Published in final edited form as:

Optom Vis Sci. 2011 December ; 88(12): 1470–1476. doi:10.1097/OPX.0b013e3182303644.

Cup Size Predicts Subsequent Functional Change in Early Glaucoma

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Abstract

Purpose—To identify structural predictors of functional change in patients with early glaucoma or risk factors for development of glaucoma.

Methods—129 participants with either high-risk ocular hypertension, suspected or early glaucoma were followed for ten annual visits. Standard Automated Perimetry was performed at each visit, together with Confocal Scanning Laser Ophthalmoscopy (CSLO). Mean Deviation (MD) at the same visit, and the subsequent rate of change in MD, were predicted by linear regression models based on CSLO parameters together with intraocular pressure, central corneal thickness and treatment status. Models were assessed by comparing the correlations between predicted and observed perimetric results.

Results—The model using rim area predicted MD at the same visit with correlation 0.445. Using cup area the equivalent correlation was $r=0.411$, lower than the model using rim area with $p=0.096$. Using cup volume the correlation was $r=0.436$, and the comparison had $p=0.714$; using disc area $r=0.396$ and $p=0.011$. The model using rim area to predict the subsequent rate of change of MD had $r=0.539$. Models using cup area ($r=0.631$), cup volume ($r=0.649$) or disc area ($r=0.602$) were significantly better; $p=0.003$, $p=0.001$ and $p=0.044$ respectively.

Conclusions—Lower rim area, as measured by CSLO, is predictive of worse function when measured on the same date in participants with high-risk ocular hypertension, suspected and early glaucoma. However, cup area, cup volume and disc area may all be more predictive of the rate of subsequent functional change. Parameters should be chosen based on the specific purpose intended and questions asked, rather than using the same parameters in all circumstances.

Keywords

glaucoma; progression; perimetry; confocal scanning laser ophthalmoscopy

Glaucoma is the third leading cause of blindness in the USA, and the second leading cause worldwide.¹ Whether a patient's vision will deteriorate rapidly, slowly or remain relatively stable is one of the most important questions in glaucoma management.² It has been estimated that 15% of patients with glaucoma will have visual field damage within their lifetime that is so severe that it falls outside the dynamic range of automated perimetry.³ However, predicting the rate of progression remains challenging. This is partly because little is known about the exact course of the disease over time, due to there being limited information from well-controlled longitudinal studies, and due to the variability of currently

available testing methods. Individuals progress differently, and diagnostic test procedures are constantly being refined. While glaucoma is commonly diagnosed and followed using a combination of structural and functional tests, the most important practical issue for patients is loss of visual function and its impact on their quality of life and activities of daily living.^{4, 5} Therefore, predicting the rate of functional change remains a high priority. The most widely used functional test for glaucoma is Standard Automated Perimetry (SAP), in which contrast sensitivities for small white stimuli displayed on a uniform white background are measured at numerous locations throughout the visual field.⁶

Various factors have been reported to be associated with an increased probability of future progression, and/or the rate of future progression. These include higher Intraocular Pressure (IOP),^{2, 7–10} IOP fluctuation,^{7, 11} increased age^{3, 7–10} and being of a certain race,^{3, 9, 12} although some of these factors have been disputed.^{2, 10, 12, 13} It has also been reported that structural damage is often detectable before functional loss with the tools currently available,¹⁴ so it may be predictive of future functional change (although it has also been reported that for other patients functional loss is detectable first¹⁵). Given that measurements of structure are generally better tolerated by patients than visual field testing,¹⁶ it is appealing to use such tests as part of a prognostic evaluation. However, the agreement between structural and functional measures of progression is relatively weak,^{15, 17, 18} and individual patients can follow very different disease courses. Neuroretinal rim area in particular has been shown to be both globally and topographically correlated with retinal nerve fiber layer thickness and with function,^{19–21} and has been reported to be the structural parameter from Confocal Scanning Laser Ophthalmoscopy (CSLO) that is best related to current functional status.²² However, its usefulness as a predictor of subsequent functional progression is uncertain. The CSLO Ancillary Study to the Ocular Hypertension Treatment Study (OHTS) found that a decreased rim area, among other CSLO parameters, was predictive of reaching a primary open angle glaucoma endpoint.²³ However, the study incorporated not only functional but also structural endpoints (determined using the examination of stereophotographs). Perhaps more importantly, such an endpoint-based analysis is dependent not only on the stage of disease, but also on the exact endpoint used, and provides only limited information about the rate at which functional progression may occur. Therefore we aim to determine the utility of CSLO parameters to predict the rate of subsequent functional change.

