

## Original Investigation

# Structural Characteristics of the Acquired Optic Disc Pit and the Rate of Progressive Retinal Nerve Fiber Layer Thinning in Primary Open-Angle Glaucoma

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**IMPORTANCE** The optic disc pit (ODP) has been considered a region of localized susceptibility to the damage of glaucoma.

**OBJECTIVE** To determine whether the rate of retinal nerve fiber layer (RNFL) thinning differs according to the presence and structural characteristics of an ODP in primary open-angle glaucoma.

**DESIGN, SETTING, AND PARTICIPANTS** We performed a prospective case-control study that included 163 eyes with primary open-angle glaucoma (83 with an ODP and 80 without an ODP) from Glaucoma Clinic of Seoul National University Bundang Hospital. Participants were enrolled from the ongoing Investigating Glaucoma Progression Study from January 1, 2012, through May 31, 2014. Mean (SD) follow-up was 3.32 (0.49) years (through May 31, 2014). Optic nerve heads underwent swept-source optical coherence tomography (OCT) to determine the presence of focal lamina cribrosa alteration and its structural characteristics. Eyes with and without photographic ODPs and corresponding microscopic laminar alterations were assigned to the ODP and non-ODP groups, respectively. The rates of progressive thinning of global and 6 sectoral spectral-domain OCT RNFL thicknesses were determined by linear regression and compared between the 2 groups. We used a general linear model to determine the factors associated with the rate of RNFL thinning; data obtained from September 21, 2009, through May 31, 2014, were used to calculate the rate of RNFL thinning.

**MAIN OUTCOMES AND MEASURES** The relationship between the presence and structural characteristics of ODPs and the rate of progressive OCT RNFL thinning.

**RESULTS** Thinning of the RNFL was faster in the ODP group than in the non-ODP group in the global (mean [SD],  $-1.44$  [1.31] vs  $-0.93$  [1.10] [95% CI,  $-0.97$  to  $-0.19$ ]  $\mu\text{m}/\text{y}$ ;  $P = .008$ ), temporoinferior (mean [SD],  $-4.17$  [4.15] vs  $-1.97$  [3.26] [95% CI,  $-3.36$  to  $-1.04$ ]  $\mu\text{m}/\text{y}$ ;  $P < .001$ ), and temporal (mean [SD],  $-1.92$  [2.62] vs  $-0.89$  [1.62] [95% CI,  $-1.70$  to  $-0.35$ ]  $\mu\text{m}/\text{y}$ ;  $P = .003$ ) sectors. The rate of RNFL thinning was maximum in the temporoinferior sector (mean [SD],  $-4.17$  [4.15]  $\mu\text{m}/\text{y}$ ) and corresponded to the frequency distribution of ODPs. Regression analysis revealed that faster global RNFL thinning was related to a higher untreated intraocular pressure ( $\beta = -0.07$ ; 95% CI,  $-0.11$  to  $-0.03$ ;  $P = .001$ ), episodes of disc hemorrhage ( $\beta = -0.74$ ; 95% CI,  $-1.79$  to  $0.31$ ;  $P = .003$ ), the presence of  $\beta$ -zone parapapillary atrophy ( $\beta = -0.47$ ; 95% CI,  $-1.13$  to  $0.20$ ;  $P = .02$ ), and the presence of ODPs ( $\beta = -0.41$ ; 95% CI,  $-1.14$  to  $0.32$ ;  $P = .02$ ). The maximum rate of RNFL thinning was associated with higher untreated intraocular pressure ( $\beta = -0.24$ ; 95% CI,  $-0.35$  to  $-0.13$ ;  $P < .001$ ), disc hemorrhage ( $\beta = -1.54$ ; 95% CI,  $-2.88$  to  $-0.19$ ;  $P < .001$ ), and the presence ( $\beta = -1.04$ ; 95% CI,  $-2.14$  to  $0.07$ ;  $P = .004$ ), far-peripheral location ( $\beta = -1.75$ ; 95% CI,  $-3.05$  to  $-0.46$ ;  $P = .008$ ), and partial-thickness depth ( $\beta = -1.45$ ; 95% CI,  $-2.75$  to  $-0.16$ ;  $P = .03$ ) of an ODP.

**CONCLUSIONS AND RELEVANCE** The presence and structural characteristics of ODPs were associated with global and focal progression as assessed by the rate of OCT RNFL thinning. The assessment of ODP structure using swept-source OCT may help to predict the location of future progression.

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The acquired optic disc pit (ODP) frequently presents as one of the localized optic nerve changes in glaucoma. An acquired ODP has been considered a region of localized susceptibility to the damaging effects of elevated intraocular pressure (IOP)<sup>1-3</sup> and has been associated with glaucoma progression.<sup>4-6</sup>

The presence of an ODP has been confirmed based on the findings of ophthalmoscopic examination or fundus photography. The advent of enhanced-depth spectral-domain optical coherence tomography (OCT) has made examination of the detailed structure of ODPs at the microscopic level possible.<sup>7,8</sup> Choi et al<sup>9</sup> recently described the structural characteristics of ODPs using enhanced-depth spectral-domain OCT and showed that ODPs present as various forms of localized lamina cribrosa alteration. The structural characteristics of these alterations appear to be associated with different clinical characteristics of glaucoma, such as paracentral involvement of visual field defects or optic disc hemorrhage, both of which have been implicated in the pathogenesis of glaucoma.<sup>10-16</sup> These findings suggest that the ODP characteristics represent the site of glaucomatous damage and are closely associated with the underlying pathologic process.

