to 56.6)	<0.0001	55.7 (51.2 to 60.3)	0.0001	0.2521
TemQ Thick	54.3 (49.4 to 59.1)	40.3 (32.5 to 48.1)	0.0029	21.5 (19.5 to 23.4)	<0.0001	<0.0001
NasQ Thick	61.8 (57.5 to 66.1)	39.1 (34.1 to 44.1)	<0.0001	32.8 (30.3 to 35.2)	<0.0001	0.0224

Abbreviations: 95% CI= 95% confidence interval; HD-OCT= high definition optical coherence tomography; SLP-VCC= scanning laser polarimetry with VCC mode; SLP-ECC= scanning laser polarimetry with ECC mode; Avg Thick= average thickness; SupQ Thick= superior quadrant average thickness; InfQ Thick= inferior quadrant average thickness; TempQ Thick= inferior quadrant average thickness; NasQ Thick= nasal quadrant average thickness.

+ TSNIT average thickness in SLP

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* Differences between HD-OCT and SLP-VCC
** Differences between HD-OCT and SLP-ECC
*** Differences between SLP-VCC and SLP-ECC

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Table 3. Pearson correlation coefficients (95% confidence interval)* for retinal nerve fiber layer thickness parameters of High-definition optical coherence tomography (HD-OCT) and Scanning laser polarimetry (SLP) in the overall population, control and glaucoma group.

	Overall study population (n=88)					
HD-OCT Parameter	**SLP-VCC parameter (95% CI)**	**P value***	**SLP-ECC parameter (95% CI)**	**P value***	**Difference** Z statistics**	**P value****
Avg. Thick.	0.54 (0.37 to 0.68)	<0.0001	0.80 (0.71 to 0.86)	<0.0001	-3.22	0.0013
SupQ.	0.74 (0.62 to 0.82)	<0.0001	0.80 (0.71 to 0.87)	<0.0001	-0.96	0.3342
InfQ.	0.72 (0.60 to 0.81)	<0.0001	0.72 (0.60 to 0.81)	<0.0001	-0.03	0.9758
TempQ.	0.08 (-0.13 to 0.29)	0.4479	0.41 (0.22 to 0.58)	0.0001	-2.31	0.0205
NasQ.	0.50 (0.32 to 0.65)	<0.0001	0.40 (0.21 to 0.57)	0.0001	0.81	0.4127
	Control group (n=55)					
HD-OCT Parameter	**SLP-VCC parameter (95% CI)**	**P value***	**SLP-ECC parameter (95% CI)**	**P value***	**Difference** Z statistics**	**P value****
Avg. Thick.	0.48 (0.25 to 0.66)	0.0002	0.62 (0.42 to 0.76)	<0.0001	-1.03	0.3030
SupQ.	0.62 (0.42 to 0.76)	<0.0001	0.67 (0.49 to 0.80)	<0.0001	-0.43	0.6620
InfQ.	0.50 (0.27 to 0.68)	0.0001	0.51 (0.27 to 0.68)	0.0001	-0.06	0.9454
TempQ.	0.20 (-0.06 to 0.44)	0.1367	0.46 (0.22 to 0.65)	0.0005	-1.50	0.1331
NasQ.	0.37 (0.12 to 0.58)	0.0050	0.30 (0.03 to 0.53)	0.0301	0.40	0.6874
	Glaucoma group (n=33)					
HD-OCT Parameter	**SLP-VCC parameter (95% CI)**	**P value***	**SLP-ECC parameter (95% CI)**	**P value***	**Difference** Z statistics**	**P value****
Avg. Thick.	0.54 (0.22 to 0.76)	0.0021	0.77 (0.56 to 0.88)	<0.0001	-1.61	0.1070
SupQ.	0.70 (0.45 to 0.85)	<0.0001	0.75 (0.54 to 0.87)	<0.0001	-0.40	0.6824
InfQ.	0.64 (0.37 to 0.82)	0.0001	0.68 (0.42 to 0.83)	<0.0001	-0.27	0.7835
TempQ.	0.35 (-0.01 to 0.63)	0.0579	0.53 (0.21 to 0.75)	0.0024	-0.87	0.3842
NasQ.	0.61 (0.31 to 0.79)	0.0004	0.26 (-0.10 to 0.57)	0.1536	1.71	0.0863