In this study, we examine the relations between CSLO parameters and both the current functional status and the rate of subsequent functional change. Although clinical decisions are unlikely to be made based on the value of one index at a single time point, assessing the predictive strength of a measure can remove much of the uncertainty caused by confounding factors, and would be expected to be indicative of the utility of that measure in a more complete predictive model. Such a predictive model may be helpful in the management of patients over time.

METHODS

Data for this study was obtained from the Portland Progression Project, an ongoing longitudinal study of progression in participants with early and suspected glaucoma, at Devers Eye Institute in Portland, Oregon, USA. The protocol was approved by the Legacy Health Institutional Review Board. The study adheres to the tenets of the Declaration of Helsinki and complies with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Each participant provided written informed consent, after having the risks and benefits of participation explained to them.

Initially, participants were tested annually with a variety of structural and functional tests. In the last year, participants were tested at six-monthly intervals. Overall, the mean inter-visit interval was 352 days (interquartile range 343–380 days). At study entry, participants either had early glaucoma with visual field loss less severe than -6 dB for Mean Deviation (MD), or ocular hypertension (untreated IOP greater than 22mmHg on at least 2 occasions) plus one or more risk factors for glaucoma as determined by their clinician (e.g. age > 70, systemic hypertension, migraine, diet controlled diabetes, peripheral vasospasm, African ancestry or self-reported family history of glaucoma) and/or previously diagnosed glaucomatous optic neuropathy or suspicious optic nerve head appearance (cup-disc ratio asymmetry >0.2, neuroretinal rim notching or narrowing, disc hemorrhage).^{21, 24} Participants with other diseases or medications likely to affect the visual field, or who had undergone ocular surgery (except for uncomplicated cataract surgery), were excluded. Participants with SAP Mean Deviation (MD) worse than -6dB or with visual acuity worse than 20/40 in either eye at study entry were excluded to ensure that participants had no more than mild glaucoma and no worse than mild media change or cataract respectively.

SAP visual field testing was performed using a Humphrey Field Analyzer II⁶ (Carl Zeiss Meditec Inc, Dublin, CA, USA), employing the 24-2 test pattern and conventional test procedures. The SITA standard algorithm²⁵ was used for all testing. An optimal lens correction was placed before the tested eye, and the fellow eye was occluded with a translucent eye patch. All participants had previous experience with visual field testing prior to entering the study, and most had performed multiple previous tests. Visual field tests with >33% fixation losses, or false negatives or >15% false positives were excluded as being unreliable. CSLO optic nerve head scanning was performed using a Heidelberg Retina Tomograph Classic (a.k.a. HRT1; Heidelberg Engineering, GmbH, Heidelberg, Germany) and software version 3.15, following standard operating procedures.²⁶ Acceptable image quality (SD<25) was required for each scan, and contour lines were drawn by an experienced operator viewing the participant's entire sequence of scans. Intraocular pressure (IOP) was measured using Goldmann Applanation Tonometry (Haag-Streit, Bern, Switzerland) with the participant seated at a slit lamp. Central Corneal Thickness (CCT) was measured using an ultrasonic pachymeter (DGH Technology, Exton, PA, USA). Note that CCT was not always measured at the initial visit used for analysis, since it was introduced to the study protocol at a later stage. In these cases the first available reading was used (this was within two years of the initial visit in all cases). The age of the participant and their treatment status (whether or not they reported that they were taking IOP-reducing medication, used in preference to whether they had been prescribed medication due to the low compliance rates that have been reported²⁷) were recorded.