An association between focal lamina cribrosa defects and glaucomatous visual field progression has recently been demonstrated by Faridi et al.<sup>5</sup> However, the associations of glaucoma progression presented by retinal nerve fiber layer (RNFL) thinning with the differences in the structural characteristics of ODPs have yet to be established. Swept-source (SS)-OCT may allow better visualization of the peripheral lamina cribrosa structure, where the ODP is frequently located, than spectral-domain OCT because SS-OCT penetrates deeper into the tissue and has a higher resolution.<sup>17-19</sup> Thus, the purpose of the present study was to determine the relationship between the presence of an ODP and its structural characteristics as assessed by SS-OCT and the rate of progressive RNFL thinning.

## Methods

The participants in this study consisted of patients from the Investigating Glaucoma Progression Study (IGPS), an ongoing prospective study of primary open-angle glaucoma that has been under way since August 2011 at the Glaucoma Clinic of Seoul National University Bundang Hospital. This study was approved by the institutional review board of the Seoul National University Bundang Hospital and conformed to the tenets of the Declaration of Helsinki. All participants provided written informed consent.

### Study Participants

We reviewed the database of patients included in the IGPS from January 1, 2012, through May 31, 2014. The patients who were enrolled in the IGPS underwent a complete ophthalmic examination, including assessment of visual acuity, refraction, slitlamp biomicroscopy, gonioscopy, Goldmann applanation tonometry, and dilated stereoscopic examination of the optic disc. They also underwent measurements of corneal curvature (KR-1800; Topcon), central corneal thickness (Orbscan II;

### At a Glance

- This prospective study has determined the association between the optic disc pit (ODP) and the rate of retinal nerve fiber layer (RNFL) thinning in primary open-angle glaucoma.
- Eyes with ODP showed faster RNFL thinning, with this thinning being most noticeable near the ODP.
- The rate of RNFL thinning was faster in the ODPs associated with a partial-thickness lamina cribrosa defect located in the far-peripheral lamina cribrosa.
- The assessment of ODP structure using swept-source optical coherence tomography may help to predict the location of future progression.

Bausch & Lomb Surgical), and axial length (IOL Master, version 5; Carl Zeiss Meditec); stereoscopic disc photography (EOS D60 digital camera, Canon); SS-OCT of the optic disc (DRI-OCT1 Atlantis; Topcon); circumpapillary RNFL thickness measurement using spectral-domain OCT (Spectralis OCT; Heidelberg Engineering); and standard automated perimetry (24-2 Swedish interactive threshold algorithm and Humphrey Field Analyzer II 750; Carl Zeiss Meditec).

