Agreement between Spectral-Domain Optical Coherence Tomography, Standard Automated Perimetry and Stereophotography in the detection of glaucomatous progression.

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Brief Title: Agreement between Optical Coherence Tomography, Standard Automated Perimetry and Stereophotography in the detection of glaucomatous progression.

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PURPOSE. To evaluate the agreement between spectral domain optical coherence tomography, standard automated perimetry and optic disc stereophotos in the detection of glaucomatous progression.

METHODS. Observational cohort study enrolling 246 eyes (148 patients) followed-up for an average of 31.8 ± 9 months. Images were obtained every 6-12 months with optical coherence tomography, visual field and optic disc stereophotos. Progression was determined in OCT with the Glaucoma Progression Analysis software (GPA), in perimetry with the Humphrey Field Analyzer GPA and by masked assessment of stereophotographs series. Agreement among methods was reported using the Kappa coefficient (K), PABAK (prevalence-adjusted bias-adjusted kappa), Gwet's AC1, overall percentage agreement (OPA), percentage of positive agreement (Ppos) and percentage of negative agreement (Pneg).

RESULTS. Progression via stereophotos, SAP and OCT was found in 17 (6.9%), 37 (15%) and in 63 eyes (25.6%) respectively. Most cases with detectable changes were only identified by one examination method resulting in low Ppos (<33%). On the contrary, 147 eyes (59.7%) were identified as non-progressing cases by all 3 methods, showing high OPA (72.8 to 89.8) and high Pneg (83.8 to 94.5). PABAK and AC1 between methods reach 0.67-0.88. Measures of agreement showed a trend toward better agreement between photos and VF than by photos-OCT. SD-OCT parameters reflected a tendency toward better agreement with stereophotos than with VF.

CONCLUSION. Methods obtained acceptable agreements outcomes in terms of PABAK, AC1 and OPA. However, most cases with detectable changes were identified by only one examination method resulting in low percentage of positive agreement (Ppos).

Key words: *glaucoma, progression, Optical Coherence Tomography, agreement*

INTRODUCTION

Early detection and control of disease progression or worsening is one of the most important and difficult challenges in glaucoma management. Conventional methods used to identify progression, such as stereophotography or standard automated perimetry (SAP), differ in their abilities to identify changes and show poor agreement ⁽¹⁻⁶⁾. One of the limitations of functional tests like SAP when performing the task of progression detection is high test-retest variability ⁽⁷⁻⁸⁾. Imaging devices are less dependent on patient performance, and in particular the latest SD-OCT (spectral domain optical coherence tomography) versions offer highly reproducible measurements ⁽⁹⁾. Many studies found excellent intra-visit and inter-visit reproducibility of peripapillary RNFL (retinal nerve fiber layer) measurements based on the interclass correlation coefficient, coefficient of variation and test-retest Standard Deviation in normal subjects and glaucoma patients ⁽¹⁰⁻¹¹⁾. This high reproducibility offers a good theoretical basis to enable the detection of structural changes over time. Progression algorithms have recently been applied to imaging technologies such as scanning laser polarimetry (GDx), confocal scanning laser ophthalmoscopy (HRT or Heidelberg Retinal Tomograph) and OCT. These algorithms could be useful tools to identify progression ⁽¹²⁻²⁰⁾ not requiring active patient participation. However, they require thorough clinical evaluation to determine their capabilities and limitations.

The purpose of this study is to evaluate agreement between SD-OCT GPA (Guided Progression Analysis) with Humphrey Field Analyzer GPA software and with expert assessment of optic disc stereophotos for detection of glaucomatous progression. Will OCT and series of stereo-photographs, both structural diagnostic tests, show a trend toward better agreement than with a functional test as SAP? Do OCT event parameters have better agreement in identifying progression with VF event analysis than with VF trend algorithm? How do OCT event and trend parameter's rates of progression detection differ? In this study, we sought to answer these queries. To the best of our knowledge, this is the first longitudinal study to report a thorough

appraisal of all Cirrus SD-OCT GPA parameters agreement with well-established modalities such as stereophotos and SAP.

MATERIALS AND METHODS

This is an observational cohort study. Two hundred and forty six eyes of 148 patients were participants on a larger prospective study conceived to assess diagnostic performance of different structural and functional modalities in glaucoma and were chosen on the basis of minimum number of exams with VF, SD-OCT and stereophotos (see below).

Patients with glaucoma, glaucoma suspects and healthy patients were consecutively enrolled as they presented at our clinic, Institut Català de la Retina at Barcelona, Spain, and were evaluated by pre-established protocol series of structural and functional diagnostic procedures.

