CAN VISUAL FIELD PROGRESSION BE PREDICTED BY CONFOCAL SCANNING LASER OPHTHALMOSCOPIC IMAGING OF THE OPTIC NERVE HEAD IN GLAUCOMA? (AN AMERICAN OPHTHALMOLOGICAL SOCIETY THESIS)

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ABSTRACT

Purpose: To determine whether confocal scanning laser ophthalmoscopic imaging (Heidelberg retinal tomography [HRT]) can predict visual field change in glaucoma.

Methods: The study included 561 patients with glaucoma or ocular hypertension whose clinical course was followed at the Mount Sinai Faculty practice. Humphrey visual fields (HVFs) and HRT images were collected on one randomly selected eye per patient. Glaucoma progression was determined by the presence of two sequential statistically significant negative slopes in mean deviation (MD) or visual field index (VFI) at any point during the study period. Trend-based analysis on HRT parameters was used to determine progressive changes and whether these occurred before or after HVF change. Sensitivity and specificity of HRT to predict HVF change were calculated. HVF rate of change was correlated to the rate of change detected by HRT imaging.

Results: Approximately 17% of patients progressed by either MD or VFI criteria. MD and VFI correlated highly and identified overlapping sets of patients as progressing. HRT global parameters had poor sensitivity (~42%) and moderate specificity (~67%) to predict HVF progression. Regional stereometric parameters were more sensitive (69%-78%) but significantly less specific (24%-27%). Sensitivity of global stereometric parameters in detecting HVF change was not significantly affected by the level of visual field damage (P=.3, Fisher exact test). HVF rate of change did not correlate with rate of change of HRT parameters.

Conclusions: Trend-based analysis of HRT parameters has poor sensitivity and specificity in predicting HVF change. This may be related specifically to HRT imaging or may reflect the fact that in some patients with glaucoma, functional changes precede structural alterations.

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INTRODUCTION

The term *glaucoma* describes a group of progressive intraocular pressure–dependent optic neuropathies that exhibit characteristic optic nerve head alterations (cupping) that coexist with specific visual field defects.[1] These two aspects of the definition of glaucoma that refer to alterations from the normal anatomy and physiology have been respectively termed *structural* and *functional* changes.[2] It has been extensively debated whether structural changes precede functional changes in glaucoma or whether the inverse is true.[3] Various studies suggest that in some patients structural changes do precede visual field changes, in other patients the inverse is true, and in an additional subset of patients, structural and functional changes occur at about the same time.[4-7] The difference in the order in which these changes occur has been attributed mainly to the methodology used[3] as well as the stage of the disease.[8-10] Structural changes are thought to be more easily detected early in the disease, whereas functional changes are more apparent in later stages of the disease.[11]

Most of the studies examining the relationship between functional and structural changes were performed under well-controlled conditions, in terms of both imaging and visual field testing. Such conditions, although important from a scientific standpoint in attempting to determine which change occurs earlier in glaucoma, do not necessarily reflect the realities of day-to-day clinical practice. In the clinical setting, the physician needs to predict the development of glaucomatous damage in an individual patient based on currently available data (which often have their own set of limitations) and, if possible, prevent it from occurring. Such prediction of development of glaucomatous damage before it occurs would also be valuable in identifying patients at high risk for progression, who could then be used in clinical trials of agents with potential neuroprotective activities. For a number of reasons, characteristic visual field defects are currently considered the "gold standard" that the US Food and Drug Administration uses to evaluate efficacy of such medications.[12,13] In addition, visual field performance is what is ultimately important to patients who are worried about maintaining the ability to see. In the current thesis we attempted to determine whether using parameters derived from optic nerve head and retinal fiber layer imaging can predict future deterioration of visual fields in glaucoma in a real-world patient cohort. Our hypothesis was that specific imaging parameters can be used to predict this visual field change with relatively high sensitivity and reasonable specificity to allow use in selecting high-risk populations for future progression of their disease. This study complements and shares similarities with a number of other excellent studies on the same topic.[14-17]

METHODS

This study was approved by the Mount Sinai School of Medicine Institutional Review Board prior to the collection and analysis of any data and was performed in accordance with the Declaration of Helsinki and all federal and New York state laws.

We used all data from computerized visual fields performed as standard of care for patients with glaucoma (any type), as well as

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patients suspected of having glaucoma, by the two contributors (J.S. and J.D.) at the Mount Sinai School of Medicine Faculty Practice. Patients had at least two computerized visual fields performed from 1984 until 2011. In addition, we used imaging data from the same group of patients performed at the Mount Sinai Medical Center Faculty Practice from 1983 until 2011. Not all patients whose visual field data were analyzed had sufficient imaging data to be used in the structure/function portion of the analysis.