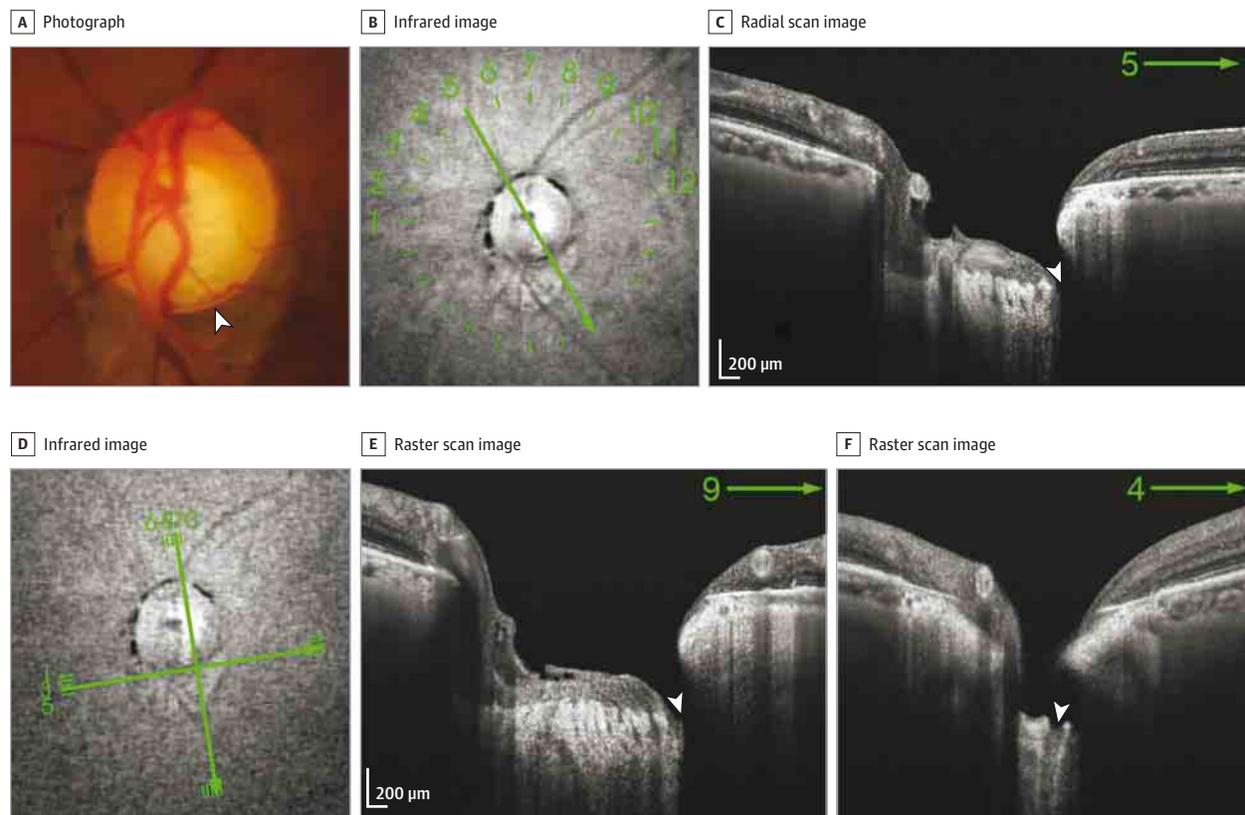
Detailed criteria for inclusion and exclusion in the IGPS have been described previously (eAppendix in the [Supplement](#)).<sup>9</sup> Patients included in the present study were required to have undergone optic nerve head scanning using SS-OCT and to have at least 5 serial spectral-domain OCT circumpapillary RNFL thickness measurements performed at intervals of 6 months to 1 year, with the interval based on the expected rate of progression in individual eyes. If an eye showed progressive RNFL thinning based on the spectral-domain OCT RNFL thickness measurement and an assessment of the circumpapillary B-scan images, the next spectral-domain OCT examination was performed earlier than its regular schedule.

Eyes with ODPs (ODP group) were defined as having an isolated ODP visible on stereoscopic disc photographs and an altered lamina cribrosa contour on SS-OCT images at the location corresponding to the photographed ODP.<sup>7-9</sup> Eyes without ODPs (non-ODP group) were defined as those without an ODP or lamina cribrosa alteration on optic disc photographs or SS-OCT images, respectively. The patients in each group were matched for age, untreated elevated IOP, axial length, and visual field mean deviation using a frequency-matching method.

Patients with any abnormalities in the circumpapillary region that affected the scan ring where the OCT RNFL thickness measurements were obtained were excluded from this study. A history of cataract or glaucoma surgery before the baseline examination was not an exclusion criterion, but patients who underwent such procedures during the study period were excluded because both may affect the RNFL thickness data.<sup>20,21</sup> When both eyes were eligible, 1 eye was selected randomly.

Untreated IOP was defined as the mean of 2 measurements obtained before IOP-lowering treatment. We obtained the mean follow-up IOP measurement by calculating the mean IOP measured at 6-month intervals; we calculated IOP fluctuation using the SD of these values. We detected optic disc hemorrhage by results of a slitlamp examination using a

Figure 1. Evaluation of the Structure of the Optic Disc Pit (ODP) Using Swept-Source Optical Coherence Tomography



A, Photographic ODP (arrowhead). B, Location where the 12 radial scans were obtained. C, Scan image obtained at location 5 in part B. Full-thickness lamina cribrosa alteration is seen at far-peripheral lamina cribrosa (white arrowhead). D-F, When radial scan images could not reveal the detailed ODP structure, 2 sets of 5-line raster scans were additionally obtained at the location of ODP scan images. Images obtained at locations 9 in part E and 4 in part F (green arrows in part D) show full-thickness lamina cribrosa alteration (white arrowheads).

78-diopter lens or fundus photography, either of which was performed at each follow-up visit during the study period.

#### Photographic and Microscopic Evaluation of the ODP

The presence or absence of an ODP was determined on stereoscopic disc photographs and SS-OCT images. A detailed description of SS-OCT optic disc scanning is found in the eAppendix in the Supplement. We defined a photographic ODP in accordance with the criteria used by Javitt et al<sup>2</sup> (eAppendix in the Supplement). Optic disc pits that were not associated with glaucomatous optic neuropathy were excluded. At the time of the photographic ODP evaluation, the presence of  $\beta$ -zone peripapillary atrophy<sup>22</sup> was also recorded.

We examined the SS-OCT image (Figure 1A) to identify any structural alteration of the lamina cribrosa corresponding to the location of the photographic ODP, first in 12 radial scans (Figure 1B and C) and then in 5-line cross scans centered on the ODP when necessary (Figure 1D-F). Alterations of the lamina cribrosa were defined as described by Kiumehr et al<sup>7</sup> (eAppendix in the Supplement). The presence of lamina cribrosa alterations was examined only at the temporal periphery and not at the nasal periphery because the nasal periphery lamina cribrosa frequently was obscured by vascular

or neural tissue. Patients with a suspected lamina cribrosa defect in an area not corresponding to that of the photographic ODP were excluded.