Medical history and full ophthalmic examination were performed at baseline and during follow-up visits. They were electronically recorded on a predesigned glaucoma visit form. Ocular examinations included visual acuity (Early Treatment Diabetic Retinopathy Study chart), manifest refraction, Goldmann applanation tonometry, slit-lamp biomicroscopy, gonioscopy and dilated fundus evaluation using a 78D hand-held lens. VFs with 24-2 SITA standard strategy (Carl Zeiss Meditec, Jena, Germany) were performed every 6 months and optic disc stereophotos with TRC-NW7SF fundus camera (Topcon, Tokyo, Japan) were acquired every year. Images of the optic disc and peripapillary region were obtained annually with Cirrus SD-OCT (Carl Zeiss Meditec, Jena, Germany) using the Optic Disc Cube 200x200 protocol.

In the present study, the inclusion criteria were as follows: subjects 18 years of age or over, best-corrected visual acuity 20/30 or better, spherical refractive error +5 to -5 diopters, less than 3 diopters of cylinder and open angle; defined as ≥ 3 in the Shaffer classification. Subjects were excluded if they had a history of surgical or laser retina procedures, or any ocular or systemic

disease that could cause optic disc or retina abnormalities or visual field loss. Patients with severely depressed VFs in which HFA GPA couldn't perform both Event and Trend analysis were excluded. There were no exclusion criteria regarding type of glaucoma. Patients with mild cataract could be included.

Examinations

After subsequent visits, the sample was divided into four groups: (1) glaucoma, (2) glaucoma suspect, (3) ocular hypertension and (4) normal, based on two subsequent fields, optic disc appearance and ocular pressure. Glaucoma was considered if they presented consistent glaucomatous visual field defects congruent with optic nerve damage on more than two occasions. Glaucomatous visual field defect was defined as having three or more significant non-edge contiguous points outside the 95% normal limits in the pattern deviation plot ($p < 5\%$), with at least one at the $p < 1\%$ level in at least two consecutive examinations, or a glaucoma hemifield test result (GHT) outside normal limits. Optic nerve damage was defined by the presence of a localized notch, or rim thinning, or cup disc ratio > 0.8 , or a difference in this ratio between the two eyes > 0.2 , or disc hemorrhage, or retinal nerve fiber layer defects. Eyes classified as glaucoma suspects had normal visual fields but glaucomatous optic disc appearance. Patients with ocular hypertension (OHT) had high IOP (> 21 mmHg), normal fields and normal discs in 3 different consecutive examinations. Normal subjects had no history of high IOP (> 21 mm hg) in 3 different consecutive examinations, reliable normal visual field with no defects outside 95% normal limits in the pattern deviation plot, GHT result within normal limits at two consecutive examinations and normal fundus examination.

During the follow-up period each patient was treated at the discretion of the attending ophthalmologist. The study was conducted according to the principles of the Declaration of

Helsinki. All subjects gave their informed consent, and the study was approved by the Ethics Committee of the Hospital Universitari Sagrat Cor.

Main outcome measurements were the identification of change in stereophotos, VF and SD-OCT.

1. Stereophotos were assessed by two independent expert graders. These experts were masked to both patient data and temporal sequence of the images. Baseline and follow-up photographs were compared using a stereoscopic viewer 'Screen-Vu PS Mfg., Portland, OR 97202, USA'. The experts were asked to look for rim thinning, increase in cup/disc ratio or disc asymmetry, disc hemorrhage or onset of or enlargement of retinal nerve fiber defects. Graders were required to get chronological sequence right in order to classify a progressing case. If consensus was not reached a third independent grader decided if progression was present.

2. Visual fields. Only VF series with at least 5 reliable tests (fixation losses <30%, false-positive <20% and false -negative rates <30%) were included in the analysis. GPA event and trend analysis were used to assess the presence of VF change. GPA event analysis compares the changes between baseline and follow-up examinations. Significant progression is considered if the change detected is greater than the deterioration expected to occur less than 5% of the time at the location in a stable glaucoma patient ($p < 0.05$). GPA Alert messages of *possible progression* (significant deterioration in 3 locations in 2 consecutive tests) or *likely progression* (significant deterioration in 3 locations in 3 consecutive tests) in the last VF visit, were classified as VF progression. GPA trend analysis was applied calculating the rate of progression of visual field index (VFI) with a regression equation represented at the VFI plot (21). Significant negative slopes with $p < 5\%$ were considered as visual field progression.