Visual field data had been obtained with various generations of Humphrey Zeiss perimeters. Testing procedures during the period covered by the study were similar, and the perimeters were serviced on a regular basis. Although technical staff directing patients did undergo some turnover during the years covered by the study, overlapping senior technicians remained the same for most of the study period, and testing protocols had not been substantially altered. With the introduction of the HFA II (model 740-*i*), the database of all available fields was imported into the new perimeters and was used for obtaining visual field indices. Single-field printouts of all the visual fields within the aforementioned time period were prepared and used to record the following summary parameters: mean deviation (MD), pattern standard deviation (PSD), and visual field index (VFI). Only one eye per patient was selected at random by staff who had no involvement in the analysis of data.

The vast majority of the visual fields used had been obtained using threshold strategies. Visual fields that were obtained using a suprathreshold approach were excluded from any analysis. Summary parameters (already described) from all available threshold fields, together with a unique patient identifier, the date of the test, and the testing strategy (full threshold vs SITA threshold) and pattern used, were entered in an Excel worksheet that was subsequently used for data analysis. Visual fields that were flagged as having poor or reduced reliability were also excluded from analysis. These fields with poor reliability accounted for 900 (~13.5%) of the total 6673 threshold visual fields initially entered in the analysis.

Correlations of the three summary parameters (MD, PSD, and VFI) with each other were performed.

To determine visual field progression in individual patients/eyes, the aforementioned parameters were plotted over time, and the slope of the individual parameter over time, as well as the correlation coefficient, was determined for each patient/eye at each time point using all available data up to that point. Slope values were compared at each time point with zero (indicating no change). Negative slopes that deferred significantly from zero in MD or VFI at individual time points were considered to indicate progression. Concordance of progression detected by MD and VFI was determined. The percentages of patients detected as progressing by each parameter were determined and compared.

To determine the relationship between progression detected by visual field analysis and optic nerve imaging in a way that would be relevant to clinical care, we used the data from all visual fields collected.

Because of data presented in the "Results" section, the presence of two consecutive visual fields with significantly negative slopes was considered proof of progression and was used to understand the potential predictive ability of structural changes to predict visual field change in that particular patient/eye.

To utilize imaging in a meaningful way from the same patients/eyes that were included in the visual field analysis, we used imaging parameters generated from Heidelberg retinal tomography (HRT) during roughly the same time period. The images were obtained at the Mount Sinai Faculty Practice by experienced ophthalmic photographers from as early as 1993 until 2008 through three successive generations of HRT instruments (HRT I, II, and III).

Summary global and regional parameters (18 global and 12 each from the temporal, temporal/superior, temporal/inferior, nasal, nasal/superior, nasal/inferior regions) were exported in CSV file format from the HRT III machine for each individual patient at each individual point. The following global parameters were collected: cup area, rim area, cup-disc area ratio, rim-disc area ratio, cup volume, rim volume, mean cup depth, maximum cup depth, height variation contour, cup shape measure, mean retinal nerve fiber layer (RNFL) thickness, RNFL cross-sectional area, horizontal cup-disk ratio, vertical cup-disk ratio, maximum contour elevation, maximum contour depression, contour modulation line (CML) temporal-superior, and CML temporal-inferior. For comparison with the visual field data, only the data from the eye selected for visual field analysis were retained and imported into an Excel worksheet. Similarly to visual field analysis, slopes of each of the exported parameters over time were calculated at each time point, and negative slopes statistically significantly different from zero were used to define progression in specific global or regional parameter for individual patients at each time point.

For patients with confirmed progressive visual field change (see previous discussion), HRT slopes were determined for the various parameters for the time point immediately preceding the visual field change. For patients without documented visual field progression during the whole study, HRT slopes were determined for the point closest to the midpoint of the time of follow-up and were used to determine the negative predictive value of imaging to predict visual field change.

Analysis of these complex databases was performed with Excel software, and statistical evaluations were performed using the NCSS statistical package. Significance level was set at $P<.05$. No corrections were performed for multiple comparisons of HRT parameters.

RESULTS

Analysis included 5,864 threshold fields from 561 patients/eyes. The average (±SD) follow-up for these patients was 8.6±5 years, whereas the average (±SD) number of fields per patient was 10.5±9.6. Mean deviations ranged from −23.3 to 3 dB with a mean (±SD) of 3.9±4.8 dB.