We also examined SS-OCT images in eyes without photographic ODPs to rule out the possible presence of a microscopic lamina cribrosa defect that was not detected on disc photography. Only eyes without a focal lamina cribrosa alteration in SS-OCT images were assigned to the non-ODP group.

Eyes with ODPs were further divided into 2 groups according to the depth of the lamina cribrosa defect (full vs partial thickness) and the distance between the defect and the neural canal wall (midperipheral vs far peripheral). The detailed method of classifying the structure of ODPs is described elsewhere<sup>9</sup> (eAppendix in the Supplement).

The circumferential location of the ODP was determined based on the 6 sectoral locations as defined in the circular diagram of the spectral-domain OCT circumpapillary RNFL thickness measurement report. This measurement was achieved by overlapping disc photographs on the infrared images in the circumpapillary RNFL thickness report. We rotated the disc photographs manually to correct the alignment between the disc photographs and infrared images using commercial software (Photoshop CC; Adobe Systems, Inc) (eFigure 1 in the Supple-

Table 1. Comparison of the Rate of RNFL Thinning Between the ODP and Non-ODP Groups

Sector	Rate of Thinning, Mean (SD), $\mu\text{m}/\text{y}$				
	ODP Group (n = 83)	Non-ODP Group (n = 80)	Difference Between Groups	95% CI	P Value <sup>a</sup>
Global	-1.44 (1.31)	-0.93 (1.10)	-0.51 (0.20)	-0.97 to -0.19	.008
Nasosuperior	-0.09 (2.50)	0.60 (2.07)	-0.15 (0.36)	-0.86 to 0.56	.67
Nasal	-0.58 (2.09)	-0.54 (1.42)	-0.05 (0.28)	-0.60 to 0.51	.87
Nasoinferior	-2.01 (2.30)	-1.48 (2.57)	-0.52 (0.44)	-1.39 to 0.34	.23
Temporoinferior	-4.17 (4.15)	-1.97 (3.26)	-2.20 (0.59)	-3.36 to -1.04	<.001
Temporal	-1.92 (2.62)	-0.89 (1.62)	-1.03 (0.34)	-1.70 to -0.35	.003
Temporosuperior	-0.65 (2.39)	-0.68 (2.37)	0.02 (0.37)	-0.71 to 0.76	.95
With fastest RNFL thinning	-5.37 (3.76)	-4.07 (2.43)	-1.30 (0.50)	-2.28 to -0.32	.01
With ODP	-4.40 (4.03)	NA	NA	NA	NA

Abbreviations: RNFL, retinal nerve fiber layer; NA, not applicable; ODP, optic disc pit.

<sup>a</sup> Comparison between groups was performed using the independent-samples *t* test.

ment). By synchronous viewing of infrared images and temporal-superior-nasal-inferior-temporal graphs, the location of the ODP was fitted to one of the following 6 sectors: nasosuperior (>90° to 135°), nasal (>135° to 225°), nasoinferior (>225° to 270°), temporoinferior (>270° to 315°), temporal (>315° to 45°), and temporosuperior (>45° to 90°).

The photographic ODP was determined on stereoscopic disc photographs obtained before the first measurements of circumpapillary RNFL thickness on spectral-domain OCT. The SS-OCT examinations could not be performed at the time of the first spectral-domain OCT examinations; therefore, we analyzed the SS-OCT images obtained at the final follow-up examinations.

The stereoscopic disc photographs and SS-OCT images were evaluated carefully and independently by 2 glaucoma specialists (S.H.L. and E.J.L.) who were blinded to the clinical information of the participants to determine the presence or absence of an ODP and, if present, the circumferential location and microscopic classification. A final decision was made by consensus between the 2 ophthalmologists, and disagreements were resolved by a third adjudicator (T.-W.K.). Good interobserver agreements have been reported for determination of the presence or the absence of an ODP via stereoscopic disc photography ( $\kappa = 0.83$ ) and for categorization of the ODP structure ( $\kappa = 0.79$ ).<sup>9</sup>

### Statistical Analysis

We performed linear regression analysis (ordinary least squares) against time for global mean RNFL thicknesses based on the SD-OCT data obtained from September 21, 2009, to May 31, 2014, for each patient to determine the rate of change of RNFL thickness. Between-group comparisons were performed using the independent-samples *t* test for continuous variables and the  $\chi^2$  test for categorical variables. The raw data for the *t* tests were subjected to the Bonferroni correction on the basis of the number of comparisons within each analysis. A general linear model was used to investigate the factors influencing the rate of RNFL thinning, first with a univariable model and then with a multivariable model that included variables from the univariable model with  $P < .10$ . All statistical analyses were performed using SPSS software (version 19.0; SPSS, Inc). Except

where stated otherwise, the data are presented as mean (SD) values, and the cutoff for statistical significance was set at  $P < .05$ .