The study was designed to measure the ability of CSLO parameters from the first visit in a series to predict the MD on the same visit, and the subsequent rate of change of MD as determined by the slope of a linear regression of MD over time. The worst eye per participant was defined as the eye with the worst (i.e. most negative or least positive) rate of MD change, and this was the eye used for all subsequent analyses. Four CSLO parameters were considered: Rim Area, Cup Area, Cup Volume and Disc Area. For each parameter, four linear regression models were constructed:

1. Predict MD at visit 1 based on CSLO, Age, IOP, CCT and Treatment status at visit 1.
2. Predict rate of change of MD over visits 2–7 based on MD, CSLO, Age, IOP, CCT and Treatment status at visit 1.
3. Predict MD at visit 2 based on CSLO, Age, IOP, CCT and Treatment status at visit 2.

4. Predict rate of change of MD over visits 3–7 based on MD, CSLO, Age, IOP, CCT and Treatment status at visit 2.

Upon performing these regressions, Age was not found to be a significant predictor ($p > 0.05$ in all cases), and so was removed from the models (as expected, since MD is age referenced). IOP, CCT and Treatment status were found to be significant predictors in some but not all cases, but were retained in all models for consistency and to facilitate direct comparisons.

For inclusion in the first two analyses, participants were required to have performed visual field tests at seven or more visits (i.e. over approximately a six year period), along with CSLO testing at the first visit in the sequence. For inclusion in the third and fourth analyses, participants were required to have performed visual field tests at six or more visits (i.e. over approximately a five year period), along with CSLO testing at the first visit in this shorter sequence. In each case, if more than the minimum number of visits had taken place, data from the most recent visits meeting these requirements were used. Therefore, the third and fourth analyses included the participants eligible for the first two (seven-visit) analyses, using data from visits 2–7 of the longer sequence, together with participants with data available from only six visits (which will also be referred to as visits 2–7 for consistency). 113 participants were eligible for the first two (seven-visit) analyses, and an additional 16 participants were eligible for the third and fourth (six-visit) analyses giving a total of 129 participants. Although the estimate of rate of change of MD based on visits 2–7 is closely related to that based on visits 3–7 for each participant, it should be noted that none of the CSLO scans used for the first two analyses were also used for the third and fourth analyses. Therefore, the inclusion of the third and fourth analyses allows findings based on the first two analyses to be confirmed in a separate CSLO dataset, even though the outcome variables are not independent (and indeed the estimate of rate of change of MD based on visits 3–7 is less reliable since fewer time points are being used). Although this does not constitute a true validation of the results since it does not involve an independent dataset, it does provide some indication of the robustness of the findings.

For each regression model, the Pearson multiple correlation coefficient between the predicted and actual values of the outcome variable was recorded (equivalent to the square-root of the R^2 for the regression). These correlations were compared using the Z_2^* test statistic, which follows an asymptotic standard normal distribution $N(0,1)$ under the null hypothesis that the two correlations are equal.²⁸ While this reduces the power of the test to detect a difference when compared with using the simple Z statistic, it is more valid since it accounts for the fact that the correlations come from data drawn from the same participants.

RESULTS

Table 1 summarizes the dataset. The visual field index (VFI)²⁹ at visit 1 had a median value of 99.8%, indicating that the majority of the participants did not have sufficiently severe glaucoma to show damage or change over time by that index (the median change over the follow-up period was $-0.05\%/yr$). Indeed, the average MD was greater than zero at both visits 1 and 2. However, the average rate of change of MD was significantly worse than zero ($p < 0.001$, 95% confidence interval -0.29 to $-0.17dB/yr$), indicating that visual field change (most likely due to glaucoma) was occurring, even though the VFI was unable to detect this progression. Since MD is age-adjusted, a normal eye would be expected to have a rate of change of MD equal to zero. 108 of the 113 participants eligible for the seven-visit analyses had stereo optic disc photographs (3-Dx; Nidek Co., Ltd., Gamagori, Japan) taken upon study entry. Of these, 61 (56%) exhibited glaucomatous optic neuropathy as judged by two masked experienced clinicians.³⁰ The cup-to-disc area ratio, as measured by CSLO, averaged 0.3 at both visits 1 and 2.

