Published in final edited form as:

Curr Opin Pharmacol. 2013 February ; 13(1): 115–122. doi:10.1016/j.coph.2012.10.010.

Combining Structure and Function to Evaluate Glaucomatous Progression: Implications for the Design of Clinical Trials

Renato Lisboa, M.D.^{1,2}, Robert N. Weinreb, M.D.¹, and Felipe A. Medeiros, M.D., Ph.D.¹

¹Hamilton Glaucoma Center and Department of Ophthalmology, University of California, San Diego

²Federal University of São Paulo, Department of Ophthalmology, Brazil

Abstract

The selection of a suitable method for assessment of glaucomatous progression and estimation of rates of change is an essential component of the design of clinical trials investigating neuroprotective therapies for the disease. Due to the limitations of currently available tests, approaches combining structural and functional tests are essential in order to provide reliable detection of endpoints. This could also potentially enable shorter clinical trials with relatively smaller sample size requirements. A recent approach for estimating rates of retinal ganglion cell loss using a combination of structural and functional tests has been shown to perform better than isolated parameters from conventional tests for diagnosing, staging and detecting glaucoma progression and may prove useful as an outcome measure in clinical trials of the disease.

Introduction

Glaucoma is a leading cause of irreversible blindness and visual impairment in the world. The disease is characterized by progressive retinal ganglion cell (RGC) losses with associated characteristic structural changes at the level of the optic nerve and retinal nerve fiber layer which may lead to loss of visual function. The fundamental goal of glaucoma management is to prevent patients from developing visual impairment that is sufficient to produce disability in their daily lives and impair their health-related quality of life. However, due to the generally slowly progressive course of glaucoma, direct observation of disability endpoints is generally unfeasible for clinical trials testing new treatments for the disease.

This review discusses limitations of endpoints traditionally used in clinical trials involving glaucoma patients. It also discusses developments in the field, such as the proposed use of structural measurements of the optic disc and retinal nerve fiber layer for assessing

© 2012 Elsevier Ltd. All rights reserved.

Corresponding author: Felipe A. Medeiros, M.D., Ph.D. Hamilton Glaucoma Center University of California, San Diego 9500 Gilman Drive, La Jolla, CA 92093 fmedeiros@glaucoma.ucsd.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Financial Disclosure(s):

The author(s) have made the following disclosure(s):

Renato Lisboa – None

Robert N. Weinreb – Research Support from Carl-Zeiss Meditec, Inc; Consultant to Carl-Zeiss Meditec, Inc.

Felipe A. Medeiros – Research Support from Carl-Zeiss Meditec, Inc

progressive glaucomatous damage, emphasizing their combined use along with functional measurements as a potential endpoint in the disease.

Limitations of current endpoints

Although intraocular pressure (IOP) has traditionally been used as an endpoint in clinical trials, it is an imperfect surrogate for the clinically relevant outcomes of the disease. Many patients can progress despite low IOP levels and others remain stable despite having IOP measurements that are consistently high.¹⁻³ Further, IOP is not a suitable endpoint for clinical trials investigating certain treatment modalities for glaucoma, such as neuroprotective therapies. The use of visual fields as the sole endpoint in glaucoma trials is also potentially limited by the need for large samples, long-term follow-up and variability of results.⁴ In the past two decades, a large bulk of evidence has accumulated with regard to the role of structural measurements of the optic disc and retinal nerve fiber layer (RNFL) for diagnosing and detecting glaucoma progression. There is now substantial evidence that many patients can develop structural changes before appearance of detectable change in functional measures.⁵⁻¹² Several studies have shown that optic disc and RNFL assessment by different imaging technologies such as optical coherence, confocal scanning laser ophthalmoscopy and scanning laser polarimetry can provide objective and reliable assessment of rates of structural change in the disease. The use of structural measurements as surrogate endpoints in glaucoma clinical trials would have a number of advantages, including faster acquisition of a sufficient number of endpoints with reduction in sample size requirements, enabling shorter and less expensive trials.