Mean deviation correlated strongly with VFI ($R^2=0.89$, $P<.0001$) (Figure 1).

Correlation of MD with PSD was, as expected, nonlinear and weaker ($R^2=0.72$, second-order polynomial) (Figure 2).

Correlation of VFI and PSD was also nonlinear but very strong ($R^2=0.89$, second-order polynomial) (Figure 3).

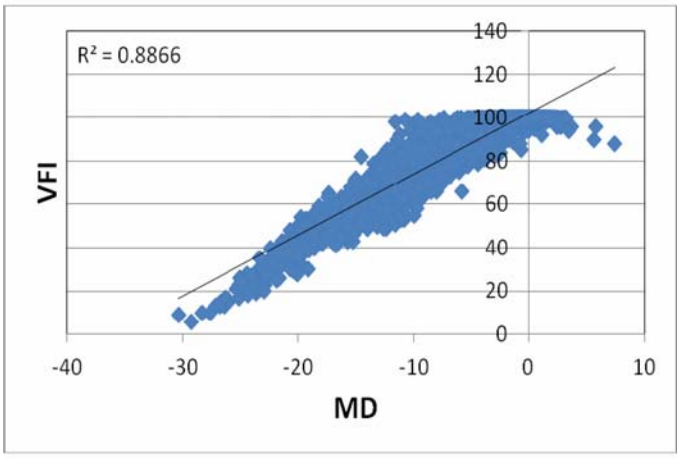

FIGURE 1

Correlation of mean deviation (MD) with visual field index (VFI) for all reliable threshold visual fields analyzed (N=5,864) from a cohort of 561 patients with glaucoma seen in an academic glaucoma practice.

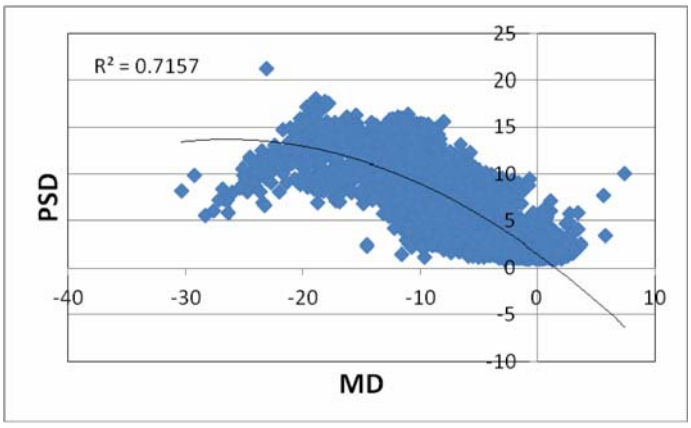

FIGURE 2

Correlation of mean deviation (MD) with pattern standard deviation (PSD) for all reliable threshold visual fields analyzed (N=5,864) from a cohort of 561 patients with glaucoma seen in an academic glaucoma practice. Correlation is not linear but is described well by a second-order polynomial function.

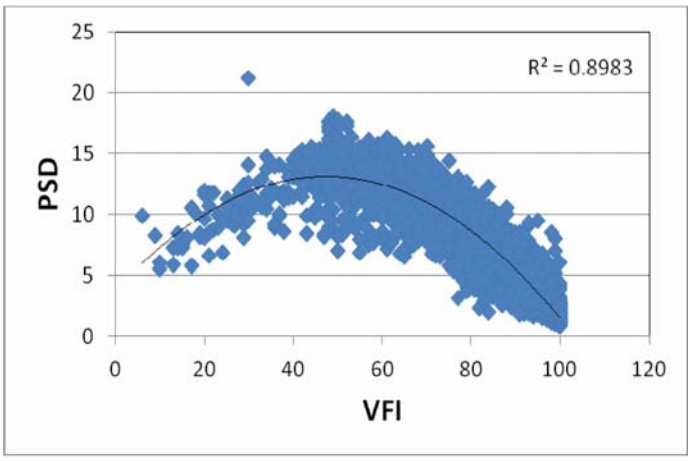

FIGURE 3

Correlation of visual field index (VFI) with pattern standard deviation (PSD) for all reliable threshold visual fields analyzed (N=5,864) from a cohort of 561 patients with glaucoma seen in an academic glaucoma practice. Correlation is not linear but is described well by a second-order polynomial function.