Figure 1 plots the MD at visit 1 (upper plots), and the subsequent rate of change of MD over visits 2–7 (lower plots), against the values of each CSLO parameter (rim area, cup area, cup volume and disc area) at visit 1. Note that the data distribution is skewed. This may have an effect on the Pearson correlation. The ‘true’ level of correlation (such as would be obtained were the data to be transformed to give a Gaussian error distribution) is likely to be similar but not exactly the same; such a transformation has not been performed since it would be purely empirical with no physiological or pathophysiological underpinning. It should be noted that the skewness does not negate the p-values for comparisons among models, and so the conclusions below remain valid.

Table 2 presents the correlations achieved when using CSLO parameters from visit 1 to predict the MD at visit 1 and the rate of change of MD over visits 2–7, together with p-values showing whether the correlation was significantly different from using Rim Area as the predictive CSLO parameter. All correlations were significant with $p < 0.001$. It should be emphasized that the correlations reported are those between the predicted and actual values of MD / rate of change of MD in a model taking into account IOP and treatment status, rather than the direct correlation between the CSLO parameters and MD / rate of change of MD in a simplified model that does not take these factors into account. These correlations are equivalent to the square root of R^2 for the linear regression in each case; they are presented in this manner instead of as R^2 because the statistical comparison between models is based on correlations.

A worse MD, and a worse subsequent rate of change of MD, is associated with a decreased neuroretinal Rim Area but with an increased Cup Area, Cup Volume and Disc Area (although note that the correlations in Tables 2 and 3 are between the predicted and observed perimetric outcomes, rather than between the raw CSLO parameters and the observed perimetric outcomes, and so are all positive). Predictions made using different CSLO parameters were highly correlated. The correlations between predictions of MD at visit 1 made using Rim Area and those made using Cup Area / Cup Volume / Disc Area were 0.900, 0.883 and 0.895 respectively; and the correlations between predictions of rate of change of MD made using Rim Area and those made using Cup Area / Cup Volume / Disc Area were 0.862, 0.844 and 0.844 respectively.

Table 3 shows the equivalent results achieved when using CSLO parameters from visit 2 to predict the MD at visit 2 and the rate of change of MD over visits 3–7. Again, all correlations were significant with $p < 0.001$.

Rim Area may be a better predictor than Cup Area, Cup Volume or Disc Area of the MD at the same visit, although the comparison was not always statistically significant. However, use of the Z_2^* test statistic shows that the models using Rim Area provided significantly worse predictions of the subsequent rate of change of MD than models using these other measures.

DISCUSSION

The main conclusion to be drawn from these results is that the structural features best correlated with visual function at the same time point may not be the same features that are most predictive of subsequent functional change. This may imply that the features being considered do not change at the same point in the disease process. This is important not just clinically, but also when using cross-sectional data to answer questions about the longitudinal nature of the disease.

In this study, a large Cup Area, Cup Volume or Disc Area was more predictive of future functional change than reduced neuroretinal Rim Area. This may provide support for

changes to the topography of the cup occurring prior to the loss of retinal ganglion cell axons (which would be expected to be detectable as a reduction in Rim Area and concomitant loss of function). This hypothesis would be consistent with posterior bowing of the lamina cribrosa and/or enlargement of the scleral canal in early glaucoma, either diffusely or regionally, prior to substantial loss of retinal ganglion cells and their axons.^{31, 32}