The Structure and Function Relationship in Glaucoma and Implications for Detection of Progression

Frequent disagreements are seen when structural and functional tests are used to monitor glaucoma patients for progression and this has led to confusion in the literature and among clinicians. These disagreements, however, are easily reconciled when one understands the nature of the structure and function relationship in the disease.¹³ In fact, the very existence of disagreements is what makes it beneficial to employ combined approaches using both structure and function to increase the number of endpoints in clinical trials of the disease. The apparent disagreement between structural and functional measurements of the disease seem to be largely derived from the different algorithms and measurement scales as well as the different variability characteristics of the tests commonly used to assess structural and functional losses.¹³⁻¹⁵ In fact, Harwerth and colleagues¹⁴ demonstrated that structural and functional tests are in agreement as long as one uses appropriate measurement scales for neural and sensitivity losses and considers factors such as the effect of aging and eccentricity on estimates of neural losses. In a series of investigations, they demonstrated that estimates of RGC losses obtained from clinical standard automated perimetry (SAP) agreed closely with estimates of RGC losses obtained from RNFL assessment by optical coherence tomography.¹⁴ The results of their model provided a common domain for expressing results of structural and functional tests, i.e., the estimates of RGC losses, opening the possibility of combining these different tests to improve the reliability and accuracy of estimates of the amount of neural losses and develop a combined index for staging and detecting glaucomatous progression that could be used in clinical trials.

Combining Structure and Function to Diagnose and Stage Glaucomatous Damage

A combined structure and function index (CSFI) was described by Medeiros et al¹⁶ with the purpose of merging the results of structural and functional tests into a single index that could

be used for diagnosis, staging and detecting glaucomatous progression. The index uses estimates of RGC counts obtained by previously derived empirical formulas. The estimates of RGC counts are obtained from two sources: one structural, RNFL thickness assessment optical coherence tomography; and one functional, standard automated perimetry. These estimates are then combined using a weighted average to provide a single estimate of the RGC count for a particular eye. For each eye, the CSFI represents the percent estimate of RGC loss compared with the age-expected number of RGCs (Figure 1). By combining structural and functional tests into a single estimate of RGC loss, the index provides a very intuitive parameter to be used in clinical practice.

The CSFI has been shown to perform better than isolated structural and functional parameters for diagnosing and staging glaucomatous damage. Medeiros et al.¹⁶ evaluated the CSFI performance in a cross-sectional study involving 333 glaucomatous eyes and 165 healthy subjects. From the 333 glaucomatous eyes, 295 (89%) had perimetric glaucoma and 38 (11%) had preperimetric glaucoma. The mean CSFI, representing the mean estimated percent loss of RGCs, was 41% and 17% in the perimetric and preperimetric groups, respectively. The index had excellent diagnostic performance to detect glaucomatous eyes, with an area under the receiver operating characteristic (ROC) curve of 0.94. The index was also able to successfully detect eyes with pre-perimetric glaucoma, with ROC curve area of 0.85. This compared favorably to the usual parameters provided by SAP and spectral domain optical coherence tomography (OCT). Figure 1 shows an example of an eye with preperimetric glaucomatous damage. This eye had evidence of documented progressive optic disc glaucomatous damage on stereophotographs. However, the visual field exam was still within normal limits. Results of the OCT exam showed superior and inferior RNFL thinning, with global average thickness of 62µm. The CSFI for this eye was 41%, indicating an estimated 41% loss of RGCs compared to what would be expected for the age. This case illustrates the significant amount of RGC loss that can occur despite statistically normal visual fields.

The CSFI was also shown to successfully stage different degrees of glaucomatous damage, which is an essential requirement for any method proposed to detect disease progression over time. To separate eyes with early from moderate visual field loss, the CSFI had ROC curve area of 0.94 compared to only 0.77 for spectral-domain OCT average thickness ($P<0.001$). Similarly, for separating moderate from advanced glaucomatous field loss, the ROC curve area of the CSFI was 0.96, which was again significantly better than that for average RNFL thickness (ROC area = 0.70; $P<0.001$). Figure 2 illustrates two eyes with different degrees of visual field loss (MDs of -13.3dB and -24.5dB) successfully discriminated by the CSFI but not by OCT results.