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Abbreviations: 95% CI= 95% confidence interval; HD-OCT= high definition optical coherence tomography; SLP-VCC= scanning laser polarimetry with VCC mode; SLP-ECC= scanning laser polarimetry with ECC mode; Avg Thick= average thickness; SupQ= superior quadrant average thickness; InfQ= inferior quadrant average thickness; TempQ= inferior quadrant average thickness; NasQ= nasal quadrant average thickness.

* Correlation coefficients (95% confidence interval) were established between:
Avg Thick and TSNIT average thickness
HD-OCT SupQ and SLP SupQ
HD-OCT InfQ and SLP InfQ
HD-OCT TempQ and SLP TempQ
HD-OCT NasQ and SLP NasQ

** Difference and comparison between Pearson correlation coefficients HD-OCT--SLP-VCC and HD-OCT--SLP-ECC.

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Table 4. Concordance Correlation Coefficient (95% confidence interval)* for retinal nerve fiber layer thickness parameters between High-definition optical coherence tomography (HD-OCT) and Scanning laser polarimetry (SLP) in the overall population, control and glaucoma group.

Overall study population (n=88)		
HD-OCT parameter	**SLP-VCC parameter (95% CI)**	**SLP-ECC parameter (95% CI)**
Avg. Thick.	0.11 (0.06 to 0.16)	0.12 (0.08 to 0.15)
SupQ.	0.19 (0.13 to 0.25)	0.21 (0.14 to 0.27)
InfQ.	0.22 (0.15 to 0.28)	0.22 (0.15 to 0.29)
TempQ.	0.03 (-0.04 to 0.11)	0.03 (0.01 to 0.05)
NasQ.	0.15 (0.08 to 0.21)	0.06 (0.02 to 0.10)
Control group (n=55)		
HD-OCT parameter	**SLP-VCC parameter (95% CI)**	**SLP-ECC parameter (95% CI)**
Avg. Thick.	0.03 (0.01 to 0.06)	0.04 (0.02 to 0.06)
SupQ.	0.08 (0.04 to 0.12)	0.08 (0.04 to 0.12)
InfQ.	0.07 (0.03 to 0.12)	0.07 (0.03 to 0.11)
TempQ.	0.03 (-0.01 to 0.07)	0.02 (0.00 to 0.04)
NasQ.	0.07 (0.01 to 0.13)	0.03 (0.00 to 0.06)
Glaucoma group (n=33)		
HD-OCT parameter	**SLP-VCC parameter (95% CI)**	**SLP-ECC parameter (95% CI)**
Avg. Thick.	0.23 (0.06 to 0.38)	0.14 (0.06 to 0.22)
SupQ.	0.28 (0.12 to 0.42)	0.27 (0.13 to 0.39)
InfQ.	0.32 (0.14 to 0.48)	0.36 (0.18 to 0.53)
TempQ.	0.25 (-0.00 to 0.48)	0.05 (0.01 to 0.10)
NasQ.	0.24 (0.08 to 0.38)	0.04 (-0.01 to 0.09)

Abbreviations: 95% CI= 95% confidence interval; HD-OCT= high definition optical coherence tomography; SLP-VCC= scanning laser polarimetry with VCC mode; SLP-ECC= scanning laser polarimetry with ECC mode; Avg Thick= average thickness; SupQ=

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superior quadrant average thickness; InfQ= inferior quadrant average thickness; TempQ= inferior quadrant average thickness; NasQ= nasal quadrant average thickness.