Other CSLO parameters were also considered, with Cup Area and Cup Volume producing the best correlations between the actual and predicted subsequent rates of change of MD. In particular, the Cup-to-Disc ratio, which is highly correlated with Cup Area, showed an improvement in the correlation with subsequent rate of change in MD when compared with Rim Area ($r=0.607$, comparison has $p=0.011$). No parameters produced better correlations than Rim Area between the actual and predicted value of MD at the same time point, agreeing with the results of previous studies that recommended Rim Area as being correlated with function at the same time point.^{19–22}

Correlations between baseline CSLO parameters and the subsequent rate of functional change were not high enough to use as accurate predictors, without taking other factors into account. However, they were of the same magnitude as correlations between baseline MD and the subsequent rate of change in MD in the same dataset.³³ No adjustment was made for multiple comparisons,³⁴ and the small yet significant improvement in correlation observed when using Pearson correlations (which may be higher than the true correlations, since they assume a Gaussian error distribution which is unlikely to be exactly true) was not consistently significant when Spearman correlations (which are likely to underestimate the true correlations, since they assume no structure to the error distribution) were used. It is also possible that our findings would be different in a cohort of patients with more advanced disease or with different inclusion/exclusion criteria. Only 56% of participants exhibited glaucomatous optic neuropathy when entering the study. Using liberal criteria for the definition of glaucoma (repeatable glaucomatous optic neuropathy and/or progressive disc change and/or a visual field defect consistent with glaucomatous damage), 84% of participants had glaucoma in at least one eye, but more conservative criteria would obviously reduce this percentage. The findings as to exactly which CSLO parameters to use are potentially important, but they need to be confirmed in another dataset and/or in a prospective study.

A further caveat is that change in MD can result from developing cataract, in the absence of glaucomatous progression. The alternative Pattern Standard Deviation (PSD) index does not decline monotonically with damage; it increases with damage early in the disease process, but decreases again once pointwise sensitivities approach 0dB. We have previously shown that it is less predictable than MD.³³ These factors motivated the development of the VFI, based on pattern deviation rather than total deviation values, which aims to remove the effect of generalized loss. However, the VFI not only loses information concerning generalized glaucomatous loss, but is also insensitive to early glaucomatous damage, due to a pronounced ‘ceiling effect’.³⁵ VFI has been shown to be no better than MD at detecting progression,³⁶ and introduces extra sources of variability in moderate and severe damage,³⁷ and so may not be ideal for monitoring glaucomatous progression especially in early glaucoma where the ‘ceiling effect’ is prominent. In this dataset, the average VFI at visit 1 was 99.8%, and this ‘ceiling effect’ meant that very few participants were seen to progress by this measure. However, the mean rate of change in visual acuity was -0.006 LogMAR/yr, not significantly different from zero (t -test, $p=0.45$). Therefore it is unlikely that the changes in MD seen in this study were entirely due to worsening cataract.

Our main conclusion is that models that produce the best predictive outcomes for glaucomatous progression may not include the same structural features that best represent

the current status of the patient. The size of the cup may be more predictive of future functional progression than the amount of neuroretinal rim remaining, even though the latter may be better correlated with current functional status. The choice of structural (and indeed functional) parameters should be tailored to the specific purpose intended and question being asked, rather than using the same parameter in all circumstances.

Acknowledgments

This project was funded in part by NIH grants NEI R01-EY-03424 (to author CAJ) and NEI R01-EY-019674 (to author SD). No authors have any financial/conflicting interests to disclose.

