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# Importance of Normal Aging in Estimating the Rate of Glaucomatous Neuroretinal Rim and Retinal Nerve Fiber Layer Loss

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***Purpose:*** To describe longitudinal rates of change of neuroretinal parameters in patients with glaucoma and healthy controls, and to evaluate the influence of covariates.

***Design:*** Prospective longitudinal study.

***Participants:*** Treated patients with glaucoma (n = 192) and healthy controls (n = 37).

***Methods:*** Global disc margin–based neuroretinal rim area (DMRA) was measured with confocal scanning laser tomography, while Bruch's membrane opening-minimum rim width (BMO-MRW), BMO area (BMOA), and peripapillary retinal nerve fiber layer thickness (RNFLT) were measured with optical coherence tomography at 6-month intervals. Individual rates of change were estimated with ordinary least-squares regression, and linear mixed effects modeling was used to estimate the average rate of change and differences between the groups, and to evaluate the effects of baseline measurement and baseline age on rates of change.

***Main Outcome Measures:*** Rates of change for each parameter.

***Results:*** Subjects were followed for a median (range) of 4 (2–6) years. The proportion of controls who had significant reduction of neuroretinal parameters was 35% for BMO-MRW, 31% for RNFLT, and 11% for DMRA. The corresponding figures for patients with glaucoma were not statistically different (42%, $P = 0.45$; 31%, $P = 0.99$; 14%, $P = 0.99$, respectively). Controls had a significant reduction of BMO-MRW (mean: −1.92 μm/year, $P < 0.01$) and RNFLT (mean: −0.44 μm/year, $P = 0.01$), but not DMRA (mean: $-0.22\times10^{-2}$ mm$^2$/year, $P = 0.41$). After adjusting for covariates, patients with glaucoma had faster, but not statistically different, rates of deterioration compared with controls, by −1.26 μm/year ($P = 0.07$) for BMO-MRW, −0.40 μm/year ($P = 0.11$) for RNFLT, and $-0.38\times10^{-2}$ mm$^2$/year ($P = 0.23$) for DMRA. Baseline BMO-MRW and RNFLT significantly influenced the respective rates of change, with higher baseline values relating to faster reductions. Older age at baseline was associated with a slower reduction in rates of BMO-MRW. Reductions in intraocular pressure were related to increases in BMO-MRW and DMRA. There was a tendency for BMOA to decrease over time ($-0.38\times10^{-2}$ mm$^2$/year; $P = 0.04$).

***Conclusions:*** Age-related loss of neuroretinal parameters may explain a large proportion of the deterioration observed in treated patients with glaucoma and should be carefully considered in estimating rates of change. *Ophthalmology 2015;122:2392-2398 © 2015 by the American Academy of Ophthalmology.*

*Supplemental material is available at www.aaojournal.org.*

Progression of open-angle glaucoma is usually assessed by determining how indices of structural and functional damage change over time. Examples include retinal nerve fiber layer thickness (RNFLT), optic nerve head (ONH) neuroretinal rim area, and visual field mean deviation (MD).

The presence of clinically significant progression is usually guided by the rate of change of the index over time and its statistical significance. However, because there is accumulating evidence that aging in otherwise healthy subjects also results in statistically significant change,[1–3] often with patterns resembling those in glaucoma,[3] the clinical assessment of glaucomatous progression can be challenging.

Other factors can influence the rate of observed changes. Most studies reported that thicker baseline measurements of RNFLT are related to faster deterioration, both in healthy subjects[1,2] and in patients with glaucoma.[4,5] In addition, factors that affect individual measurements can affect rates of change. For example, reduction in intraocular pressure (IOP) was related to increase in disc margin–based neuroretinal rim area (DMRA) measured with confocal scanning laser tomography (CSLT).[6,7] In patients with treated glaucoma, this effect can potentially lead to errors in estimating rates of change and should be considered, particularly when there is significant IOP change.

The purpose of this study was to describe longitudinal rates of change in healthy subjects and patients with glaucoma, and to evaluate the impact of related factors or covariates. Three neuroretinal parameters (Bruch's



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membrane opening-minimum rim width [BMO-MRW], RNFLT, DMRA), 1 functional parameter (MD), and 1 anatomic parameter (BMO area [BMOA]) were studied. To our knowledge, this is the first published longitudinal report of BMO-MRW and BMOA.

# Methods

## Participants

Study participants included treated patients with open-angle glaucoma and healthy controls who were recruited from 2 prospective longitudinal observational studies being carried out at the Eye Care Centre, Nova Scotia Health Authority, Halifax, Nova Scotia, Canada. The study was approved by the Nova Scotia Health Authority Ethics Review Board. In accordance with the Declaration of Helsinki, all participants gave informed consent. If both eyes were eligible, 1 eye was randomly selected as the study eye.

For patients, inclusion criteria were (1) clinical diagnosis of open-angle glaucoma, including primary, pseudoexfoliative, or pigmentary glaucoma; (2) clinically determined glaucomatous ONH changes with stereo-disc photography or CSLT; (3) a positive Glaucoma Hemifield Test[8] result with standard automated perimetry (Swedish Interactive Thresholding Algorithm[9] program 24-2 of the Humphrey Field Analyzer [Carl Zeiss Meditec, Dublin, CA]); and (4) best-corrected visual acuity $\geq$0.3 logarithm of the minimum angle of resolution (equivalent to $\geq$20/40) in the study eye. Exclusion criteria were (1) concomitant ocular disease and systemic medication known to affect the optic nerve and (2) refractive error exceeding $\pm$6.00 diopters (D) sphere or $\pm$3.00 D astigmatism.