* Concordance Correlation Coefficients (95% confidence interval) were established between:
Avg Thick and TSNIT average thickness
HD-OCT SupQ and SLP SupQ
HD-OCT InfQ and SLP InfQ
HD-OCT TempQ and SLP TempQ
HD-OCT NasQ and SLP NasQ

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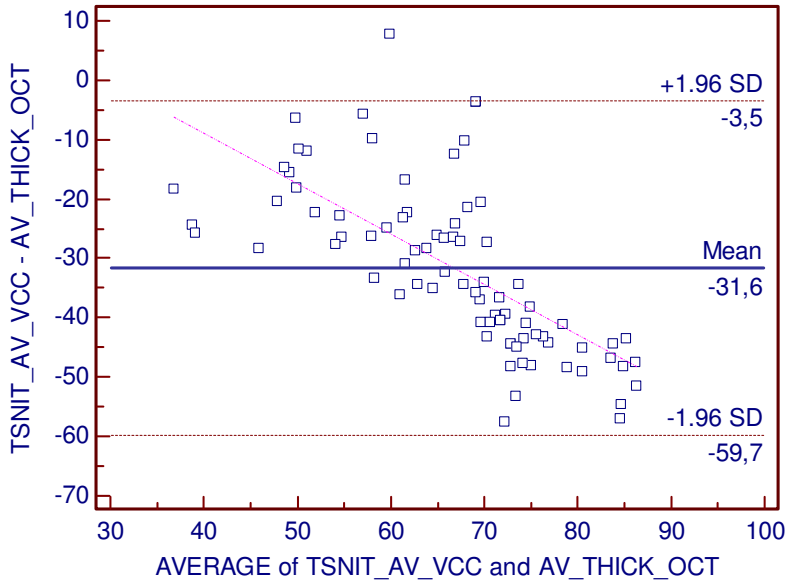
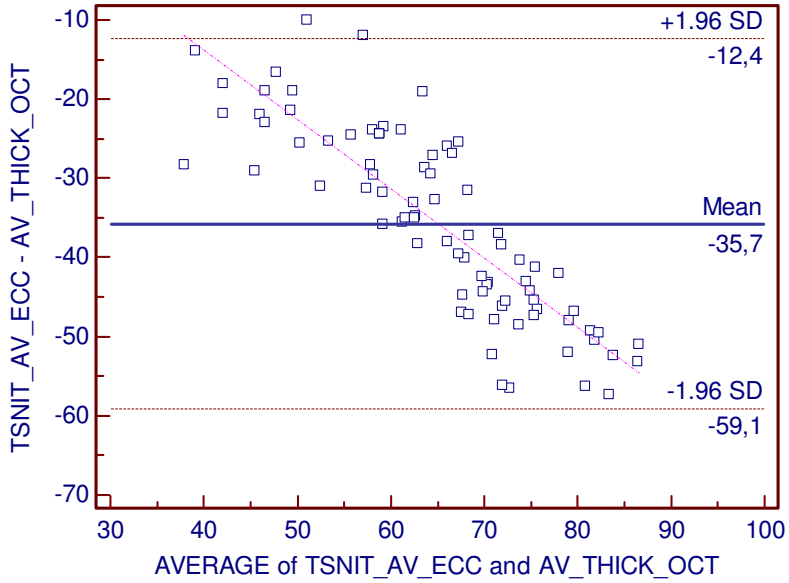
Figure 1. a) Difference plot for Average Thickness HD-OCT and Average Thickness SLP-VCC in the overall population in the study with regression line of differences versus averages. B) Difference plot for Average Thickness HD-OCT and Average Thickness SLP-ECC in the overall population in the study with regression line of differences versus averages.

a)



b)



Abbreviations: HD-OCT= high definition optical coherence tomography; SLP-VCC= scanning laser polarimetry with VCC mode; AV_THICK_OCT= average thickness in HD-OCT; TSNIT_AV_ VCC= average thickness in SLP-VCC.SLP-ECC= scanning laser polarimetry with ECC mode; AV_THICK_OCT= average thickness in HD-OCT; TSNIT_AV_ ECC= average thickness in SLP-ECC.