Some potential limitations of the CSFI are worth noting. The CSFI used empirically-derived formulas to estimate the number of RGCs from SAP and OCT data based on previous experimental studies in monkeys.¹⁴ Although estimates obtained from these formulas have been validated in multiple external cohorts including human data,¹⁴ no studies have compared actual CSFI estimates with histological estimates of human glaucomatous eyes. It should be noted that there have been little to no histological validations of measures such as ganglion cell complex or even RNFL thickness as performed by OCT instruments. However, this carries little significance as long as one shows that these measurements have clinical relevance. Also, the original formula for estimating RGCs from OCT data was based on an older version of the OCT technology, time-domain OCT. It is possible that modifications might be necessary when using estimates based on spectral domain (SDOCT) technology. Another potential limitation of the index is that the presence of media opacities could potentially affect SAP-derived estimates of RGCs and, therefore, calculations of the CSFI. This is a potential limitation of most visual field-based staging systems, as they

usually base their classifications at least in part on values of the MD index. However, by combining functional and structural measurements, the approach potentially reduces the effect of media opacities by relatively decreasing the influence of SAP-derived data on the final estimates of neuronal losses. Nevertheless, clinicians should be aware of the effect of media opacities when evaluating functional changes and quality of imaging test results in glaucoma patients.

Combining Structure and Function to Assess Glaucoma Progression

As described above, frequent disagreements are seen when structural and functional tests are used to detect glaucomatous progression.¹³ While SAP has relatively low sensitivity to identify progression at initial stages of the disease, structural assessment often performs poorly to identify change at advanced stages of damage.¹³ Differences in performance of structural and functional tests have been recently investigated in a study comparing structural and functional measurements to estimates of RGC counts in glaucoma.¹³ In that study, analysis of the relationship between visual field data and RGC counts indicated that, at early stages of the disease, significant losses of RGCs would correspond to relatively small changes in visual field parameters. This finding agrees with the large amount of evidence indicating that progressive optic disc or RNFL changes can frequently be seen before the appearance of statistically significant defects on SAP.^{1, 3, 5-7, 12, 15, 17, 18} Scaling of perimetric stimulus intensities has been incorporated into standard perimetric testing, where the stimulus intensities are scaled by a logarithmic transformation to decibel units of attenuation for both the intensity staircase procedure for threshold measurements as well as for the report of the final threshold intensity. Several investigators have suggested that such scaling may introduce an artifactual relationship between structural and functional measurements in glaucoma.^{15, 17, 19, 20} The logarithmic scale would accentuate sensitivity changes in the visual field at low decibel values and minimize changes at high decibel levels, so that perimetry would be more suitable for detection of moderate to severe damage. On the other hand, analysis of the relationship between RNFL thickness and estimated RGC counts indicated that imaging instruments could be used to gauge information on rates of neural losses in early disease, when SAP evaluation can be misleading. However, at moderate to severe stages of the disease, evaluation of progressive damage with SDOCT becomes less helpful when the instrument reaches a floor level where it cannot detect further changes anymore.

Approaches combining structure and function can take advantage of the different performance of these tests according to the stage of damage in order to provide a reliable method for detecting change throughout the spectrum of the disease. It is important to emphasize that an optimal method for detecting glaucomatous progression should not only give an indication of whether or not the eye is changing over time, but also should estimate the rate of deterioration. Although most glaucoma patients will show some evidence of progression if followed long enough, the rate of deterioration can be highly variable among them.²¹⁻²⁵ While most patients progress relatively slowly, others have aggressive disease with fast deterioration that can eventually result in blindness or substantial impairment unless appropriate interventions take place. The use of rates of change as the outcome variable may also result in decreased sample size requirements compared to the use of categorical classifications.