3. Change in SD-OCT images was analyzed with SD-OCT GPA software version 5.0. Only scans with signal strength >5, well centered and without artifacts, were included. SD-OCT GPA also

uses event and trend analyses. It compares retinal nerve fiber layer thickness in follow-up images to that of baseline images (event analysis) and determines whether a statistically significant change has occurred since baseline. The software also calculates the rate of change (trend analysis). The first two good quality scans were established as baseline examinations. A minimum of three examinations are needed to generate a GPA printout. If a statistically significant change is detected once in follow-up scans, a yellow alert message of *possible progression* is indicated. When significant thinning is noted in two consecutive examinations, a red *likely progression* message is indicated. Both alert messages, if observed in any of the progression parameters in the last OCT acquirement visit, were considered as progression in SD-OCT. The following parameters were analyzed. Event analysis: RNFL Thickness Map progression (Thickness Map) and RNFL Thickness Profiles Progression (Thickness Profile). Trend analysis: Average RNFL Thickness Progression (Average Thickness), Overall Thickness, Superior Thickness and Inferior Thickness. Figures 1A-B show an example of good agreement between changes detected by VF and OCT.

Statistical analysis

Statistical analyses were performed using SPSS (ver. 20.0; SPSS Inc., Chicago, IL) and WINPEPI (PEPI-for-Windows 11.15). In all the analyses $p < 0.05$ was considered as statistically significant. A Venn diagram was drawn showing cases with progression identified by the different tests and baseline group classification of these cases (Figure 2). Agreement among the different methods was reported using the Kappa coefficient (K), adjusted Kappa PABAK (prevalence-adjusted bias-adjusted kappa), Gwet's first order agreement coefficient (AC1), overall percentage agreement (OPA), Cicchetti-Feinstein indices percentage of positive agreement (Ppos) and percentage of negative agreement (Pneg). Table 1 presents the Formulas used in this study.

Kappa coefficient is a chance-corrected statistic widely used for measuring level of agreement between raters. Kappa ranges from -1 (perfect disagreement) to +1 (perfect agreement), when has the value zero, indicates no agreement better than chance. It is highly dependent on the prevalence of the condition, and decreases greatly where there is an imbalanced predominance of either “yes” or “no” answers (22- 23). For this reason evaluation of agreement using other indices is recommended. PABAK is used to adjust Kappa in imbalance situations. PABAK also ranges from -1 to +1 and assumes an average of the prevalence of each category of the two raters and absence of bias and is more consistent with OPA than Kappa. Gwet's first order agreement coefficient AC1 is a novel and robust chance-corrected statistic based upon the assumption that only a portion of the observed ratings will potentially lead to agreement by chance. This index is also less influenced by differences in the propensity to give positive ratings and differences in prevalence of the response category, avoiding paradoxical results. AC1 also ranges in value from -1 to +1 (22). OPA, (ranging from 0 to 100%), is not corrected for chance agreement and tends to be high when there is an imbalanced prevalence of the condition (very high or low). In addition, OPA does not differentiate between agreement on the positives and agreement on the negatives. Cicchetti-Finstein indices Ppos and Pneg (ranging from 0 to 100%) are measures proposed to overcome the limitations of OPA. They are concordant ratings, positive or negative as a percentage of all positive or negative ratings. They represent the probability that if a subject has been given a certain rating by a typical observer, a second typical observer would assign the same rating (22). Frequency table showing different tests and algorithms rates of progression detection and specificity values are presented in table 3.

RESULTS

276 patients were chosen on the basis of minimum number of exams with VF, SD-OCT and stereophotos, 5, 3 and 2 respectively. However, 128 participants were excluded because of poor quality test. In the current study, 246 eyes of 148 subjects (59 males, 89 females) were

recruited and followed up for an average of 31.8 ± 9 months. Patient mean age was 65.1 ± 12.25 (34 to 86 years). 97 eyes (39.4%) were classified as glaucomatous, 63 eyes (25.6%) as suspects, 69 eyes (28%) as OHT and 17 eyes (6.9%) were classified as normal. The demographic characteristics of the study sample are summarized in Table 2.

Progression by stereophotos was found in 17 eyes (6.9%). Agreement between graders was obtained in 83.9% of cases (207 cases), with 18.2% Ppos agreement for judging progression (5 cases) and 91.1% Pneg for judging non-progression (202 cases). The inter-observer agreement (Kappa) was poor, 0.12, however PABAK was 0.68 and AC1 was 0.8. In 39 cases the third grader was required to grade.

