Relationships of Macular Functional Impairment With Structural and Vascular Changes According to Glaucoma Severity

Hye Seong Hwang,[1] Eun Ji Lee,[2] Hyunjoong Kim,[3] and Tae-Woo Kim[2]

[1]Department of Ophthalmology, Chungbuk National University College of Medicine, Chungbuk National University Hospital, Choengju, Korea
[2]Department of Ophthalmology, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Korea
[3]Department of Applied Statistics, Yonsei University, Seoul, Korea

Correspondence: Eun Ji Lee, Department of Ophthalmology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, No. 82, Gumi-ro 173 Beon-gil, Bundang-gu, Seongnam 13620, Korea; opticdisc@gmail.com.

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Purpose. To determine the pointwise relationships of central visual field (VF) defects with macular ganglion cell loss and macular vessel density (VD) loss during various stages of glaucoma.

Methods. Eyes with primary open-angle glaucoma (POAG) were subjected to optical coherence tomography (OCT) and OCT angiography (OCTA) to evaluate macular ganglion cell layer (GCL) thickness and macular VD in the superficial and deep vascular complexes (SVC and DVC). OCT, OCTA, and VF locations were matched after correcting for retinal ganglion cell (RGC) displacement. Pointwise correlations of GCL thickness and VDs of the SVC and DVC with central VF sensitivity (VFS) were evaluated by Pearson's correlation analysis and compared in eyes with early and advanced POAG by Meng's test.

Results. Of the 100 eyes, 52 and 48 were classified as early and advanced POAG. Macular VD showed overall better correlation with central VFS than GCL thickness in both the early and advanced groups. SVC density showed the strongest correlation with central VFS in all groups ($R = 0.327$ in early group, $R = 0.325$ in advanced group, all $P < 0.001$). Although DVC density showed better correlation with VFS ($R = 0.311$) than GCL thickness ($R = 0.212$) in the early group ($P < 0.001$), the correlation was comparable in the advanced group ($R = 0.199$ and 0.176, respectively, $P = 0.254$).

Conclusions. After adjustment for RGC displacement, macular SVC density was better correlated with central VFS than macular GCL thickness in both early and advanced POAG. Macular DVC density showed better correlation with VFS than GCL thickness in early but not in advanced POAG, indicating that DVC loss may be involved in early central VF loss.

Keywords: central visual field, optical coherence tomography angiography, primary open angle glaucoma, ganglion cell layer thickness

Central visual function is directly associated with vision-related quality of life.[1,2] The density of retinal ganglion cells (RGCs) is highest in the macula,[3] and structural changes in the macula may be indicators of impaired central visual function in glaucoma.[4,5] Because structural changes precede functional impairment during the early stage of glaucoma, evaluation of macular structure may be useful in predicting early impairment of central vision.[6,7] Macular evaluation may also be useful in monitoring advanced stage glaucoma, because the macula is less influenced by the floor effect of retinal vessels and connective tissues, after which further changes are not observable.[8–10]

Vessel density (VD) measured using optical coherence tomography (OCT) angiography (OCTA) has been shown to be a better indicator of visual function in eyes with glaucoma than OCT measurements of structural thickness.[11–15] Reduced macular VD was detected earlier than structural changes in the macula in eyes with suspected glaucoma and normal eyes.[16] In addition, OCTA was more resistant to the floor effect and showed better correlations with visual field (VF) parameters than retinal nerve fiber layer (RNFL) thickness[12,13] and ganglion cell complex thickness,[11,12] particularly in advanced glaucoma.[11–14,17]

The macular vasculature includes superficial (SVC) and deep (DVC) vascular complexes, the former supplying blood to the retina inside the ganglion cell layer and the latter perfusing the retina outside the inner nuclear layer. Studies using OCTA have mainly focused on the SVC, because it is directly associated with the tissues that are affected in glaucoma. However, decreased DVC density has been observed in several retinal diseases with impaired autoregulation.[18–22] Autoregulatory dysfunction is also involved in the pathogenesis of glaucoma, suggesting a need to determine the association of DVC with central visual function in glaucoma. One

study found that decreased deep macular VD was an independent risk factor for parafoveal scotoma in patients with normal tension glaucoma.[23]

Understanding the relationships of functional impairment with structural and vascular changes in the macula during the early and advanced stages of glaucoma, respectively, is of great concern to glaucoma specialists.[24] Evaluations of these relationships must consider that central VF location may correspond to slightly different areas of the retina due to displacements between RGCs and their corresponding photoreceptors.[24,25] Although macular structure-function relationships have been found to improve after adjusting for the average displacement of RGCs in the central macula,[26] studies evaluating the macular structure-vascularity-function relationships have not considered RGC displacement.[27] Moreover, most studies to date have assessed central VF using 24-2 VF tests, but only a small central portion of these test points correspond to the macular RGCs.