## Results

### Baseline Characteristics

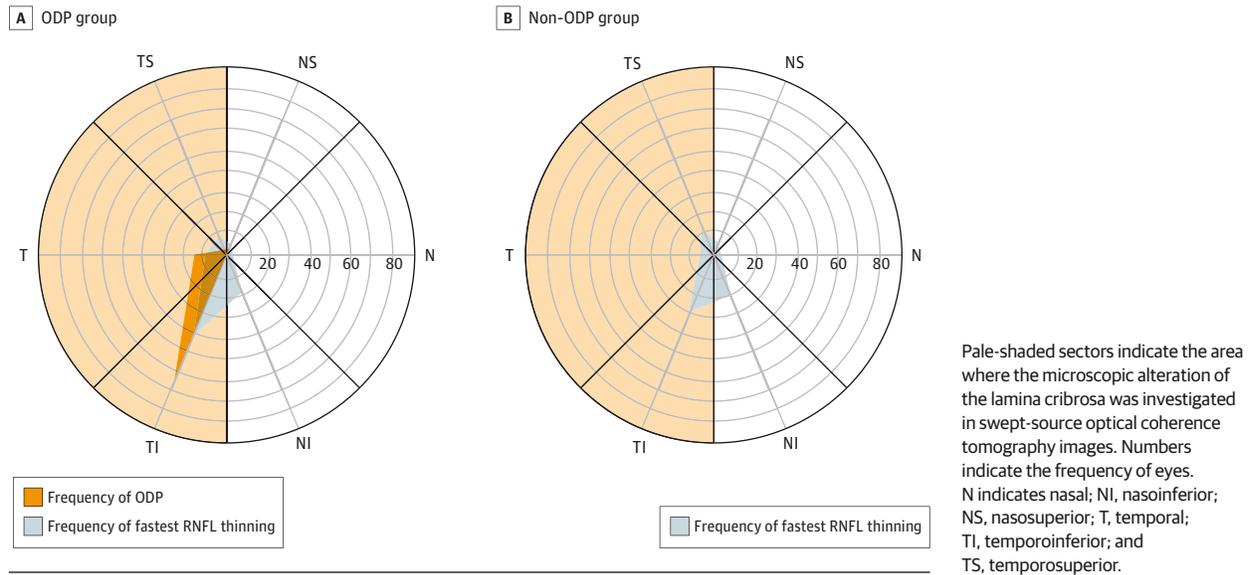
We initially included 205 patients with primary open-angle glaucoma (205 eyes), of whom 103 had photographically evident ODPs and 102 did not. Of these, 8 eyes with and 12 eyes without ODP were excluded because of a suspected lamina cribrosa defect in an area not corresponding to that of the photographic ODP or the poor image quality, respectively. After matching the groups for age, untreated elevated IOP, axial length, and visual field mean deviation, 83 eyes remained in the ODP group and 80 eyes in the non-ODP group. Baseline clinical characteristics of each group are given in eTable 1 in the Supplement. Mean follow-up was 3.32 (0.49) years (through May 31, 2014).

### Rate of RNFL Thinning Relative to Presence of an ODP

Table 1 and eFigure 2 in the Supplement present comparisons of the rates of RNFL thinning between the ODP and non-ODP groups. The mean global RNFL thinning was faster in the ODP group than in the non-ODP group (-1.44 [1.31] vs -0.93 [1.10] [95% CI, -0.97 to -0.19]  $\mu\text{m}/\text{y}$ ;  $P = .008$ ). In addition, the mean RNFL thinning was faster in the ODP group than in the non-ODP group in the temporoinferior (-4.17 [4.15] vs -1.97 [3.26] [95% CI, -3.36 to -1.04]  $\mu\text{m}/\text{y}$ ;  $P < .001$ ) and temporal (-1.92 [2.62] vs -0.89 [1.62] [95% CI, -1.70 to -0.35]  $\mu\text{m}/\text{y}$ ;  $P = .003$ ) sectors.

We also compared the mean rate of RNFL thinning in the sector with the fastest progression (ie, the maximum rate of RNFL thinning) between the 2 groups, and thinning was found to be faster in the ODP group (-5.37 [3.76] vs -4.07 [2.43] [95% CI, -2.28 to -0.32]  $\mu\text{m}/\text{y}$ ;  $P = .01$ ) (Table 1). In the ODP group, the mean rate of RNFL thinning at the location of the ODP (-4.40 [4.03]  $\mu\text{m}/\text{y}$ ) did not differ from the mean maximum rate of RNFL thinning of the non-ODP group (-4.07 [2.43] [95% CI, -0.70 to 0.37]  $\mu\text{m}/\text{y}$ ;  $P = .52$ ). We found good correspondence between the frequency distributions of the sector with

**Figure 2.** Frequency Distributions of the Sector With an Optic Disc Pit (ODP) and the Sector With the Fastest Retinal Nerve Fiber Layer (RNFL) Thinning



