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The Evolving Role of the Relationship between Optic Nerve Structure and Function in Glaucoma

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The relationship between functional vision loss and structural changes of the optic nerve head and retinal ganglion cells is the hallmark of glaucoma diagnosis. Understanding and measuring this relationship has been the focus of numerous studies, the goal of which have been to improve glaucoma diagnosis and detection of glaucoma worsening. In this review, a historical perspective is used to understand structure–function relationships in glaucoma and their application to improve glaucoma diagnosis and monitoring. Initially, histologic studies that link visual field sensitivity to retinal ganglion cell count are discussed. Additionally, those studies that determined the mathematical relationship between visual field sensitivity and ganglion cell number are reviewed. Next, those studies that attempt to create a map of the structure–function relationship using fundus photography and visual field sensitivity are examined. Subsequently, studies that use more recent imaging technology, such as optical coherence tomography, confocal scanning laser ophthalmoscopy, or scanning laser perimetry, to measure structure quantitatively in vivo and to correlate these measures with automated perimetry are explored. Among these studies that use advanced imaging, those that use cross-sectional data to explore structure–function relationships to improve glaucoma diagnosis first are discussed. Second, those studies that use longitudinal data to improve detection of worsening are reviewed. Finally, areas of further research and steps needed to implement structure–function relationships clinically are explored. *Ophthalmology 2017;124:S66-S70 © 2017 by the American Academy of Ophthalmology*

Glaucoma, a leading cause of blindness worldwide,[1] is a progressive condition characterized by structural changes in the optic nerve head (ONH) and retinal ganglion cell (RGC) layer which results in a functional loss of visual field.[2] Automated perimetry, a quantitative assessment of visual field status, was conceptualized in the 1970s[3] and came into widespread clinical use in the 1980s and 1990s. The major clinical trials of the 1990s and early 2000s, such as the Collaborate Initial Glaucoma Treatment Study,[4] the Early Manifest Glaucoma Trial,[5] and the Ocular Hypertension Treatment Study,[6] used automated perimetry to diagnose glaucoma and monitor for worsening.

During this period, although detailed quantitative functional information was available through automated perimetry, assessment of structure was based on qualitative or semi-quantitative observations of the ONH or retinal nerve fiber layer (RNFL). Structural and functional relationships were developed during this period to convert our detailed perimetric (functional) knowledge into a quantification of RGC loss.

The later application of confocal scanning laser ophthalmoscopy (CSLO),[7] scanning laser perimetry (SLP),[8] and optical coherence tomography (OCT)[9] to glaucoma has allowed for more quantitative structural data to compliment the functional data from automated perimetry.[10–12] As more advanced imaging technology allowed us to measure in vivo structure in a more detailed manner, we discovered that the correlation between structural and functional loss was imperfect.[13,14] One possibility is that measures of optic nerve structure and function may contain distinct information that may be combined to improve glaucoma diagnosis and monitoring. Indeed, as detailed below, the combined use of detailed functional and structural data has made diagnosing glaucoma and monitoring glaucoma worsening more sensitive and specific.

In this review, we trace the development of the structure–function relationship in glaucoma through a historic perspective. We begin by reviewing the early studies that link histologic structure with automated perimetry to define important structure–function relationships in glaucoma. We then discuss studies that map the anatomic relationship between RGCs and perimetric points. Finally, although current structure–function relationships are far from perfect, we examine more recent studies that improve the structure–function relationship using modern imaging technologies such as CSLO, SLP, and OCT to improve diagnosis of glaucoma and make monitoring of glaucoma worsening more accurate.

Early Studies of Structure and Function: The Establishment of Relationships between Histologic Characteristics and Perimetry

In the late 1980s, Quigley et al[15] performed some of the earliest work defining structure–function relationships in

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glaucoma by coupling histologic analysis with automated perimetry. These investigators examined 5 postmortem eyes and 1 enucleated eye of patients with a history of glaucoma who had undergone automated perimetry between 1 day and 17 months before the specimens were analyzed. In the central 30° of the visual field measured by automated perimetry, a 20% RGC loss was required for a 5-dB loss of sensitivity and a 40% loss was required for a 10-dB change.

