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Association between Intraocular Pressure and Rates of Retinal Nerve Fiber Layer Loss Measured by Optical Coherence Tomography

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Purpose: To evaluate the relationship between intraocular pressure (IOP) and rates of retinal nerve fiber layer (RNFL) thickness change over time measured by spectral-domain (SD) optical coherence tomography (OCT).

Design: Observational cohort study.

Participants: The study involved 547 eyes of 339 patients followed up for an average of 3.9±0.9 years. Three hundred eight (56.3%) had a diagnosis of glaucoma and 239 (43.7%) were considered glaucoma suspects.

Methods: All eyes underwent imaging using the Spectralis SD OCT (Heidelberg Engineering GmbH, Heidelberg, Germany), along with IOP measurements and standard automated perimetry (SAP). Glaucoma progression was defined as a result of "Likely Progression" from the Guided Progression Analysis software for SAP. Linear mixed models were used to investigate the relationship between average IOP during follow-up and rates of RNFL thickness change, while taking into account potential confounding factors such as age, race, corneal thickness, and baseline disease severity.

Main Outcome Measures: The association between IOP and rates of global and sectorial RNFL thickness loss measured by SD OCT.

Results: Forty-six eyes (8.4%) showed progression on SAP during follow-up. Rates of global RNFL thickness change in eyes that progressed by SAP were faster than in those that did not progress (−1.02 vs. −0.61 μm/year, respectively; $P = 0.002$). For progressing eyes, each 1-mmHg higher average in IOP during follow-up was associated with an additional average loss of 0.20 μm/year (95% confidence interval [CI]: 0.08 to 0.31 μm/year; $P < 0.001$) of global RNFL thickness versus only 0.04 μm/year (95% CI: 0.01 to 0.07 μm/year; $P = 0.015$) for nonprogressing eyes. The largest associations between IOP and rates of RNFL change were seen for measurements from the temporal superior and temporal inferior sectors, whereas the smallest association was seen for measurements from the nasal sector.

Conclusions: Higher levels of IOP during follow-up were associated with faster rates of RNFL loss over time measured by SD OCT. These findings support the use of SD OCT RNFL thickness measurements as biomarkers for the evaluation of the efficacy of IOP-lowering therapies to slow down the rate of disease progression. *Ophthalmology 2016;■:1−8 © 2016 by the American Academy of Ophthalmology.*

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Glaucoma is a progressive optic neuropathy characterized by degeneration of retinal ganglion cells and their axons that results in visual field loss and a characteristic appearance of the optic disc.[1] Intraocular pressure (IOP) is still considered the most important risk factor for the development and progression of primary open-angle glaucoma and also remains the only known modifiable risk factor.[1]

Several clinical trials have provided evidence for the role of average IOP in the disease and the benefit of IOP-lowering treatment.[2−7] The Ocular Hypertension Treatment Study demonstrated that the cumulative incidence of primary open-angle glaucoma was 4.4% in the medication group and 9.5% in the observation group after 5 years of follow-up.[3,4] The Early Manifest Glaucoma Trial showed that progression was less frequent in treated patients with primary open-angle glaucoma than in nontreated patients, thereby reducing visual field loss in the treated group.[5] Additionally, in the Advanced Glaucoma Intervention Study, eyes that maintained IOP less than 18 mmHg during follow-up showed less progression based on visual fields.[2] Most of the previous studies evaluating the role of IOP in glaucoma used visual fields as the sole end

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point for estimating disease development and progression. However, there is evidence that many patients can progress by structural tests while not showing detectable change by functional measures.[4,8,9] In addition, these structural changes have been shown to be predictive of future functional losses and a decrease in quality of life in glaucoma patients.[8–12]

Optical coherence tomography (OCT) has become a widely used method for assessment of structural damage in glaucoma.[13–15] The technology can provide quantitative and reproducible measurements of the peripapillary retinal nerve fiber layer (RNFL), which have been shown to be helpful in the diagnosis and assessment of disease progression.[16,17] The more recently introduced spectral-domain (SD) OCT has enhanced resolution, decreased scan acquisition time, and improved reproducibility compared with older versions of the technology.[18–21] However, despite the widespread use of SD OCT for assessment of glaucomatous changes over time, no investigation has evaluated yet the impact of IOP on longitudinal SD OCT measurements in glaucoma. Evaluation and quantification of this relationship is important to validate this technology and also to provide a better understanding of the role of IOP as a risk factor for structural damage in the disease. The purpose of this study was to evaluate the relationship between IOP and longitudinal changes in the RNFL as assessed by SD OCT in a cohort of individuals with glaucoma and suspected of having the disease who were followed up over time.