Progression by SD-OCT was identified in 63 eyes (25.6%). Thickness Map and Thickness Profile, both event parameters, detected significant change in 52 eyes (21.1%), and in 31 eyes (12.6%) respectively. Average Thickness, a parameter that groups trend analysis parameters, detected progression in 31 eyes (12.6%). Overall Thickness, Superior Thickness and Inferior Thickness identified progression in 17 (6.9%), 11 (4.4%) and 14 (5.6%) eyes, respectively.

Progression by VF was observed in 37 eyes (15%). VF event analysis detected change in 26 eyes and VF trend analysis in 20 cases.

The 3 techniques obtained good outcomes in terms of specificity (82%-100%). Stereophotos and OCT trend analysis parameters Overall thickness and Superior thickness reported the highest specificity results, 100% (table 3).

Complete agreement detecting progression by the 3 modalities was found in 3 eyes (1.2%), while 147 eyes (59.7%) were identified as non-progressing cases by all 3 methods (Fig.2). Most cases with detectable changes were only identified by one examination method resulting in low Ppos; 27.9% and 32.4% for VF event and VF trend analysis with stereophotos, and all under 25%

for SD-OCT parameters and stereophotos. Nevertheless, concordance in cases with “No progression detected” was high, showing high OPA (72.8 to 89.8%) and high Pneg (83.8 to 94.5%). The highest OPA, Ppos and Pneg were found between stereophotos and VF trend analysis, followed by stereophotos and Overall Thickness (Table 4). Despite the high OPA values (all over 70, most over 80), Kappa coefficient between SD-OCT, VF and stereophotos was poor (less than 0.3). The highest Kappa values were obtained with photos-VF trend analysis and photos-VF event analysis, 0.27 and 0.21 respectively (Table 4). This inconsistency between OPA and Kappa is known as Kappa’s paradoxical values. Measures of agreement showed a trend toward better agreement between photos and VF trend analysis and between stereophotos and overall thickness than by any other pair, obtaining acceptable PABAK and AC1 values (>0.78 and 0.88 respectively). SD-OCT parameters reflected a tendency toward better agreement with stereophotos than with VF. Additionally, OCT parameter obtained better agreement coefficients outcomes with VF trend analysis than with VF event analysis. Finally, photos and VF trend analysis tended to agree more than photos-VF event analysis in all indices (Table 4).

DISCUSSION

The detection of the worsening of glaucomatous damage is not a simple task. There are three main difficulties; firstly, differentiating real change from instrument variability; secondly, there is limited knowledge about the amount of change that is clinically relevant; and thirdly, there is no ideal gold standard test to compare with the rest of the tests. In fact, consensus using conventional methods is difficult to achieve, even among glaucoma experts (6,24). The present study evaluated the agreement between two structural tests (optic disc stereophotos and SD-OCT) and one functional test, standard automated perimetry.

The progression detection rate using stereophotos (6.9%) was similar to that observed by Alencar et al (3.7%) (5) and Heijl et al (4%) in the treatment group of the EMGT study (25). Our results show that SD-OCT-GPA has a higher propensity to classify presence of progression (25%) than VF GPA (15%) or photographs with the given definitions of change.

In this study, conventional modalities detected less number of progressing cases. Are these OCT positive ratings 'false positives'? Or is it because over the span of 3 to 4 years few eyes will meet the requirements for being classified by SAP as *possible progression* or as abnormal change identified in series of photographs. Are these OCT positive ratings clinically useful? Will standard methods detect these progressing cases in future years? There is a clear necessity to expand the study and include more patients over a longer follow-up period in order to elucidate these questions.

It seems evident though, that these diagnostic modalities provide data about very different aspects of the glaucomatous disease process. Several studies suggest that test performance for detecting progression could vary throughout the different stages of the disease. Subtle progression of glaucoma in the early stages is probably undetectable in disc photos or VF but could be identified in the RNFL and, contrarily, changes in advanced stages are better assessed by VF (1,17, 26,29,30). All of them indicate the need to combine functional and structural tests when assessing changes in glaucoma (3,27-28), and to thoroughly evaluate any progression algorithm. Our results agree with these statements. In our study most OCT progressing cases, 37 of 63 cases (58.7%), were initially classified at baseline as OHT (33.3%) or as glaucoma suspects cases (25.4%). In contrast, most VF progressing cases, 21 of 37 (56.8%) were initially described as glaucoma cases. SAP, only detected abnormal change in 8 glaucoma suspects (21.6%) and in 5 OHT cases (13.5%). When Analyzing Venn diagram, we can observed most agreement on progressing cases on glaucomatous eyes (8) and ONH suspects (7) while in only two OHT cases diagnostic tests concurred classifying progression.