Of the patients with HRT imaging data, 248 of 559 (44.3%) were male. The average age (±SD) at the time of initial imaging was 58.2±14.6 years. The average global pixel SD was 41.4 μm, and the median was 28 μm. In 79.4% of the images, global pixel SD was less than 50 μm.

A statistically significant negative slope in MD was identified at least once in 170 of 561 patients (30.3%). The chance of a second sequential statistically significant negative slope in MD was approximately 91%, and the chance of a third sequential statistically significant negative slope (after two sequential ones) was approximately 96%. Similarly for VFI, a statistically significant negative slope was identified at least once in 172 of 561 patients (30.7%). Two sequential statistically significant negative slopes were followed

96% of the time by a third one. On the basis of these findings, we elected to use two sequential negative slopes (in either MD or VFI [separate analyses]) as indicators of visual field progression.

Mean deviation and VFI identified progression (defined as a statistically significant negative slope in two consecutive visual fields) in 97 of 561 patients (17.3%) and 98 of 561 patients (17.5%), respectively (P>.05, chi-square test). Progression was identified by both MD and VFI in 74 of 561 patients (13.2%) (Figure 4), although progression was identified *concurrently* by both MD and VFI in only 25 of 561 (4.5%). At each time point, concordance of whether there was progression or not between MD and VFI was 90.4% (4,053 of 4,481 visual fields).

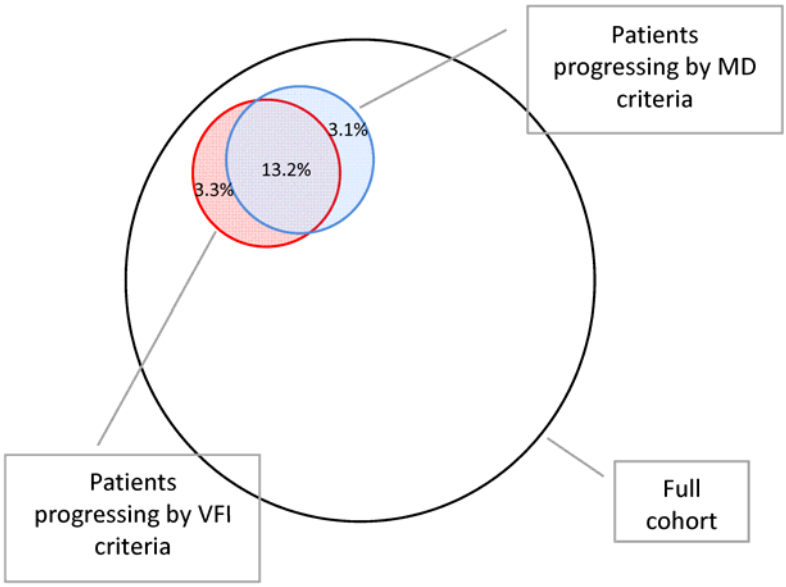

FIGURE 4

Schematic Venn diagram to illustrate the overlapping nature of patients in whom visual field progression was detected among the glaucoma patients analyzed (N=561) using either mean deviation (MD) or visual field index (VFI) criteria.

Of the patients where progression was detected by two sequential statistically significant negative slopes in MD, 61 had enough imaging sessions prior to the onset of visual field progression to allow for calculation of a time-dependent slope in the imaging parameters. Twenty-five of the 61 patients (41%) had at least one global stereometric parameter and 17 of 61 (27.9%) had at least two such parameters with a statistically significant negative slope prior to visual field progression.

Of the patients where progression was detected by two sequential statistically significant negative slopes in VFI, 61 had enough imaging sessions prior to the onset of visual field progression to allow for calculation of a time-dependent slope in the imaging parameters. Twenty-seven of the 61 patients (44.3%) had at least one global stereometric parameter and 17 of 61 (27.9%) had at least two such parameters with a statistically significant negative slope prior to visual field progression.

In patients with visual field progression (defined as two sequential statistically significant negative slopes in MD), 46 had enough imaging sessions *after* the onset of visual field progression to allow for calculation of a time-dependent slope in the imaging parameters. Thirty-one of the 46 (67.4%) had at least one global stereometric parameter and 23 of 46 (50%) had at least two such parameters with a statistically significant negative slope after the time point when visual field progression was detected.

In patients with visual field progression (defined as two sequential statistically significant negative slopes in VFI), 54 had enough imaging sessions after the onset of visual field progression to allow for calculation of a time-dependent slope in the imaging parameters. Thirty-five of the 54 patients (64.8%) had at least one global stereometric parameter and 24 of 54 (44.4%) had at least two such parameters with a statistically significant negative slope after the time point when visual field progression was detected.