Methods

This was a longitudinal, observational cohort study consisting of participants from the African Descent and Glaucoma Evaluation Study and the Diagnostic Innovations in Glaucoma Study. The 3-site African Descent and Glaucoma Evaluation Study collaboration includes the Hamilton Glaucoma Center at the Department of Ophthalmology, University of California, San Diego; the New York Eye and Ear Infirmary; and the Department of Ophthalmology, University of Alabama at Birmingham. The Diagnostic Innovations in Glaucoma Study includes participants recruited at the University of California, San Diego. By design, the protocols of the 2 studies are identical. Methodologic details have been described previously.[22] The institutional review boards at the University of California, San Diego, the New York Eye and Ear Infirmary, and the University of Alabama at Birmingham approved the methods, and written informed consent was obtained from all participants. The study complied with the Health Insurance Portability and Accountability Act, and all study methods adhered to the tenets of the Declaration of Helsinki regarding human subject research. The African Descent and Glaucoma Evaluation Study and Diagnostic Innovations in Glaucoma Study were registered at www.clinicaltrials.gov (identifers, NCT00221923 and NCT00221897, respectively).

All participants underwent a comprehensive ophthalmologic examination including review of medical history, visual acuity, slit-lamp biomicroscopy, IOP measurement, corneal pachymetry, gonioscopy, dilated funduscopy examination using a 78-diopter lens, stereoscopic optic disc photography, and standard automated perimetry (SAP) using 24-2 Swedish interactive threshold algorithm standard. Only subjects with open angles on gonioscopy were included. Subjects were excluded if they had undergone glaucoma filtering surgery or showed any other ocular or systemic disease that could affect the optic nerve or the visual field.

The study included patients diagnosed with glaucoma as well as those suspected of having the disease. Eyes were classified as glaucomatous if they had 2 or more repeatable glaucomatous visual field defects at baseline, defined as a pattern standard deviation with $P < 0.05$, or glaucoma hemifield test results outside normal limits. Eyes were classified as glaucoma suspects if they had a history of elevated IOP (>21 mmHg), suspicious or glaucomatous appearance of the optic nerve, but normal and reliable visual field results at baseline, or both. If both eyes from the same patient were eligible for the study, both eyes were included in the analysis, and statistical procedures were used to take into account the correlation between measurements within the same patient.

Subjects were followed up every 6 months. A minimum follow-up of 2 years and a minimum of 5 separate visits were required for inclusion in this study. Figure 1 shows a flowchart depicting the selection of eyes and subjects for the study. The SD OCT images were obtained using the Spectralis (Heidelberg Engineering GmbH, Heidelberg, Germany). The study included a total of 4068 visits, with an average of 7.4±1.6 visits per eye (range of the number of visits, 5–13) and an average follow-up of 3.9±0.9 years. Eligible subjects were required to undergo IOP measurement and SD OCT at the same visit and a visual field examination soon either before or after this visit. During the follow-up period, each patient was treated at the discretion of the attending ophthalmologist.

Intraocular Pressure

Intraocular pressure measurements were obtained with a Goldmann applanation tonometer model AT 900 (Haag-Streit International, Köniz, Switzerland). Only measurements obtained on the same day of the SD OCT RNFL scans were included in the study. Average IOP during the follow-up period was calculated.

Spectral-Domain Optical Coherence Tomography

Spectralis SD OCT (software version 5.4.7.0) was used to measure peripapillary RNFL thickness in this study. Principles of operation of SD OCT have been described in detail previously.[19,23] Peripapillary RNFL measurements were obtained in a circle scan centered on the optic disc. The circle scan contains 1536 A-scan points from a 12° circle, which equates to a retinal diameter of 3.5 mm in eyes with standard corneal curvature. The acquisition rate is 40 000 A-scans per second at an axial resolution of approximately 4 μm and a lateral resolution of 6 μm. The temporal margin (9-o'clock position in the right eye and 3-o'clock position in the left eye) was designated 0°, and degrees were counted in a clockwise direction on the right eye and in a counterclockwise direction on the left eye. The RNFL also was assessed by sectors provided by the software, divided as temporal (316°–45°), temporal superior (46°–90°), nasal superior (91°–135°), nasal (136°–225°), nasal inferior (226°–270°), and temporal inferior (271°–315°). The software also provides the quality score that indicates the signal strength. Quality scores range from 0 dB (poor) to 40 dB (excellent). Images with noncentered scans, inaccurate segmentation of the RNFL, or quality scores of 15 dB or less were excluded. As part of the protocol of the study, at least 3 scans were acquired at each visit and only the best quality scan was chosen for inclusion in the analysis (Fig 1).

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