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Structure-Function relationships using the Cirrus Spectral Domain Optical Coherence Tomograph and Standard Automated Perimetry

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Abstract

Purpose—To evaluate the relationship between glaucomatous structural damage assessed by the Cirrus Spectral Domain OCT (SDOCT) and functional loss as measured by standard automated perimetry (SAP).

Methods—Four hundred twenty two eyes (78 healthy, 210 suspects, 134 glaucomatous) of 250 patients were recruited from the longitudinal Diagnostic Innovations in Glaucoma Study (DIGS) and from the African Descent and Glaucoma Evaluation Study (ADAGES). All eyes underwent testing with the Cirrus SDOCT and SAP within a 6-month period. The relationship between parapapillary retinal nerve fiber layer thickness (RNFL) sectors and corresponding topographic SAP locations was evaluated using locally weighted scatterplot smoothing (LOWESS) and regression analysis. SAP sensitivity values were evaluated using both linear as well as logarithmic scales. We also tested the fit of a model (Hood) for structure-function relationship in glaucoma.

Results—Structure was significantly related to function for all but the nasal thickness sector. The relationship was strongest for superotemporal RNFL thickness and inferonasal sensitivity ($R^2 = 0.314$, $P < 0.001$). The Hood model fitted the data relatively well with 88% of the eyes inside the 95% confidence interval predicted by the model.

Conclusion—RNFL thinning measured by the Cirrus SDOCT was associated with correspondent visual field loss in glaucoma.

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INTRODUCTION

Glaucoma is a chronic and progressive disease characterized by typical retinal nerve fiber layer (RNFL) thinning and changes to the optic nerve head that leads to a specific pattern of visual field loss.¹ Evaluation of the relationship between structural and functional damage is of importance in diagnosing, staging and monitoring glaucomatous patients. Furthermore, it may provide valuable insight on how visual function behaves according to the degree of structural loss, thus, helping our understanding of glaucoma.

With greatly enhanced resolution and reduced scan acquisition times compared to older versions of this technology, spectral-domain optical coherence tomography has improved the measurement reproducibility² and, possibly, the ability to detect small changes in RNFL thickness.

Previous studies of structure-function relationship in glaucoma have used various imaging technologies^{3–5} to evaluate structural losses and different types of perimetry^{6–9} to quantify functional loss. However, there is no consensus concerning which function, linear or non-linear, yields the best correlation between structural and functional damage.^{3,9,10} For example, Bowd et al.³ found no advantage of logarithmic function over linear function using the confocal laser ophthalmoscope. In contrast, Leung et al.¹¹ found that non-linear function described structure-function relationship better than linear functions using confocal laser ophthalmoscope and time-domain optical coherence tomography (OCT) to quantify structure. Garway-Heath et al.^{9,12} and Hood et al.,¹⁰ reported that the structure-function relationship is linear when the decibel (dB) scale from the visual field is converted to a linear (1/Lambert) scale. However, their studies used early versions of the OCT. Therefore, it is important to revisit structure-function relationships with the new generation of OCT.

The purpose of our study was to evaluate structure-function relationships using the Cirrus SDOCT (Cirrus SDOCT; Carl Zeiss Meditec, Inc., Dublin, CA) and SAP in a single population of glaucomatous, suspects and healthy subjects.

METHODS

This was an observational cross-sectional study. Subjects included in this study were recruited from the longitudinal Diagnostic Innovations in Glaucoma Study (DIGS; Diagnostic Innovations in Glaucoma Study) and from the African Descent And Glaucoma Evaluation Study (ADAGES) conducted at the Hamilton Glaucoma Center (University of California, San Diego). Informed consent was obtained from all participants. The University of California San Diego Human Subjects Committee approved all protocols and the methods described adhered to the tenets of the Declaration of Helsinki.

All participants underwent a complete ophthalmologic examination including review of medical history, best corrected visual acuity, slit lamp biomicroscopy, intraocular pressure (IOP) measurement, gonioscopy, dilated fundoscopic examination with a 78-D lens, stereoscopic optic disc photography, and automated perimetry with the 24-2 Swedish Interactive Threshold Algorithm (SITA standard; Carl Zeiss Meditec, Inc.). To be included, all participants had to have best-corrected visual acuity of at least 20/40, spherical refraction within ± 5.0 D, cylinder correction within ± 3.0 D, and open angles on gonioscopy. Eyes with coexisting retinal disease, uveitis, or non-glaucomatous optic neuropathy were also excluded from the investigation.