Estimates of RGC counts from a combination of structural and functional tests have been shown to be able to detect glaucomatous progression and estimate rates of disease deterioration.²⁶ In a longitudinal study of 213 eyes followed for an average of 4.5 years, 47 (22.1%) showed statistically significant rates of estimated RGC loss that were faster than the age-expected decline. The mean rate of estimated RGC loss in these eyes was -33369 cells/

year (range: –8332 cells/year to –80636 cells/year). In addition, estimates of RGC losses detected a significantly larger number of progressing eyes compared to isolated measures of function and structure at the same specificity level.²⁶

Figures 3 and 4 illustrate detection of glaucoma progression using estimated RGC counts. Figure 3 shows an example of an eye with preperimetric damage that was detected as progressing by the rate of RGC loss and by the rate of global RNFL thickness change, but not by visual fields. In contrast, Figure 4 shows an example of an eye that was detected as progressing by rate of RGC loss and by rate of visual field loss, but not by global RNFL thickness.

Limitations of the CSFI for staging the disease as described above would also apply for detection of glaucomatous progression over time, such as the possible influence of media opacities. In addition, original calculations of estimated RGC counts and CSFI have only considered global measurements. Due to the localized aspect of glaucomatous damage in many eyes, it is possible that a sectorial approach focusing on detection of localized RGC losses may improve detection of progressive damage.

Other approaches have been suggested to combine structural and functional tests to detect glaucomatous progression, including the use of Bayesian methodologies to allow combination of different tests.^{27, 28} These approaches are effective in combining results of different tests to improve the estimates of rate of change and have the advantage of being capable of incorporating other covariates, such as demographic and clinical risk factors, to increase the accuracy and precision of the estimates.²⁹ However, Bayesian analyses have the disadvantage of not being intuitive for the majority of clinicians. Further studies are necessary to evaluate which approach provides the best use of resources for clinical trials in glaucoma.

Conclusion

The use of combined approaches potentially provides a more effective means for detection of glaucoma progression and estimation of rates of change than structural or functional testing alone. Combined approaches also may provide more reliable identification of endpoints, potentially reducing sample size requirements for clinical trials investigating new therapies to prevent glaucomatous progression. A recently described approach estimating rates of retinal ganglion cell loss from a combination of structural and functional tests offers promise as a method for diagnosing, staging, detecting progression and estimating rates of glaucomatous deterioration. Its use in clinical trials may potentially overcome the limitations of currently available conventional parameters.

Acknowledgments

Supported in part by NIH/NEI grants EY021818 (FAM) and an unrestricted grant from Research to Prevent Blindness (New York, NY)

REFERENCES

1. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol.* 2002; 120(6):701–13. discussion 829-30. [PubMed: 12049574]
2. Drance SM. The Collaborative Normal-Tension Glaucoma Study and some of its lessons. *Can J Ophthalmol.* 1999; 34(1):1–6. [PubMed: 10088056]