A statistically significant slope in at least one or two of the global stereometric parameters *prior to* the midpoint of follow-up was detected in 45 of 132 patients (34.1%) or 19 of 132 patients (14.4%), respectively, *without* significant visual field change (by MD criteria) over the follow-up period and with adequate imaging sessions. Similarly, a statistically significant slope in at least one or two of the global stereometric parameters *prior to* the midpoint of follow-up was detected in 41 of 128 patients (32%) or 17 of 128 patients (13.3%), respectively, without significant visual field change (by VFI criteria) over the follow-up period that also had adequate imaging sessions.

A statistically significant slope in at least one or two of the global stereometric parameters *after* the midpoint of follow-up was detected in 64 of 128 patients (50%) or 31 of 128 patients (24.2%), respectively, without significant visual field change by MD over

the follow-up period that also had adequate imaging sessions. Similarly, a statistically significant slope in at least one or two of the global stereometric parameters *after* the midpoint of follow-up was detected in 60 of 124 patients (48.4%) or 27 of 124 patients (21.8%), respectively, without significant visual field change by VFI over the follow-up period that had adequate imaging sessions.

Based on the aforementioned findings, the presence of at least one global HRT parameter with negative statistically significant slope has a sensitivity of 41% (or 44.3%) and a specificity of 65.9% (or 68%) to predict visual field progression by MD (or VFI) criteria. The corresponding positive predictive value of the same measure is 35.7% (or 39.7%), whereas the negative predictive value is 70.7% (or 71.9%).

Of the individual stereometric parameters, rim-disc area ratio was the most sensitive in predicting progression by both MD and VFI criteria (sensitivity, 18% for both), and cup-disc area ratio was the most specific (specificity, 100% for both). Regional stereometric parameters were more sensitive at predicting progression, but they were significantly less specific (Table 1).

TABLE 1. SENSITIVITY AND SPECIFICITY OF REGIONAL STEREOMETRIC HRT PARAMETERS IN PREDICTING CHANGE IN GLOBAL VISUAL FIELD INDICES

	ANY REGIONAL STEREOMETRIC PARAMETER WITH STATISTICALLY SIGNIFICANT NEGATIVE SLOPE	ANY 2 REGIONAL STEREOMETRIC PARAMETERS WITH STATISTICALLY SIGNIFICANT NEGATIVE SLOPES	ANY 5 REGIONAL STEREOMETRIC PARAMETERS WITH STATISTICALLY SIGNIFICANT NEGATIVE SLOPES
Sensitivity to predict progression			
Progression defined by MD change	68.9% (42/61)	68.9% (42/61)	45.9 % (28/61)
Progression defined by VFI change	78.7% (48/61)	77% (47/61)	49.2% (30/61)
Specificity to predict progression			
Progression defined by MD change	23.5% (31/132)	24.2% (32/132)	50.8% (67/132)
Progression defined by VFI change	24.2% (31/128)	26.6% (34/128)	63.3% (81/128)

HRT, Heidelberg retinal tomography; MD, mean deviation; VFI, visual field index.

Sensitivity of global stereometric parameters in detecting change in visual field MD was not significantly affected by the level of visual field damage, as the proportion of eyes showing structural progression that also had MD above the median value (−6.84 dB) was similar to that of eyes showing structural progression with MD below the median value (P=.3, Fisher exact test).

Among patients who progressed, neither MD rate of change (Figure 5) nor VFI rate of change (Figure 6) correlated significantly (P>.05) with the rate of change of cup-disc area ratio or other global stereometric parameters at the time progression was initially identified.

DISCUSSION

Automated visual field testing and optic nerve imaging are the two methods used for diagnosis and monitoring of glaucoma. In the United States, the bulk of automated visual field testing has until recently been performed with Humphrey-Zeiss perimeters. Tests patterns most commonly used in the care of patients with glaucoma determine the sensitivity of a defined number of points within 30 degrees from the point of fixation.