The study included glaucoma patients, suspects of having glaucoma and normal individuals. Patients were classified with glaucoma if they had at least two consecutive and reliable standard automated perimetry (SAP) examinations with either a pattern standard deviation

(PSD) outside the 95% normal limits or a glaucoma hemifield test (GHT) result outside the 99% normal limits, regardless of the optic disc appearance. Patients considered suspects of having glaucoma had either an IOP greater than 22mmHg or suspicious appearance of the optic nerve head with two reliable normal visual fields, defined as a PSD within 95% confidence limits and a GHT result outside normal limits.

Normal control subjects were recruited from the general population and had IOP<22mmHg with no history of elevated IOP and with at least two reliable normal visual fields, defined as a PSD within 95% confidence limits and a GHT result within normal limits.

Imaging

Spectral-domain OCT was performed using the Cirrus SDOCT (software version 4.0, Carl Zeiss Meditec Inc., Dublin, CA). Briefly, the machine uses a super luminescent diode laser with a wavelength of 840nm and an acquisition rate of 27,000 A-scans per second that is almost 70 times faster than time-domain OCT. The optic disc cube protocol used in this study is based on a tridimensional scan of a 6×6 mm² area centered in the optic disc and information from a 1024 (depth) × 200 × 200-point parallelepiped is collected. Then, a 3.46mm circular scan is placed around the optic disc and the information about parapapillary RNFL thickness is obtained. Because of the reduced acquisition time, measurements with this instrument are theoretically less prone to ocular movement artifacts compared to time-domain OCT, leading to more reproducible images.²

Cirrus RNFL thickness parameters used in this study were average thickness (360° measure), superonasal (91° – 135°), nasal (136° – 225°), inferonasal (226° – 270°), inferotemporal (271° – 315°), temporal (316° – 45°), and superotemporal (46° – 90°). Each sector was calculated by combining clock hours thickness available from the Cirrus SDOCT printout. Those sectors were selected based on the structure-function correspondence map proposed by Garway-Heath et al.,⁹ shown in Figure 1. All images were reviewed for movement artifacts and had to have a signal strength >7 for inclusion in the analysis. One measure per eye was included in this study.

Visual Field Testing

All patients underwent SAP testing using SITA-standard strategy less than 6 months apart from imaging. Visual fields were reviewed by the UCSD VisFACT (Visual Field Assessment CenTer) to identify the presence of artifacts such as lid and rim artifacts, fatigue effects, inattention or inappropriate fixation. In addition, they were reviewed for the presence of non-glaucomatous abnormalities such as homonymous hemianopia.

SAP total deviation points were grouped into 6 sectors: superonasal, nasal, inferonasal, inferotemporal, temporal and superotemporal according to the structure-function correspondence map described by Garway-Heath et al.⁹

Statistical Analysis

To account for the fact that both eyes per patient were used, comparison of global measurements in healthy, glaucomatous and suspects was performed using nested analysis of variance with eyes nested within participants. Pair-wise comparison was estimated using Tukey honestly significant difference (HSD) setting α to 0.05.

In the present study, we evaluated visual field sensitivity using both a logarithmic as well as a linear scale. First, the SAP total deviation (TD) points (difference between age-expected threshold and patient's measured threshold, provided in the printout of the exam) in decibels were converted into a linear scale by un-logging each point and, subsequently, averaging

them according to their visual field sector. We then obtained an average SAP sensitivity value for each sector in linear scale. This averaged value was transformed back into logarithmic scale to obtain an average SAP sensitivity value measured in dB. The rationale for this is based on the theory that two portions of an arcuate region, one with a normal complement of retinal ganglion cells ($TD = 0\text{dB}$) and the other with all the retinal ganglion cells destroyed ($TD = -30\text{dB}$), would average -15dB , which represents 1/30 loss in sensitivity on a decibel scale. However, it is expected that the average RNFL thickness for the same portion to be approximately half of the normal thickness. By taking the anti-log of total deviation points prior to averaging them, the average would be -3dB , representing nearly half of the normal sensitivity, thus matching with structural loss.