3. Miglior S, Zeyen T, Pfeiffer N, et al. Results of the European Glaucoma Prevention Study. *Ophthalmology*. 2005; 112(3):366–75. [PubMed: 15745761]
4. Katz J, Congdon N, Friedman DS. Methodological variations in estimating apparent progressive visual field loss in clinical trials of glaucoma treatment. *Arch Ophthalmol*. 1999; 117(9):1137–42. [PubMed: 10496384]
5. Leung CK, Cheung CY, Weinreb RN, et al. Evaluation of retinal nerve fiber layer progression in glaucoma: a study on optical coherence tomography guided progression analysis. *Invest Ophthalmol Vis Sci*. 2010; 51(1):217–22. [PubMed: 19684001]
6. Medeiros FA, Alencar LM, Zangwill LM, et al. Prediction of functional loss in glaucoma from progressive optic disc damage. *Arch Ophthalmol*. 2009; 127(10):1250–6. [PubMed: 19822839]
7. Strouthidis NG, Scott A, Peter NM, Garway-Heath DF. Optic disc and visual field progression in ocular hypertensive subjects: detection rates, specificity, and agreement. *Invest Ophthalmol Vis Sci*. 2006; 47(7):2904–10. [PubMed: 16799032]
8. Medeiros FA, Zangwill LM, Alencar LM, et al. Detection of glaucoma progression with stratus OCT retinal nerve fiber layer, optic nerve head, and macular thickness measurements. *Invest Ophthalmol Vis Sci*. 2009; 50(12):5741–8. [PubMed: 19815731]
9. Medeiros FA, Zangwill LM, Alencar LM, et al. Rates of progressive retinal nerve fiber layer loss in glaucoma measured by scanning laser polarimetry. *Am J Ophthalmol*. 2010; 149(6):908–15. [PubMed: 20378095]
10. Medeiros FA, Zangwill LM, Bowd C, et al. Use of progressive glaucomatous optic disk change as the reference standard for evaluation of diagnostic tests in glaucoma. *Am J Ophthalmol*. 2005; 139(6):1010–8. [PubMed: 15953430]
11. Leung CK, Chiu V, Weinreb RN, et al. Evaluation of retinal nerve fiber layer progression in glaucoma: a comparison between spectral-domain and time-domain optical coherence tomography. *Ophthalmology*. 2011; 118(8):1558–62. [PubMed: 21529954] * This study shows the potential benefit of the newer spectral-domain optical coherence technology compared to time-domain technology for detection of glaucomatous progression.
12. Wollstein G, Schuman JS, Price LL, et al. Optical coherence tomography longitudinal evaluation of retinal nerve fiber layer thickness in glaucoma. *Arch Ophthalmol*. 2005; 123(4):464–70. [PubMed: 15824218]
13. Medeiros FA, Zangwill LM, Bowd C, et al. The Structure and Function Relationship in Glaucoma: Implications for Detection of Progression and Measurement of Rates of Change. *Invest Ophthalmol Vis Sci*. 2012
14. Harwerth RS, Wheat JL, Fredette MJ, Anderson DR. Linking structure and function in glaucoma. *Prog Retin Eye Res*. 2010; 29(4):249–71. [PubMed: 20226873] ** Excellent review of the relationship between results of different structural and functional tests in glaucoma supported by extensive experimental studies.
15. Hood DC, Kardon RH. A framework for comparing structural and functional measures of glaucomatous damage. *Prog Retin Eye Res*. 2007; 26(6):688–710. [PubMed: 17889587]
16. Medeiros FA, Lisboa R, Weinreb RN, et al. A combined index of structure and function for staging glaucomatous damage. *Arch Ophthalmol*. 2012; 130(5):E1–10. [PubMed: 22826832] ** This is the first study in the literature describing a single index for estimating retinal ganglion cell counts from a combination of structural and functional tests in glaucoma. The index was shown to successfully diagnose and stage the disease.
17. Harwerth RS, Carter-Dawson L, Smith EL 3rd, et al. Neural losses correlated with visual losses in clinical perimetry. *Invest Ophthalmol Vis Sci*. 2004; 45(9):3152–60. [PubMed: 15326134]
18. Medeiros FA, Alencar LM, Zangwill LM, et al. The Relationship between intraocular pressure and progressive retinal nerve fiber layer loss in glaucoma. *Ophthalmology*. 2009; 116(6):1125–33. e1–3. [PubMed: 19376584]
19. Garway-Heath DF, Caprioli J, Fitzke FW, Hitchings RA. Scaling the hill of vision: the physiological relationship between light sensitivity and ganglion cell numbers. *Invest Ophthalmol Vis Sci*. 2000; 41(7):1774–82. [PubMed: 10845598]