For controls, inclusion criteria were (1) normal eye examination including a normal-appearing ONH and absence of retinal nerve fiber layer defects; (2) IOP $<$21 mmHg; and (3) normal visual field, defined as a glaucoma hemifield test, MD, and pattern standard deviation within normal limits. The exclusion criterion was refractive error exceeding $\pm$6.00 D sphere or $\pm$3.00 D astigmatism.

Study visits were conducted at 6-month intervals, when subjects underwent perimetry, imaging with spectral-domain optical coherence tomography (OCT; Spectralis; Heidelberg Engineering, Heidelberg, Germany) and CSLT (Heidelberg Retina Tomograph III; Heidelberg Engineering), Goldmann applanation tonometry, and clinical examination.

## Imaging

Two scan patterns manually centered on the ONH were used with OCT. First, a radial pattern comprising 24 angularly equidistant 15-degree linear scans was used to measure BMO-MRW.[10] Data for each B-scan were averaged from 20 to 30 individual B-scans, with 768 A-scans per B-scan. Second, a 12-degree circle was used to measure peripapillary RNFLT. Data were averaged from 16 individual B-scans, each comprising 1536 A-scans. The internal image registration and tracking software were used to significantly reduce the effects of eye movements and automatically position follow-up scans to ensure that the same locations were measured serially.[11]

With CSLT, a 15-degree scan pattern comprising 16 confocal sections (with a transverse sampling of 384$\times$384 pixels) per millimeter of scan depth was used to image the ONH. The mean topography and reflectance images were automatically computed from 3 individual images. Follow-up images were automatically aligned to baseline. In cases in which automatic alignment was not possible, manual positioning was carried out.

## Image Segmentation

Optical coherence tomography image segmentation was performed automatically with the device software (Spectralis Viewing Module 6.0.10.102; Heidelberg Engineering) and checked for accuracy. Manual corrections were made when necessary. The OCT examinations with a quality score $\leq$15 were excluded. Global averages of BMO-MRW, RNFLT, and BMOA were exported for analysis.

The optic disc margin contour line, defined as the inner limit of scleral ring, was delineated with the CSLT device software (HRT Viewing Module 3.2.0.0; Heidelberg Engineering). A reference plane for the measurements of DMRA was defined 50 µm posterior to the mean contour line height between 350° and 356° at the temporal ONH and maintained for all follow-up examinations (Moorfields reference plane).[12] The CSLT examinations with mean pixel height standard deviation $\geq$40 µm were excluded. Disc area and DMRA global values were exported for analysis.

## Data Analysis

Subjects with $\geq$5 examinations were included in the analysis. Baseline characteristics of patients and controls were compared with the Mann−Whitney test. Individual rates of change were estimated with ordinary least-squares regression. The proportion of subjects with statistically significant reduction of neuroretinal parameters (defined as a negative individual rate of change with $P < 0.05$) in the glaucoma and control groups was compared with Fisher exact test.

For each parameter, a linear mixed effects (LME) model was used to estimate the average rate of change and differences in rates between the groups, and to evaluate the effects of baseline measurement (which was not used in the follow-up data) and baseline age on the rates of change, while adjusting for other variables. Follow-up measurements were used as dependent variables. Presence of glaucoma, baseline measurement, baseline age, image quality (quality score for BMO-MRW and RNFLT, and mean pixel height standard deviation for DMRA), variability of BMOA (for the BMO-MRW model), IOP, and follow-up time (in years) were used as fixed effects. Interaction terms of follow-up time with the presence of glaucoma, baseline measurement, and baseline age were included to explore the effects on the rates of change. Random effects per subject included intercept, follow-up time, and IOP. Some covariates were not used in all models. The models used are presented in Table 1 (available at www.aaojournal.org).

For LME, baseline variables were centered at the median values of the control group, allowing better interpretation of coefficients (i.e., 65 years for age, 305 µm for BMO-MRW, 96 µm for RNFLT, 1.2 mm$^2$ for DMRA, 0.4 decibels [dB] for MD, and 1.7 mm$^2$ for BMOA). Data analysis was performed with open-source software R[13] and package "*nlme*."[14] Statistical significance was assumed at $P < 0.05$.

# Results

The study included 192 patients with glaucoma and 37 healthy controls. Patients were marginally older than controls (medians, 68.7 vs. 65.2 years, respectively; $P = 0.05$) and had a shorter follow-up (medians, 3.7 vs. 4.5 years, respectively; $P < 0.01$). Baseline BMO-MRW, RNFLT, DMRA, and MD values were all significantly lower in the glaucoma group (Table 2).

The proportion of controls who had significant reduction of the neuroretinal parameters was 35% for BMO-MRW, 31% for RNFLT, and 11% for DMRA. The corresponding figures for patients with glaucoma were 42%, 31%, and 14%, respectively, and