Threshold testing accurately determines the intensity threshold of visual perception at a specific location and is highly recommended when testing patients with glaucoma or suspected of having glaucoma as it allows for more accurate determination of the depth of any scotomas.[18] Because the vast majority of visual fields included in our data set came from patients with definite or suspected glaucoma, we restricted analysis to only those that used threshold testing. Determination of the threshold at each one of the individual locations of the visual space tested is a lengthy process, which makes the test rather tedious. In an effort to speed up the testing process, the Swedish Interactive Threshold Algorithm (SITA) was introduced in the late 1990s.[19] This algorithm uses information from adjacent points to "predict" the threshold at specific locations and thus reduce the number of intensities tested in visual threshold determinations. Overall, SITA decreases testing time by about 50%[20] without significant reduction in the accuracy and reliability of mapping of scotomas. Although SITA Standard is at least comparable in repeatability to full-threshold strategies,[21] actual threshold values from full-threshold and SITA Standard tests are not identical. Defects appear shallower with SITA,[22] possibly because of shortened test duration and thus decreased patient fatigue. Most of the patients in our data set either continued to be tested with full-threshold strategy throughout the study period or were switched from the full-threshold strategy to the SITA Standard strategy. This change would have resulted in an apparent "improvement" of visual field results and is thus unlikely to have caused an erroneous visual field progression call. Because of this, we decided to use all reliable visual fields in the current data set for analysis.

Since most of the visual field tests in the data set came from patients with long-term follow-up who were experienced test takers, only a small portion of the tests (~15%) were considered to be of low reliability and were excluded from analysis.

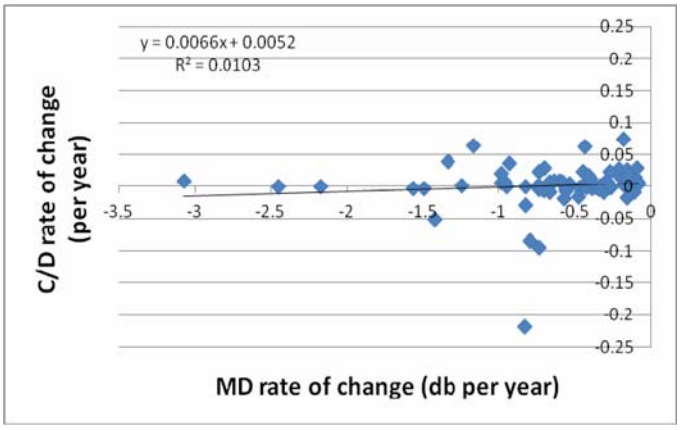

FIGURE 5

Correlation of the rate of change of mean deviation (MD) with the rate of change of cup-disc ratio area (C/D) for patients that experienced visual field progression at any point during the study. Rates of change for MD are calculated at the time visual field progression was identified. Rates of change for C/D are calculated at the time immediately preceding the time when visual field progression was identified.

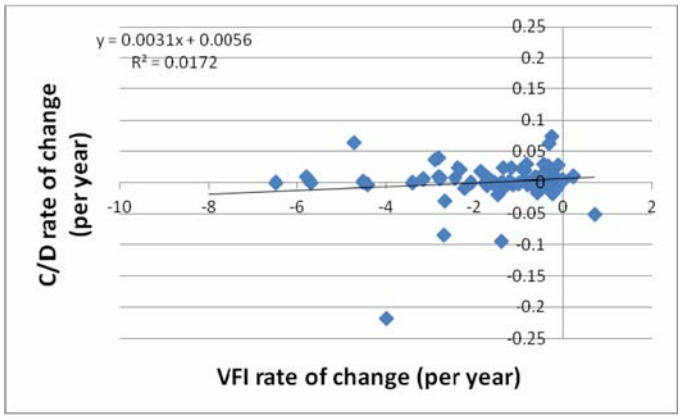

FIGURE 6

Correlation of the rate of change of visual field index (VFI) with the rate of change of cup-disc ratio area (C/D) for patients that experienced visual field progression at any point during the study. Rates of change for VFI are calculated at the time visual field progression was identified. Rates of change for C/D are calculated at the time immediately preceding the time when visual field progression was identified.

Summary parameters calculated by the earlier Humphrey-Zeiss perimeters included MD and PSD. MD is derived by comparing the thresholds at each specific location with the thresholds of a cohort of age-matched controls (subjects without any visual pathology) and averaging them.[18] MD is a measure of the total reduction of sensitivity across the visual space and thus is affected by media opacities such as cataracts. PSD is calculated by taking a location-weighted SD of all the threshold values.[18] PSD is thus insensitive to the overall average visual field depression and is strongly affected by localized defects. Its main disadvantage, though, is that it is not linear. As the visual field MD worsens, PSD initially decreases. When many of the tested positions become nondetectable because of advanced disease, PSD increases with additional visual field progression as variability across the visual field decreases.[18] This nonlinear behavior as the visual field worsens makes PSD not well suited for longitudinal follow-up of patients.