References

1. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol*. 2006; 90:262–7. [PubMed: 16488940]
2. Kass MA, Gordon MO, Gao F, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JK, Miller JP, Parrish RK, Wilson MR. Delaying treatment of ocular hypertension: the ocular hypertension treatment study. *Arch Ophthalmol*. 2010; 128:276–87. [PubMed: 20212196]
3. Broman AT, Quigley HA, West SK, Katz J, Munoz B, Bandeen-Roche K, Tielsch JM, Friedman DS, Crowston J, Taylor HR, Varma R, Leske MC, Bengtsson B, Heijl A, He M, Foster PJ. Estimating the rate of progressive visual field damage in those with open-angle glaucoma, from cross-sectional data. *Invest Ophthalmol Vis Sci*. 2008; 49:66–76. [PubMed: 18172076]
4. McKean-Cowdin R, Varma R, Wu J, Hays RD, Azen SP. Severity of visual field loss and health-related quality of life. *Am J Ophthalmol*. 2007; 143:1013–23. [PubMed: 17399676]
5. McKean-Cowdin R, Wang Y, Wu J, Azen SP, Varma R. Impact of visual field loss on health-related quality of life in glaucoma: the Los Angeles Latino Eye Study. *Ophthalmology*. 2008; 115:941–8. [PubMed: 17997485]
6. Anderson, DR.; Patella, VM. *Automated Static Perimetry*. 2. St. Louis: Mosby; 1999.
7. Leske MC, Heijl A, Hussein M, Bengtsson B, Hyman L, Komaroff E. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. *Arch Ophthalmol*. 2003; 121:48–56. [PubMed: 12523884]
8. Nouri-Mahdavi K, Hoffman D, Coleman AL, Liu G, Li G, Gaasterland D, Caprioli J. Predictive factors for glaucomatous visual field progression in the Advanced Glaucoma Intervention Study. *Ophthalmology*. 2004; 111:1627–35. [PubMed: 15350314]
9. Gordon MO, Beiser JA, Brandt JD, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JL, Miller JP, Parrish RK 2nd, Wilson MR, Kass MA. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. *Arch Ophthalmol*. 2002; 120:714–20. [PubMed: 12049575]
10. Friedman DS, Wilson MR, Liebmann JM, Fechtner RD, Weinreb RN. An evidence-based assessment of risk factors for the progression of ocular hypertension and glaucoma. *Am J Ophthalmol*. 2004; 138:S19–31. [PubMed: 15364049]
11. Hong S, Seong GJ, Hong YJ. Long-term intraocular pressure fluctuation and progressive visual field deterioration in patients with glaucoma and low intraocular pressures after a triple procedure. *Arch Ophthalmol*. 2007; 125:1010–3. [PubMed: 17698746]
12. Drance S, Anderson DR, Schulzer M. Risk factors for progression of visual field abnormalities in normal-tension glaucoma. *Am J Ophthalmol*. 2001; 131:699–708. [PubMed: 11384564]
13. Bengtsson B, Leske MC, Hyman L, Heijl A. Fluctuation of intraocular pressure and glaucoma progression in the early manifest glaucoma trial. *Ophthalmology*. 2007; 114:205–9. [PubMed: 17097736]
14. Johnson CA, Cioffi GA, Liebmann JR, Sample PA, Zangwill LM, Weinreb RN. The relationship between structural and functional alterations in glaucoma: a review. *Semin Ophthalmol*. 2000; 15:221–33. [PubMed: 17585436]
15. Keltner JL, Johnson CA, Anderson DR, Levine RA, Fan J, Cello KE, Quigley HA, Budenz DL, Parrish RK, Kass MA, Gordon MO. The association between glaucomatous visual fields and optic