We also attempted to replicate the structure-function prediction curve as proposed by Hood et al.^{10,13} This model has the following assumptions. First, the model assumes that the total RNFL thickness is composed of retinal ganglion cells (RGC) axons and a residual b that does not change in spite of visual field loss. Second, in healthy subjects there is no relationship between RNFL thickness and visual field sensitivity. Third, structure and function are linearly related when decibels are converted to a linear scale.

The equations can be written as:

$$R = So \times 10^{0.1 \times TD} + b, \text{ for } TD \neq 0,$$

$$R = So + b, \text{ for } TD = 0,$$

where R is the total RNFL average thickness measured by the Cirrus SDOCT, the So is the thickness of the RGC complex, b is the residual thickness (blood vessels and glia cells) and TD is the total deviation value in decibels from the SAP.

In our study, b was calculated as the mean RNFL thickness in advanced glaucoma for each arcuate region. Advanced glaucoma was defined as patients having visual field mean deviation (MD) worse than -10dB . So was calculated by the difference between mean RNFL thickness from healthy subjects as measured by the device and the residual b , obtained from our severe glaucomatous patients. Our 95% confidence interval was built by using ± 2 standard deviation of So , taking into account the percentage of total residual RNFL thickness for the upper and lower boundaries. Apart from the residual thickness and the normal mean value described above, the estimation of the prediction curves did not consider data from patients. To evaluate the goodness of fit of the prediction curve to our dataset, we plotted locally weighted scatterplot smoothing (LOWESS) curves and evaluated their similarity to the predicted curves.

Generalized estimating equations with robust standard errors were used to adjust for potential correlations between both eyes of the same individual. All statistical analyses were performed using commercially available software (Stata version 10; StataCorp, College Station, Tx). The alpha level (type I error) was set at 0.05.

RESULTS

The present study included 422 eyes (78 healthy, 210 suspects, 134 glaucomatous) of 250 patients. Comparison of age, race, structural parameters and visual field parameters among healthy, suspects and glaucomatous eyes are shown in Table 1. Mean age ($\pm$ standard deviation) was 60 (± 12) for healthy, 65 (± 12) for suspects and 66 (± 12) for glaucomatous participants. 78 % of participants were of European Descent and 22% of African Descent. Normal subjects were significantly younger than the suspect and glaucoma patients but age was not different between the suspect and glaucoma patients. Glaucoma patients had significantly thinner RNFL measurements for all Cirrus parameters followed by suspects

and healthy individuals ($P < 0.001$). Pair-wise comparison of the RNFL thickness showed statistically significant differences for all parameters except for the nasal thickness, which was not statistically different between suspects and glaucomatous patients. Visual field mean deviation was significantly different among the groups ($P < 0.001$), however, no difference was found between healthy and suspect eyes.

Figure 2A shows a scatterplot of visual field sensitivity in dB scale and RNFL thickness and the LOWESS plot suggests a curvilinear relationship between structure and function. In contrast, when visual field sensitivity is expressed on a linear scale, the relationship between structure and function is linear, as shown by the LOWESS plot (Figure 2B). Linear regression models fitted to these data showed that all but the nasal RNFL thickness versus temporal visual field sensitivity ($P = 0.132$) relationships were statistically significant. The greatest R^2 values were for superotemporal RNFL thickness ($R^2 = 0.314$, $P < 0.001$), inferotemporal RNFL thickness ($R^2 = 0.259$, $P < 0.001$) and average thickness ($R^2 = 0.203$, $P < 0.001$). Structural-functional correlations were only weak to moderate for all parameters evaluated in this study. Table 2 summarizes the strength (R^2) of structure-function relationships for the linear-linear model. It should be noted that because R^2 measures the strength of linear relationship, it is not an appropriate measure for evaluation of the strength of non-linear relationships such as that observed when SAP sensitivity is expressed in a dB scale. Also, R^2 values should not be used to directly compare the linear and log-linear models.

Figure 3 shows the predicted curve based on Hood et al. and our actual data for the superotemporal RNFL thickness versus the inferonasal visual field sensitivity measured in a log-linear approach. For the superotemporal RNFL thickness versus inferonasal visual field, three hundred seventy two (88%) patients were inside the 95% confidence interval of the prediction model. Similarly, for the inferotemporal sector, 87% patients were inside the 95% confidence interval of the prediction model.