In addition, results indicate substantial differences in agreement for detection of change among different SD-OCT parameters with standard methods. Higher levels of agreement between tests were obtained when analyzing with OCT trend parameters compared to OCT event parameters. This could indicate more similarities in detection capabilities and temporal appearance of change, between OCT trend analysis and conventional methods.

There is poor agreement between tests detecting progression described in many previous studies (3-5,13-15,17,26-27), (Moreno-Montañes J, *IOVS*, 2010, ARVO E-Abstract, 4015/A294). Xin et al (4) compared functional and structural changes in glaucoma assessed with Humphrey VF, frequency doubling perimetry, multifocal visual evoked potentials, Stratus OCT and stereophotos. Although progression percentages were similar with all methods (from 16.4% to 23.6%), and similar to the ones obtained in the present study (15-25%), no eye showed progression in all tests at the same time. Eleven eyes showed progression by OCT, but only 2 of these cases presented VF change and only 4 evidenced changes in stereophotos. These results were consistent with those of Leung et al.(1), who found agreement in only 3 of 40 progressing eyes both by Stratus GPA trend analysis and VF trend analysis. Similarly, Strouthidis et al (3) found poor agreement between progression assessed by HRT and VF in 198 subjects with ocular hypertension with 7 years follow-up. Alencar et al (5) reported agreement between stereophotos, VF and GDX in only 2 of 34 cases. A 0.48 kappa index and 0.92 Gwet's AC1 were found between GDX and conventional tests. These were the highest published agreement figures.

The lack of agreement among tests to identify progression in glaucoma may be due to differences in the capability of instruments and algorithms to detect changes, and/or to natural temporal differences in the appearance of structural and functional changes. Whether this is a true characteristic of the disease or a consequence of the capabilities of each method to detect progression requires further study.

From a statistical point of view, and as researchers interested in moving the field forward, we have to avoid using agreements metrics so limited and imperfect as Kappa. In our study as in many others, Kappa limitations and paradox values, sometimes absurd, were obtained. “Progression detected” categories had small percentage resulting in very low K values although high observed agreement. It is essential to identify imbalance prevalence scenarios and is highly recommended to make a thorough analysis of the agreement combining paradox-resistant coefficients as PABAK and AC1 with others like Ppos, Pneg and OPA.

Our study has certain limitations. Firstly, the follow-up time could be considered to be relatively short. However, the SD-OCT GPA was implemented in 2008, so 5 years was the longest available follow-up period. Secondly, the prevalence of progression with all three methods was relatively low, limiting performance and agreement assessment, but it was very similar to that of other studies and reflects the reality of daily glaucoma practice. Thirdly, there are certain statistically trends computed by standard automated perimetry and SD-OCT in our study that may not be clinically significant, for example a slope <1.5 VFI %/year or <1 dB/year for VF ⁽³¹⁻³²⁾ or slopes under $0.94\text{--}1.18\mu\text{m}$ loss per year in average RNFL thickness ⁽³³⁻³⁴⁾. In the current study there were only 3 cases with negative slopes under 0.5dB/year (data not presented); if these cases had been considered as not progressed, the specificity of the VF GPA trend analysis would have improved to 94% and the agreement between trend analysis and the other methods would also improve slightly. Finally, the lack of a perfect gold standard to compare with the rest of the modalities. Most clinical trials in glaucoma have used VF and/or optic disc photos despite the frequent disagreement in progression detection found between them in previous publications. Despite these limitations we believe the results increase our understanding of progression detection with available tests and algorithms.

To summarize, the three methods obtained acceptable agreements outcomes in terms of PABAK, AC1 and OPA. However, most cases with detectable changes were identified by only

one examination method resulting in low percentage of positive agreement (Ppos). Measures of agreement showed a trend toward better agreement between photos and VF than by photos and SD-OCT. SD-OCT parameters reflected a tendency toward better agreement with stereophotos than with VF. Finally, higher levels of agreement between tests were obtained when analyzing with OCT trend parameters compared to OCT event parameters.

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LEGENDS

Figures 1A-B. Example of agreement detecting glaucomatous progression between VF and OCT. VF's GPA alert detected significant deterioration in three consecutive tests at several points of the superior hemifield, indicating likely progression. Trend analysis of patient's VFI rate of progression, performed by regression line at the visual field index plot, indicated negative significant slope $p < 1\%$, considered as glaucomatous visual field progression. Significant RNFL loss in the inferior sector is detected by OCT's event parameters Thickness Map Progression and Thickness Profiles Progression; significant rates of change by trend parameters Overall thickness and Inferior Thickness progression.

Figure 2. Venn diagram. Cases with progression identified by different test.