To improve the ability of monitoring patients with glaucoma longitudinally, VFI is a newly developed index that appears to be less affected by media opacities.[23] VFI represents a percentage of the normal age-corrected sensitivity across the whole visual field.[18] It is designed to approximately reflect retinal ganglion cell loss and is thus weighted more for central locations compared to peripheral ones.[18]

In the current work, as expected,[24] MD and VFI were highly correlated (Figure 1). The larger spread of MD values for larger VFI values may reflect the effect of media opacities. This is also suggested by comparison of the relationship between MD and PSD and between VFI and PSD (Figures 2 and 3). Although both MD and VFI correlated well with PSD, this relationship was much stronger between VFI and PSD than between MD and PSD. As mentioned earlier, PSD is known to be less affected than MD by media opacities, and the same is true for VFI.

A number of methods, both trend-based and event-based, have been used to determine visual field progression in various studies.[25] Event-based methods are preferred when analyzing a relatively limited number of visual fields, but because of the subjective nature of visual field testing, they often require confirmatory tests.[25] In addition, criteria for progression often have to be tailored to the severity of the disease. Trend-based methods (especially when using global parameters) are less affected by visual field testing variability but are often less sensitive and require a larger number of tests.[26] We elected to use trend-based methods in detecting visual field change, because based on the data we had collected, we wanted to ensure that any change detected was real (rather than the result of random fluctuation), and because we had a sufficiently long follow-up and number of visual fields. We used linear regression of both the MD and VFI over time to detect change. Although sensitivity across the visual field decreases with age,[27] both MD and VFI are age-corrected[18] and therefore should not decline due to aging alone. Thus a negative slope of MD (or VFI) over time that is statistically different from zero represents a change. In addition to VFI, we performed a separate analysis using the MD (even though it is more

affected than VFI by media opacities) to allow for comparisons of the results with trials that have used it as the basis for progression detection and because many physicians are more familiar with it.

Based on the aforementioned data analysis, a similar number of patients had at least one occasion during follow-up with a statistically significant negative slope of both MD and VFI. To increase the certainty that visual field change detected was not spurious, we defined progression as the presence of two sequential negative slopes in MD (or VFI) that are statistically different from zero. Use of this more stringent criterion is novel, as most prior studies that have used trend-based analysis of MD to detect progression rely on a single statistically significant negative slope. As a result, the specificity of detection of visual field progression was increased. It is telling that in over 95% of cases, two sequential significant negative slopes were followed by a third one for both MD and VFI.

Using either MD or VFI as the basis for detecting progression revealed similar overall rates of progression in our cohort of patients. The rates detected (~17%) are higher than the rates reported by the Ocular Hypertension Treatment Study (OHTS) for ocular hypertensive patients[5] but well below those reported for patients enrolled in the Early Manifest Glaucoma Trial (EMGT).[28] This reflects the fact that the present cohort included patients with a large range of severity of the disease.

Despite a similar overall rate of progression using either the MD or VFI, it appears that the two parameters both detected only a slightly smaller subset of common visual field progressors (~13% of the cohort). Only in approximately one-third of these cases was the detection by MD and VFI concurrently defined by changes in both parameters.

To determine whether structural changes at the level of the optic nerve and nerve fiber layer in this large cohort of real-world glaucoma patients precede visual field changes, we used computerized confocal scanning laser ophthalmoscopic imaging of the optic nerve head. If, as our hypothesis predicted, specific imaging parameters precede visual field change with relatively high sensitivity and reasonable specificity, they could be used to alert the clinician of the need for more aggressive treatment of the disease. They could also allow the selection of populations at high risk for progression of glaucoma for future trials of novel therapeutic neuroprotective agents.

We elected to use confocal scanning laser imaging because a large portion of our patients had been followed up with this technology, which was state-of-the-art during the follow-up period. Although the commercial instrument used (the Heidelberg Retinal Tomograph) had undergone changes through three successive design iterations, the format of the images had remained stable and thus images obtained with the earlier versions were usable. The availability of images from patients from as early as 1993 is thus a strength of the study. We elected not to use optic nerve photographs to detect structural changes for two main reasons: (1) Although many of the optic nerve photographs obtained over the years were stereoscopic, a large portion of them were not, making comparisons difficult. In addition, the quality of many of the photographs was suboptimal. (2) Evaluation of optic nerve photographs is in large part subjective (unless planimetry is used) and would thus introduce another variable. Furthermore, planimetry has been shown to be more variable than HRT.[29] In addition, the use of photography would make results less applicable to individual practitioners, who may or may not be trained to recognize subtle optic nerve changes.