20. Swanson WH, Felius J, Pan F. Perimetric defects and ganglion cell damage: interpreting linear relations using a two-stage neural model. *Invest Ophthalmol Vis Sci*. 2004; 45(2):466–72. [PubMed: 14744886]
21. Medeiros FA, Alencar LM, Zangwill LM, et al. The Relationship between intraocular pressure and progressive retinal nerve fiber layer loss in glaucoma. *Ophthalmology*. 2009; 116(6):1125–33. e1–3. [PubMed: 19376584]
22. Weinreb RN, Khaw PT. Primary open-angle glaucoma. *Lancet*. 2004; 363(9422):1711–20. [PubMed: 15158634]
23. Anderson DR, Drance SM, Schulzer M. Natural history of normal-tension glaucoma. *Ophthalmology*. 2001; 108(2):247–53. [PubMed: 11158794]
24. Heijl A, Bengtsson B, Hyman L, Leske MC. Natural history of open-angle glaucoma. *Ophthalmology*. 2009; 116(12):2271–6. [PubMed: 19854514]
25. Medeiros FA, Zangwill LM, Alencar LM, et al. Rates of progressive retinal nerve fiber layer loss in glaucoma measured by scanning laser polarimetry. *Am J Ophthalmol*. 2010; 149(6):908–15. [PubMed: 20378095]
26. Medeiros FA, Zangwill LM, Anderson DR, et al. Estimating the Rate of Retinal Ganglion Cell Loss in Glaucoma. *Am J Ophthalmol*. 2012 ** First study in the literature to apply estimated retinal ganglion cell counts for detection of glaucomatous progression and estimating of rates of disease deterioration. The estimated retinal ganglion cell counts were obtained from a combination of structural and functional tests and performed better than conventional parameters for detection of change over time.
27. Medeiros FA, Leite MT, Zangwill LM, Weinreb RN. Combining structural and functional measurements to improve detection of glaucoma progression using Bayesian hierarchical models. *Invest Ophthalmol Vis Sci*. 2011; 52(8):5794–803. [PubMed: 21693614]
28. Russell RA, Malik R, Chauhan BC, et al. Improved estimates of visual field progression using bayesian linear regression to integrate structural information in patients with ocular hypertension. *Invest Ophthalmol Vis Sci*. 2012; 53(6):2760–9. [PubMed: 22467579]
29. Medeiros FA, Zangwill LM, Mansouri K, et al. Incorporating risk factors to improve the assessment of rates of glaucomatous progression. *Invest Ophthalmol Vis Sci*. 2012; 53(4):2199–207. [PubMed: 22410555]

Highlights

An index combining structural and functional glaucoma assessment has been developed

The combined index estimates retinal ganglion cell damage

The index performed well for diagnosing and detecting disease progression

The combined approach may be useful as an outcome measure in clinical trials

FIGURE 1.

Example of an eye with preperimetric glaucomatous damage. The eye had evidence of progressive optic disc damage on stereophotographs (superior and inferior rim thinning), but still had a visual field exam with parameters within statistically normal limits. Results of the spectral-domain optical coherence tomography (SDOCT) exam show superior and inferior retinal nerve fiber layer (RNFL) thinning with a global RNFL thickness of 62 μ m. The combined structure and function index (CSFI) was 41%, indicating a loss of 41% of retinal ganglion cells compared to the age-expected normal number. RNFL = retinal nerve fiber layer; SDOCT = spectral domain optical coherence tomography; CSFI = combined structure and function index; VFI = visual field index; MD = mean deviation; PSD = pattern standard deviation; GHT = glaucoma hemifield test; SITA Standard 24-2. Swedish Interactive Threshold Algorithm; dB = decibels; ASB = apostilbs

FIGURE 2.

Example of two eyes with advanced glaucoma (A and B). Both eyes had identical measurements of RNFL thickness of 56 μm , despite widely different degrees of visual field loss. One eye had a MD of -13.33 dB (A) and the other one had a MD of -24.47 dB (B). The CSFI showed clearly different results for the two eyes, with values of 74% for A and 91% for B. RNFL = retinal nerve fiber layer; MD = mean deviation; CSFI = combined structure and function index.

FIGURE 3.

Example of an eye detected as progressing by the rate of retinal ganglion cell loss with a slope of $-52,902$ cells/year ($P < 0.05$), and by global RNFL thickness with a slope of $-3.2\mu\text{m}/\text{year}$. Assessment of rates of visual field change with the visual field index was unable to detect significant change ($P > 0.05$). RNFL = retinal nerve fiber layer. The eye had clear progression confirmed by longitudinal assessment of optic disc stereophotographs.

FIGURE 4.

Example of an eye detected as progressing by the rate of retinal ganglion cell loss with a slope of $-65,990$ cells/year ($P < 0.05$); and by the rate of visual field loss, with a slope of $-1.8\%/year$ ($P < 0.05$). The optical coherence tomography parameter global RNFL thickness did not show a statistically significant slope ($P > 0.05$).