**Table 2.** Comparison of the Rate of RNFL Thinning According to the Depth and Marginal Location of the ODP

Variable	Depth of the ODP					Marginal Location of the ODP				
	Rate of Thinning, Mean (SD), $\mu\text{m}/\text{y}$					Rate of Thinning, Mean (SD), $\mu\text{m}/\text{y}$				
	Full Thickness (n = 35)	Partial Thickness (n = 48)	Difference Between Groups	95% CI	P Value <sup>a</sup>	Midperiphery (n = 33)	Far Periphery (n = 50)	Difference Between Groups	95% CI	P Value <sup>a</sup>
Rate of global RNFL thinning	-1.34 (0.97)	-1.50 (1.51)	0.1 (0.29)	-0.42 to 0.74	.58	-1.14 (1.03)	-1.63 (1.44)	0.49 (0.29)	-0.09 to 1.06	.10
Maximum rate of RNFL thinning	-4.62 (2.57)	-5.91 (4.38)	1.2 (0.83)	-0.54 to 2.94	.12	-3.52 (3.09)	-4.99 (4.47)	1.47 (0.89)	-0.30 to 3.25	.10
Rate of RNFL thinning at sector with the ODP	-3.18 (2.62)	-5.30 (4.63)	2.12 (0.87)	0.87 to 3.85	.01	-4.33 (2.88)	-6.05 (4.13)	1.72 (0.83)	0.07 to 3.36	.04

Abbreviations: RNFL, retinal nerve fiber layer; ODP, optic disc pit.

<sup>a</sup> Comparison between groups was performed using the paired t test.

the maximum rate of RNFL thinning and the sector containing the ODP (Figure 2).

**Rate of RNFL Thinning Relative to Marginal Location and Depth of the ODP**

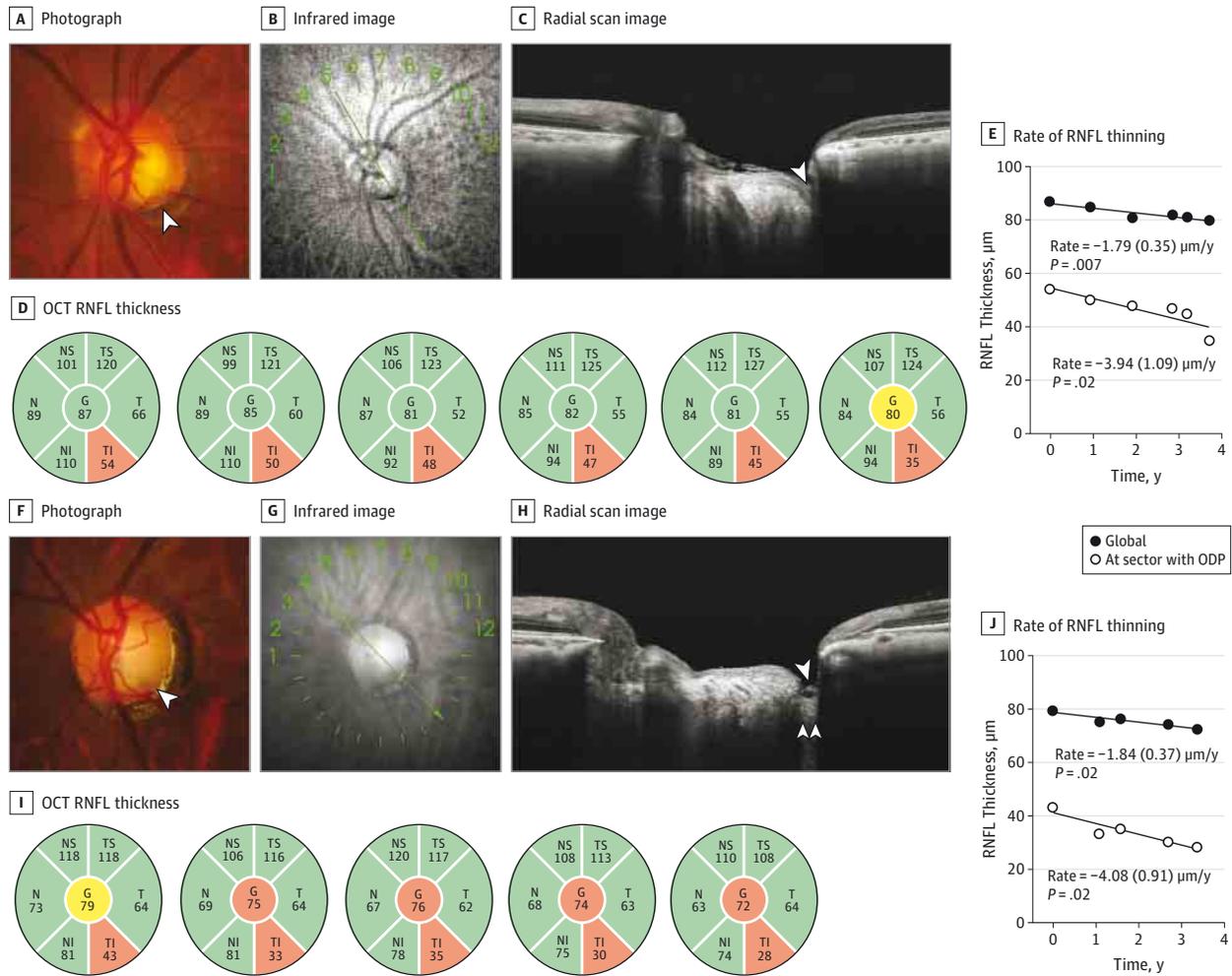
Of the 83 ODPs, 35 and 48 lamina cribrosa alterations were categorized as full- and partial-thickness lamina cribrosa defects, respectively. Of these, 18 and 17 full-thickness lamina cribrosa defects were located at the midperiphery and the far periphery, respectively; 15 and 33 partial-thickness lamina cribrosa defects were located at the midperiphery and the far periphery, respectively. The rate of global RNFL thinning and the maximum rate of RNFL thinning did not differ between eyes with full- and partial-thickness lamina cribrosa defects (Table 2). The mean RNFL thinning in the sector with the ODP was faster in eyes with a partial-thickness lamina cribrosa defect than in those with a full-thickness lamina cribrosa defect (-5.30 [4.63] vs -3.18 [2.62] [95% CI, 0.87 to 3.85]  $\mu\text{m}/\text{y}$ ;  $P = .01$ ) (Table 2). The mean rate of global RNFL thinning and the mean maximum rate of RNFL thinning did not differ between eyes with a midperipheral lamina cribrosa defect and those with a