- nerve head features in the Ocular Hypertension Treatment Study. *Ophthalmology*. 2006; 113:1603–12. [PubMed: 16949445]
16. Gardiner SK, Demirel S. Assessment of patient opinions of different clinical tests used in the management of glaucoma. *Ophthalmology*. 2008; 115:2127–31. [PubMed: 19041473]
 17. Chauhan BC, McCormick TA, Nicolela MT, LeBlanc RP. Optic disc and visual field changes in a prospective longitudinal study of patients with glaucoma: comparison of scanning laser tomography with conventional perimetry and optic disc photography. *Arch Ophthalmol*. 2001; 119:1492–9. [PubMed: 11594950]
 18. Alencar LM, Zangwill LM, Weinreb RN, Bowd C, Sample PA, Girkin CA, Liebmann JM, Medeiros FA. A comparison of rates of change in neuroretinal rim area and retinal nerve fiber layer thickness in progressive glaucoma. *Invest Ophthalmol Vis Sci*. 2010; 51:3531–9. [PubMed: 20207973]
 19. Airaksinen PJ, Drance SM. Neuroretinal rim area and retinal nerve fiber layer in glaucoma. *Arch Ophthalmol*. 1985; 103:203–4. [PubMed: 3977690]
 20. Anton A, Yamagishi N, Zangwill L, Sample PA, Weinreb RN. Mapping structural to functional damage in glaucoma with standard automated perimetry and confocal scanning laser ophthalmoscopy. *Am J Ophthalmol*. 1998; 125:436–46. [PubMed: 9559728]
 21. Gardiner SK, Johnson CA, Cioffi GA. Evaluation of the structure-function relationship in glaucoma. *Invest Ophthalmol Vis Sci*. 2005; 46:3712–7. [PubMed: 16186353]
 22. Iester M, Mikelberg FS, Courtright P, Drance SM. Correlation between the visual field indices and Heidelberg retina tomograph parameters. *J Glaucoma*. 1997; 6:78–82. [PubMed: 9098814]
 23. Zangwill LM, Weinreb RN, Beiser JA, Berry CC, Cioffi GA, Coleman AL, Trick G, Liebmann JM, Brandt JD, Piltz-Seymour JR, Dirkes KA, Vega S, Kass MA, Gordon MO. Baseline topographic optic disc measurements are associated with the development of primary open-angle glaucoma: the Confocal Scanning Laser Ophthalmoscopy Ancillary Study to the Ocular Hypertension Treatment Study. *Arch Ophthalmol*. 2005; 123:1188–97. [PubMed: 16157798]
 24. Spry PG, Johnson CA, Mansberger SL, Cioffi GA. Psychophysical investigation of ganglion cell loss in early glaucoma. *J Glaucoma*. 2005; 14:11–9. [PubMed: 15650598]
 25. Bengtsson B, Olsson J, Heijl A, Rootzen H. A new generation of algorithms for computerized threshold perimetry, SITA. *Acta Ophthalmol Scand*. 1997; 75:368–75. [PubMed: 9374242]
 26. Fingeret, M.; Flanagan, JG.; Liebmann, JM., editors. *The Essential HRT Primer*. San Ramon, CA: Jocoto Advertising, Inc; 2005.
 27. Patel SC, Spaeth GL. Compliance in patients prescribed eyedrops for glaucoma. *Ophthalmic Surg*. 1995; 26:233–6. [PubMed: 7651690]
 28. Steiger JH. Tests for comparing elements of a correlation matrix. *Psychol Bull*. 1980; 87:245–51.
 29. Bengtsson B, Heijl A. A visual field index for calculation of glaucoma rate of progression. *Am J Ophthalmol*. 2008; 145:343–53. [PubMed: 18078852]
 30. Fortune B, Demirel S, Zhang X, Hood DC, Patterson E, Jamil A, Mansberger SL, Cioffi GA, Johnson CA. Comparing multifocal VEP and standard automated perimetry in high-risk ocular hypertension and early glaucoma. *Invest Ophthalmol Vis Sci*. 2007; 48:1173–80. [PubMed: 17325161]
 31. Bellezza AJ, Rintalan CJ, Thompson HW, Downs JC, Hart RT, Burgoyne CF. Deformation of the lamina cribrosa and anterior scleral canal wall in early experimental glaucoma. *Invest Ophthalmol Vis Sci*. 2003; 44:623–37. [PubMed: 12556392]
 32. Yang H, Downs JC, Girkin C, Sakata L, Bellezza A, Thompson H, Burgoyne CF. 3-D histomorphometry of the normal and early glaucomatous monkey optic nerve head: lamina cribrosa and peripapillary scleral position and thickness. *Invest Ophthalmol Vis Sci*. 2007; 48:4597–607. [PubMed: 17898283]
 33. Gardiner SK, Demirel S, Johnson CA. Perimetric indices as predictors of future glaucomatous functional change. *Optom Vis Sci*. 2011; 88:56–62. [PubMed: 20966804]
 34. Perneger TV. What's wrong with Bonferroni adjustments. *BMJ*. 1998; 316:1236–8. [PubMed: 9553006]
 35. Artes PH, Chauhan BC. Properties of the Statpac Visual Field Index (VFI). *Invest Ophthalmol Vis Sci*. 2010; 51:E-Abstract 5494.