DISCUSSION

In the present study, we demonstrated that RNFL thickness measured by the Cirrus SDOCT was associated with corresponding visual field sensitivity. The RNFL sectors with the strongest association with visual function were the superotemporal and the inferotemporal. Previous studies using earlier imaging technologies have reported similar findings. Bowd et al.³ reported strongest associations between the inferotemporal RNFL thickness and superonasal visual field sectors using time-domain OCT and scanning laser polarimetry. However, in their study, function was measured by threshold values from the visual field and not total deviation values. In the present study, total deviation values from the visual field were used because they are less influenced by age (i.e. age-corrected) than raw threshold values and they maybe more sensitive to detect early diffuse loss compared to pattern deviation values. In fact, Artes et al evaluated visual field progression using the Ocular Hypertensive Treatment Study (OHTS) population and concluded that total deviation was more sensitive to progression than pattern deviation.¹⁴ Miglior et al.,¹⁵ also reported stronger associations for the inferotemporal RNFL thickness and its corresponding visual field loss using earlier versions of OCT. These results are in accordance to histological studies and the expected pattern of glaucomatous damage.^{16–18}

Overall, we found weak to moderate structure-function associations. Some authors have reported stronger associations. For example, Leung et al.¹¹ found R^2 values of 0.623 using the Stratus and 0.588 using the scanning laser polarimeter. However, their patients had more severe glaucoma with a mean MD of -11 dB, compared to -5 dB from our study. It has been shown that analysis of early glaucomatous, healthy individuals and glaucoma suspect eyes

have weaker correlation with visual field sensitivity than analyses that include eyes with moderate to severe glaucoma, mainly because in healthy and suspects, the range of visual field loss is narrower.^{15,19} On the other hand, in severe cases, we found a clear floor effect for structural measurements, that is, after a certain level of visual field damage, RNFL thickness will be stable despite deterioration on visual field (Figure 3). Therefore, it is possible that function may be better to follow glaucomatous loss on advanced cases. Longitudinal studies should address this issue more thoroughly.

There is still uncertainty regarding which mathematical model better describes the relationship between structural and functional loss in glaucoma.^{3,8,10,11,20–24} One of the issues is that visual fields are measured in a logarithmic scale (dB) while RNFL thickness is measured in a linear scale (μm). The logarithm scale tends to minimize changes at higher decibels, leading to a less apparent change in visual field for early disease. To address this issue, Garway-Heath et al.^{9,12} used a linear scale (1/Lambert) to quantify functional loss and concluded that structure-function relationships show a linear relationship. Hood et al.,^{10,13} also proposed a linear model to predict structure-function relationship. In addition to Garway-Heath et al.'s model, their model incorporates the concept of a residual RNFL thickness. In the present study, application of Hood's prediction model to our data demonstrated most (88%) of patients were inside the 95% prediction limits. This suggests that the Hood model may be a good representation of the structure-function relationship in glaucoma.

There are some differences between our actual data and Hood's prediction model. The original model did not include glaucoma suspect eyes. We included glaucoma suspects because they represent an important part of the disease spectrum and a challenge for clinical management. However, based on our inclusion criteria, the suspect group is made of individuals without visual field defects that have either an elevated IOP or an optic nerve with glaucomatous appearance. Therefore, some individuals are labeled suspects because of a structure-function mismatch, thus weakening structure-function associations. In fact, when we excluded the suspects from our analysis, we found stronger structure-function associations. For the superotemporal RNFL sector we obtained a R^2 of 0.463 ($P < 0.001$) in our linear model.