far-peripheral lamina cribrosa defect. The mean RNFL thinning in the sector with the ODP was faster in eyes in which the ODP was located at the far periphery than in those in which it was located at the midperiphery (-6.05 [4.13] vs -4.33 [2.88] [95% CI, 0.07 to 3.36]  $\mu\text{m}/\text{y}$ ;  $P = .04$ ) (Table 2).

**Factors Associated With the Rate of RNFL Thinning**

The factors affecting the rate of global RNFL thinning and the maximum rate of RNFL thinning were identified using regression analysis with a general linear model (eTables 2 and 3 in the Supplement). In the multivariable analysis, a higher untreated IOP ( $\beta = -0.07$  [95% CI, -0.11 to -0.03];  $P = .001$ ), episodes of optic disc hemorrhage ( $\beta = -0.74$  [95% CI, -1.79 to 0.31];  $P = .003$ ), the presence of  $\beta$ -zone parapapillary atrophy ( $\beta = -0.47$  [95% CI, -1.13 to 0.20];  $P = .02$ ), and the presence of ODPs ( $\beta = -0.41$  [95% CI, -1.14 to 0.32];  $P = .02$ ) were revealed as factors affecting the rate of global RNFL thinning (eTable 2 in the Supplement). The factors affecting the maximum rate of RNFL thinning were higher untreated IOP ( $\beta = -0.24$  [95% CI, -0.35 to -0.13];  $P < .001$ ), an episode of optic disc hemorrhage ( $\beta = -1.54$  [95% CI, -2.88 to -0.19];  $P < .001$ ), and the presence

Figure 3. Representative Cases Showing Rapid Retinal Nerve Fiber Layer (RNFL) Thinning at the Optic Disc Pit (ODP) Location



A and F, Photographic ODPs (arrowheads). B and G, Infrared images indicating the location at which the radial images were obtained (arrows). C and H, Swept-source optical coherence tomography (OCT) radial scan images show microscopic ODPs at the far-peripheral lamina cribrosa in the temporo-inferior (TI) sectors (large arrowheads). The lamina cribrosa tissue observed at the base of the lamina cribrosa defect indicates a partial-thickness

ODP (small arrowheads in part H). D and I, Thinning of the RNFL is seen in the TI sectors. Numbers represent RNFL thickness in micrometers. G indicates global; N, nasal; NI, nasoinferior; NS, nasosuperior; T, temporal; and TS, temporosuperior. E and J, Graphs demonstrate mean (SD) progressive global RNFL thinning and thinning in the sector with the ODP. P values are calculated from linear regression analysis.

( $\beta = -1.04$  [95% CI,  $-2.14$  to  $0.07$ ];  $P = .004$ ), far-peripheral location ( $\beta = -1.75$  [95% CI,  $-3.05$  to  $-0.46$ ];  $P = .008$ ), and partial-thickness depth ( $\beta = -1.45$  [95% CI,  $-2.75$  to  $-0.16$ ];  $P = .03$ ) of the ODP (eTable 3 in the Supplement).

### Representative Cases

Figure 3 shows 2 representative eyes with ODP. Progressive RNFL thinning is noticeable in the global area and TI sector, where the ODP is located.

### Discussion

This study investigated the factors associated with disease progression in primary open-angle glaucoma, with a focus on the influence of ODP on the rate of RNFL thinning. The findings

confirmed the already acknowledged factors affecting glaucoma progression—elevated IOP,<sup>23,24</sup> optic disc hemorrhage,<sup>14-16,24,25</sup> and the presence of  $\beta$ -zone peripapillary atrophy<sup>26-28</sup>—but also revealed a significant influence of the presence and structural characteristics of ODP on the rate of progressive RNFL thinning.