Garway-Heath et al[16] expanded this work by using mathematical models and normative automated perimetry and ganglion cell density data to make 2 important observations. First, the eccentricity of the retinal location under consideration modifies the structure—function relationship. Specifically, to produce a similar functional change, a greater number of retinal ganglion cells must be lost in central retinal areas compared with peripheral retina areas. Second, both structural and functional data must be in linear units for the structure—function relationship also to be linear. Specifically, decibels (a logarithmic measure) must be converted to differential light sensitivity, a linear sensitivity measurement, to have a linear relationship with RGC number.

Harwerth et al[17,18] later pioneered the use of nonhuman primate models to study structure—function relationships and verified many of the findings of Garway-Heath et al.[16] In these experiments, Harwerth et al experimentally induced glaucoma with argon laser trabeculoplasty in 16 monkeys. The investigators trained the monkeys to perform automated perimetry and after enucleation analyzed RGC status. Their histologic findings verified that eccentricity of retinal points modifies the structure—function relationship and that either a log—log or linear—linear scale must be used for the structure—function relationship be linear. Harwerth and Quigley[19] subsequently established that similar structure—function relationships were observed in human patients with glaucoma.

Drasdo et al[20,21] also found that the structure—function relationship was linear between 0 and 29 dB of visual field sensitivity using histologic data. Beyond 29 dB, they noted that the relationship becomes nonlinear and that much more ganglion cell loss is required to produce field loss. This change in linearity at higher levels of vision loss has been verified by multiple groups and came to be known as the "hockey-stick" model based on the inflection point on plots of structure versus function at higher levels of visual sensitivity.[22]

Mapping Optic Nerve Structure to Visual Function

Although the aforementioned histologic studies and mathematical models improved our understanding of the relationship between RGC number and automated perimetry sensitivity, there was still little known about the anatomic relationship between points on the ONH and the retinal locations assessed by automated perimetry. Several investigators proceeded to explore this relationship and create maps linking ONH location to automated perimetry test point location. Garway-Heath et al[23] digitally superimposed automated perimetry test locations onto color fundus images of patients with obvious RNFL defects emanating from the optic disc. Using such defects as a guide, the investigators were able to create a structure—function map by correlating perimetric points to locations on the ONH. Strouthidis et al[24] built on this work by using the structure—function map to assess interpoint sensitivity correlations between neighboring locations on automated perimetry. They found that the distance of the points mapped back to the ONH was a much stronger predictor of interpoint correlation than the distance between the points measured on the retina. Asaoka et al[25] studied RNFL thickness measured by OCT and perimetric locations centered on the fovea or optic disc. The optic disc—centered field was derived from the structure—function map developed by Garway-Heath et al.[23] This group selected the combination of perimetric points that would yield the most robust structure—function relationship and labeled this the "structure—function field." This combination of points tested fewer locations (40 total points) and yielded a stronger structure—function relationship than 24-2 pattern automated perimetry. However, Lamparter et al[26] showed that this structure—function map may vary significantly between individuals. Specifically, variation of certain parameters such as position of the optic nerve head with respect to the fovea, optic disc area, axial length, spherical equivalent, and ellipticity ratio may have a meaningful effect on that individual's structure—function map.

Improving the Structure—Function Relationship with Advanced Imaging

With the availability of quantitative optic nerve imaging, the study of structure—function relationships no longer required histologic structural data, and quantitative measures of optic nerve structure and function could be collected in vivo. This allowed for the generation of large datasets of both structural and functional parameters, which in turn allowed for the use of advanced statistical methodology to relate structure and function. Much of the early work using advanced imaging and statistical methodology to understand the structure—function relationship focused on using cross-sectional datasets to improve glaucoma diagnosis.

Bowd et al[27] used automated perimetry and OCT images of the ONH gathered from 69 glaucomatous eyes to identify the combination of testing that most accurately identified glaucoma. These investigators used various machine learning algorithms to identify glaucoma based on automated perimetry alone, OCT of the ONH alone, or automated perimetry and OCT together. The machine learning algorithms they used performed best (highest area under the receiver operating characteristic curve) when both structure (OCT) and function (automated perimetry) were included in the learning dataset.