36. Artes PH, O'Leary N, Hutchison DM, Heckler L, Sharpe GP, Nicolela MT, Chauhan BC. Properties of the Statpac Visual Field Index. *Invest Ophthalmol Vis Sci*. 2011; 52:4030–8. [PubMed: 21467169]
37. Doss LE, Mock D, Kwong A, Shaikh Y, Coleman AL, Nouri-Mahdavi K, Caprioli J. The Visual Field Index (VFI) behaves erratically near the advanced field loss mean deviation value. *Invest Ophthalmol Vis Sci*. 2011; 52:E-Abstract 5495.

Figure 1. Plots of the Mean Deviation (MD, in dB) at visit 1, and the subsequent rate of change of MD over visits 2–7, against four structural parameters measured at visit 1 (from left to right: rim area (mm^2), cup area (mm^2), cup volume (mm^3), disc area (mm^2)).

Table 1

Characteristics of the dataset. For PSD and VFI, medians are given (indicated by *) due to the non-normality of the data; for other measures, the mean is given. The rate of change of MD subsequent to visit 1 is defined by the slope of linear regression of MD over time in visits 2–7; the rate of change subsequent to visit 2 is defined by regression over visits 3–7. “% Treated” represents those participants who reported that they had been prescribed and were taking intraocular pressure reducing medication.

Parameter	Visit 1		Visit 2	
	Average	Standard Deviation	Average	Standard Deviation
Mean Deviation (MD) (dB)	1.26	2.17	0.95	2.33
Pattern Standard Deviation (PSD) (dB)	1.58*	2.02	1.65 *	2.08
Visual Field Index (VFI) (%)	99.8*	4.8	99.8 *	5.1
Subsequent rate of change of MD (dB/yr)	−0.23	0.33	−0.25	0.36
Rim Area (mm ²)	1.53	0.37	1.51	0.36
Cup-to-Disc Ratio	0.29	0.17	0.30	0.17
Age (years)	60.6	10.0	61.5	9.9
Intraocular Pressure (mmHg)	17.9	3.5	17.7	3.3
% Treated	49%		46%	

Table 2

Correlations between the values of Mean Deviation (MD) at visit 1, or the rate of change of MD over visits 2–7, predicted by regression models using each Confocal Scanning Laser Ophthalmoscopy (CSLO) parameter as a predictor along with Intraocular Pressure, Central Corneal Thickness and Treatment status, with the actual values. The p-values given are for a comparison of the correlation with that achieved using Rim Area as the predictor; all individual-model correlations had $p < 0.001$.

Predictor	MD at visit 1		Rate of change of MD in visits 2–7	
	Correlation	p	Correlation	p
Rim Area	0.445		0.539	
Cup Area	0.411	0.096	0.631	0.003
Cup Volume	0.436	0.714	0.649	0.001
Disc Area	0.396	0.011	0.602	0.044

Table 3

Correlations between the values of Mean Deviation (MD) at visit 2, or the rate of change of MD over visits 3–7, predicted by regression models using each Confocal Scanning Laser Ophthalmoscopy (CSLO) parameter as a predictor along with Intraocular Pressure, Central Corneal Thickness and Treatment status, with the actual values. As in Table 2, the p-values given are for a comparison of the correlation with that achieved using Rim Area as the predictor.

Predictor	MD at visit 2		Rate of change of MD in visits 3–7	
	Correlation	p	Correlation	p
Rim Area	0.421		0.329	
Cup Area	0.370	0.083	0.409	0.029
Cup Volume	0.400	0.495	0.423	0.014
Disc Area	0.318	0.001	0.370	0.320