An association between ODP and progressive visual field damage has been proposed by some investigators.<sup>4-6</sup> Faridi et al<sup>5</sup> recently showed that focal lamina cribrosa defects, which may be a microscopic form of ODP,<sup>8,9</sup> are associated with a faster rate of visual field deterioration. The findings of the present study demonstrate that ODPs are also associated with progressive RNFL thinning and provide additional support for the association between the ODP and glaucoma progression. Optic disc pits have been suggested to represent a localized susceptibility of the lamina cribrosa to the damaging effects of el-

evated IOP.<sup>2,3,9</sup> We speculate that the presence of an ODP provides a background to accelerate the axonal damage that might proceed to continuous progression.

Some of the findings of this study suggest the presence of a spatial correlation between the locations of ODPs and the local progression. The difference in the rate of global RNFL thinning between the OPD and non-OPD groups was attributable mainly to the difference in that rate in the temporoinferior and temporal sectors (Table 1 and eFigure 2 in the Supplement), the locations at which the glaucomatous ODPs are most frequently observed.<sup>2-4,6,9,29,30</sup> In addition, the frequency distribution of the location where the fastest progression had occurred was correlated spatially with the location of the ODP (Figure 2). Based on the findings of this study, we can speculate that the presence of an ODP affects the progression of glaucoma, especially at the location where it appears.

The presence of an ODP was associated with the rate of progressive RNFL thinning in the present study, as were its structural characteristics. In the ODP group, the RNFL thinning in the sector containing an ODP was faster in eyes with a partial-thickness ODP than in those with a full-thickness ODP and in eyes with an ODP at the far periphery compared with those with an ODP at the midperiphery. In addition, both types of ODP were associated with the maximum rate of RNFL thinning. Given that a partially altered lamina cribrosa indicates an earlier structural change where the active damaging process is ongoing, the progressive damage is more likely to occur in eyes with a partial-thickness ODP than in those with a full-thickness ODP. On the other hand, the location of a partial-thickness ODP may be under larger stress and strain because the translaminal pressure gradient may get steeper where the lamina cribrosa is thinned, which compromises the axoplasmic transport at this location.<sup>31-36</sup> On the contrary, the tissue strain and the pressure gradient may be focally absent or decreased where the lamina cribrosa is nonexistent; thus, the influence of the pressure gradient on the axonal flow can be of a lesser degree at the location of a full-thickness ODP. Hence, we find it to be relevant that the RNFL thinning was faster in eyes with a partial-thickness ODP than in those with a full-thickness ODP. On the other hand, the finding that RNFL thinning was faster at the location of far-peripheral ODPs than at midperipheral ODPs may be explained by the anatomic characteristics of the far-peripheral lamina cribrosa near its insertion, arising from the discontinuity of tissues between the lamina cribrosa and the sclera.<sup>9</sup> The discontinuity between tis-

ues might render the far-peripheral lamina cribrosa more prone to deformation by compressive or tensile forces, which may lead to posterior migration or horizontal dehiscence of the peripheral lamina cribrosa,<sup>9</sup> as had been observed frequently in several previous studies.<sup>7,9,37</sup> We speculate that the additional stress that might be imposed on the peripheral lamina cribrosa is associated with the increased possibility of a more rapid progression at the location of far-peripheral ODPs.

Our study has a few limitations. First, we excluded patients with microscopically identified ODPs that were not visible on color fundus photography. However, we believe that this exclusion allowed a stricter distinction between groups and exclusion of normal anatomic variations and artifacts from the cohort. Second, only the temporal optic nerve head region was considered for examination because of the poor visualization of the lamina cribrosa structure at the nasal periphery. However, the investigation of only the temporal periphery is unlikely to have produced a biased result because acquired ODPs associated with glaucoma are rarely observed at the nasal periphery.<sup>2-4,6</sup> Third, the microstructure of ODPs was not determined at the time of study entry but by the end of the study. The ODP microstructure might have changed during the study period, which represents a potential source of bias. Last, the interval between spectral-domain OCT circumpapillary RNFL thickness measurements differed between patients, with the tests being more frequent in eyes with progressive disease. Although this variation would not have influenced the measured rate of RNFL thickness change, the smaller amount of data from the less frequent tests may have produced less reliable statistical results, and the shorter follow-up duration resulting from the shorter test interval may not have reflected the long-term progression accurately.

## Conclusions

The progressive RNFL thinning was faster in eyes with primary open-angle glaucoma and an ODP than in those without an ODP, with the most noticeable RNFL thinning observed at the location near the ODP. The presence of an ODP and its microstructural characteristics were associated with the rate of RNFL thinning. In glaucomatous eyes with ODPs, ongoing progressive damage should be suspected at the location of the ODP, especially when the ODP is located near the optic disc margin or when it is accompanied by a partial-thickness lamina cribrosa defect.

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