Confocal scanning laser ophthalmoscopy has since been superseded by optical coherence tomography (OCT) in the management of glaucoma. However, no large cohorts of patients followed up longitudinally with modern OCT instruments for such long periods of time (15 years) are available currently.

Confocal scanning laser ophthalmoscopy has been shown to be sensitive at detecting glaucoma[30] and has low variability.[31] In addition, it has been shown to detect longitudinal change with reasonable sensitivity when compared with optic nerve head stereophotography.[32] The HRT instrument generates a number of regional and global stereometric parameters that can be used to determine progression. Although no consensus on what constitutes progression by HRT exists,[33] we elected to use a similar trend-based strategy to the one used for visual field testing despite known limitations.[34,35] To increase the sensitivity of detecting change by HRT, we used the presence of a negative slope that is statistically significantly different from zero in any of the stereometric parameters as an indicator of structural change.

The current study shares similarities with a number of other excellent studies on the same topic[14-17] that have used HRT to detect and monitor structural changes. However, it complements those studies in two important ways: (1) it reports on more patients than the number of patients included in all of these studies combined, and (2) it uses "real world" patients found in a clinical glaucoma practice. As such, it is more reflective of the mixture of patients that a clinician is likely to encounter in managing glaucoma patients.

Structural changes in the current study were detected *prior to* visual field change in only slightly more than 40% of patients, independent of whether MD or VFI was used to define visual field progression. Interestingly, visual field changes were followed by changes detected by HRT in approximately 65% of patients. This finding suggests that functional changes (as determined by analysis of HRT) in at least a number of patients with glaucoma occur before appreciable structural changes and corroborates findings from well-controlled clinical trials.[4,5,7] Since the criteria used in the detection of visual field change in the current study are more stringent than the criteria used for structural change, it is unlikely that the definition of functional progression accounts for the current findings. In fact, the criteria used here to determine structural change were so relaxed that change with HRT was detected halfway into the follow-up period in almost 50% of patients without any appreciable visual field progression at any point throughout the study.

It has been suggested that structural changes are easier to detect early in the disease process, whereas larger visual field changes in comparison to structural changes occur later in the disease process.[11] To test whether that is the case, we compared the sensitivity of HRT prediction of visual field progression in patients with MD above and below the median. Surprisingly, HRT imaging did not do any better in eyes with less visual field damage. In addition, the rate of change of visual field parameters did not correlate with the rate of change of individual global stereometric parameters. This finding is in agreement with the findings of another group that used

similar methodology in comparing visual field and HRT progression.[17]

Based on the aforementioned analysis, it appears that global HRT stereometric parameters have poor sensitivity and specificity in predicting visual field progression in patients with glaucoma in a clinical practice setting. The positive predictive value of these parameters in our cohort was also rather low, and the negative predictive value was moderate. Although regional stereometric parameters are more sensitive in detecting change, as previously reported,[36] this comes with a dramatic reduction in specificity that makes the test less useful.

Is this a problem of the technology (HRT), then, or is it an inherent issue that has to do with our limited understanding of the disease process? Although HRT has limitations in detecting change longitudinally[34,35,37] and has been clinically superseded by other methods that appear more sensitive at detecting very early changes in glaucoma, it is unclear whether it is significantly worse in its ability to detect progression when significant structural change has already occurred. Large ongoing clinical trials[38,39] may help provide an answer to that question. It is possible, though, that axons malfunction (thus causing progressive visual field defects) before they degenerate and are permanently lost.[3] Significant alterations in axoplasmic flow before axonal loss that would result in structural optic nerve head and nerve fiber layer changes in glaucoma have been detected.[40] Similarly, pruning of dendritic fields in experimental glaucoma[41,42] appears to have parallels in human disease.[43] In addition, clinical practice suggests that in certain patients, reduction of intraocular pressure (which presumably reduces the stress on compromised axons) occasionally results in improvement of visual field. It is thus possible that functional changes precede structural change in at least some patients. It is important to consider that despite a common name, glaucoma is a heterogeneous group of progressive optic neuropathies that share certain common characteristics. It would not be surprising if the rate and order of progression differ among them.

In conclusion, analysis of this large complex data set failed to support our hypothesis that specific parameters derived from computerized confocal scanning laser ophthalmoscopic imaging of the optic nerve can accurately predict visual field changes in glaucoma. It remains to be seen if newer imaging methods can be more successful in this task.

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