Another interesting aspect considered by Hood et al. is the concept of the residual RNFL thickness, that is, the glia and blood vessels that remains even after total RNFL loss. Sihota et al.,²⁵ found a residual thickness of approximately $45\mu\text{m}$ for the average thickness parameter using Stratus OCT (Stratus OCT; Carl Zeiss Meditec, Inc., Dublin, CA) in blind glaucoma patients. Hood et al.,¹⁰ found that the residual thickness correspond to approximately 33% of the total RNFL thickness for the arcuate regions, based on Stratus OCT data from anterior ischemic optic neuropathy (AION) with MD values worse than -10dB . As our study uses a different imaging technology, results from previous studies might not be applicable to our data. In fact, when we calculated the residual thickness based on the data from our advanced glaucoma patients, we found a residual thickness of $61.18\mu\text{m}$ (46% of normal RNFL thickness) for the inferotemporal arcuate region and $60.4\mu\text{m}$ (49% of normal RNFL thickness) for the superotemporal arcuate region. This thicker residual found in our study may be, at least in part, because we used glaucoma patients with a MD worse than -10dB to calculate the residual and not blind glaucoma patients or AION patients as performed in previous studies. Further, we used Cirrus SDOCT and not the Stratus OCT to determine the residual thickness. Nevertheless, the existence of a residual thickness should point out that the actual axonal loss might be greater than what we are considering. Future studies evaluating structure-function relationships should take into account the residual RNFL thickness.

Our study had some limitations. We did not have many advanced glaucoma patients in our cohort and this may have led to the thicker RNFL residuals we observed. However, using a residual thickness of 50 μ m (40% of the normal RNFL thickness), approximately 85% of patients remained inside the prediction model. In addition, it is likely that if we had incorporated more patients with advanced glaucoma, the structure-function associations could have been stronger. Because this was a cross-sectional study, we could not establish causal relationships between structure and functional loss. We did not obtain multiple measures per subject, thus we could not incorporate variability onto our model as recently suggested by Hood et al.²⁶ Although structure and function were significantly correlated, their relationship was weak to moderate. Other non-linear models, such as the one proposed by Harwerth et al.,²⁴ should be tested in future studies using a large population.

In conclusion, we demonstrated that RNFL thinning measured by the Cirrus was associated with visual field loss measured by the SAP. In addition, we demonstrated that the shape of the relationship changes with scaling of the measurements.

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Figure 1.

Structure-function correspondence map according to Garway-Heath et al.⁹ SN, superonasal; N, nasal; IN, inferonasal; IT, Inferotemporal; T, temporal; ST, superotemporal. Left - Visual field Sectors, Right - Parapapillary RNFL thickness.

Figure 2.

Result from structure-function regression models for the superotemporal RNFL thickness and inferonasal visual field sensitivity. **A.** Log-linear model: Regression using total deviation values after taking the logarithm of averaged values from the total deviation values in a linear scale. **B.** Linear-linear model: Regression using total deviation values in a linear scale.

Figure 3.
Incorporation of Hood's prediction model to our data for the superotemporal RNFL thickness and inferonasal visual field sensitivity.

Table 1

Clinical and demographic characteristics of included eyes. Values represented as mean (standard deviation).

	Healthy (n=78)	Suspect (n=210)	Glaucomatous (n=134)	P value*
Age (years)	60 (12)	66(12)	65(12)	0.007 [†]
Mean Deviation (dB)	0.05 (1.09)	−0.44 (1.43)	−5.53 (5.68)	<0.001 [‡]
Ancestry (% Blacks)	11	19	32	0.01
RNFL thickness (μm)				
Superotemporal	123 (17)	111 (18)	88 (23)	<0.001
Superonasal	107 (19)	98 (20)	85 (21)	<0.001
Nasal	72 (11)	69 (10)	66 (11)	<0.001 [†]
Inferonasal	107 (18)	100 (20)	84 (22)	<0.001
Inferotemporal	132 (20)	118 (20)	87 (29)	<0.001
Temporal	65 (12)	59 (10)	54 (12)	<0.001
Average thickness	93 (9)	85 (11)	73 (12)	<0.001

* Nested analysis of variance comparison of the three groups.

[†]Tukey pair-wise comparison showed no statistical significance between suspects and glaucomatous.

[‡]Tukey pair-wise comparison showed no statistical significance between healthy and suspects.

Table 2

Structure-Function associations (R^2) between retinal nerve fiber layer sectors and visual field sensitivity presented as a linear scale.

	Linear-linear model *
Cirrus SDOCT sector	R^2 (P value)
Superotemporal	0.314 (<0.001)
Inferotemporal	0.259 (<0.001)
Average	0.203 (<0.001)
Inferonasal	0.069 (<0.001)
Superonasal	0.056 (<0.001)
Temporal	0.037 (<0.001)
Nasal	0.007 (0.132)

* Regression model including RNFL thickness sectors in the linear scale and the average of corresponding total deviation points converted in a linear scale.