The present study was designed to evaluate how structure-function and vascularity-function relationships in the macula differ in the glaucoma continuum. Macular vasculatures were separately assessed in the SVC and DVC. For more accurate analysis, the central VF was evaluated using 10-2 tests, with the correlations assessed in a point-wise manner while considering the anatomic displacement of the RGCs.

Methods

This cross-sectional study included patients with primary open-angle glaucoma (POAG) who were enrolled in the Investigating Glaucoma Progression Study, an ongoing prospective study of patients with POAG at the Glaucoma Clinic of Seoul National University Bundang Hospital. All subjects provided written informed consent. The study protocol was approved by the institutional review board of Seoul National University Bundang Hospital and followed the tenets of the Declaration of Helsinki (IRB No. B-2303-815-103).

Participants

All participants underwent comprehensive ophthalmic examinations, including assessments of best-corrected visual acuity, Goldmann applanation tonometry, refraction tests, slit-lamp biomicroscopy, gonioscopy, stereo disc photography, red-free fundus photography (EOS D60 digital camera; Canon, Utsunomiyashi, Japan), measurement of circumpapillary RNFL thickness using spectral-domain OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany), OCTA scanning of macular area (Heidelberg Engineering), and SITA standard 24-2 central 10° VF evaluation with Humphrey Field Analyzer II 750 (Carl Zeiss Meditec, Dublin, CA, USA). Eyes were divided into those with early and advanced POAG, based on a mean deviation (MD) of −6 dB on 24-2 VF tests.[28] The classification of the VF pattern was divided into paracentral scotoma, nasal step, and others according to the ocular hypertension treatment study classification[29] based on the 24-2 VF test results. Other ophthalmic examinations included measurements of corneal curvature (KR-1800; Topcon Optical Company, Tokyo, Japan), central corneal thickness (Orbscan II; Bausch & Lomb Surgical, Rochester, NY, USA), and axial length (IOLMaster version 5; Carl Zeiss Meditec). The baseline intraocular pressure (IOP) was defined as the mean of two measurements before starting IOP-lowering treatment.

POAG was defined as an open-angle on gonioscopy, signs of glaucomatous optic nerve damage (e.g., neuroretinal rim notching, thinning, or a localized RNFL defect), and a glaucomatous VF defect. A glaucomatous VF defect was defined as a defect conforming to one or more of the following criteria: (1) results outside normal limits on glaucoma hemi field tests, (2) at least three adjacent abnormal points with a $P < 0.05$ probability of being normal and at least one with a $P < 0.01$ probability by pattern deviation, or (3) a pattern standard deviation of $P < 0.05$, confirmed on two consecutive reliable tests. VF tests were considered unreliable if fixation losses were >33%, false-negative errors were >33% (except when the VF MD was <−12 dB), or false-positive errors were >15%. All tests were reviewed for the presence of artifacts, including inappropriate fixation, fatigue, inattention or learning effects, eyelid or rim artifacts, or any evidence that the results were affected by a condition other than glaucoma (e.g., homonymous hemianopsia).

Eyes were excluded if they had a best-corrected visual acuity worse than 20/40; a spherical equivalent <−9.0 D or >+3.0 D; a cylinder correction <−3.0 D or >3.0 D; a history of intraocular surgery, except for uneventful cataract surgery or trabeculectomy; or retinal or neurologic diseases. For the eyes that underwent cataract surgery, axial length >30 mm was considered an exclusion criterion instead of spherical equivalent criterion. For the eyes that underwent trabeculectomy, images that were obtained at least six months apart from the time of the surgery was used for analysis. If both eyes of a subject were eligible, one was randomly selected for inclusion in the study.

Central Visual Field Evaluation

Threshold sensitivity in the central 10° VF was measured using the VF C10-2 pattern of a Humphrey Field Analyzer. Central VF sensitivity (VFS) was measured at 68 test locations 2° apart on vertical and horizontal axes within the 10° of the fixation point. To assess the correlations of structure and vascularity with function, the VFS values at the 68 locations were grouped to match the central macular grids of the OCT/OCTA scans accounting for the RGC displacement (Fig. 1).

OCT and OCTA Scanning of the Macula

OCT and OCTA images of the macula were acquired with a raster scan pattern of Spectralis, parallel to the fovea-Bruch's membrane opening axis centered on the fovea, using the 20° × 20° scan angle, consisting of 512 B-scans and 512 A-scans per B-scan. The image acquisition process was programmed to automatically stop for images with lower quality scores, and the images of those sections were excluded. Only eyes with a quality score >15 in all sections were included. Eyes were excluded from analysis when the quality of the OCTA images was poor or when the vascular signal was blocked by artifacts. The right eye format was used for all eyes.

The new software for the Spectralis device provides structural and vascular information simultaneously in the same volumetric scans. En face projections of the volumetric scans enable the visualization of both structural and vascular details within each segmented layer. Thickness information of each pixel in the individual segmented layers can

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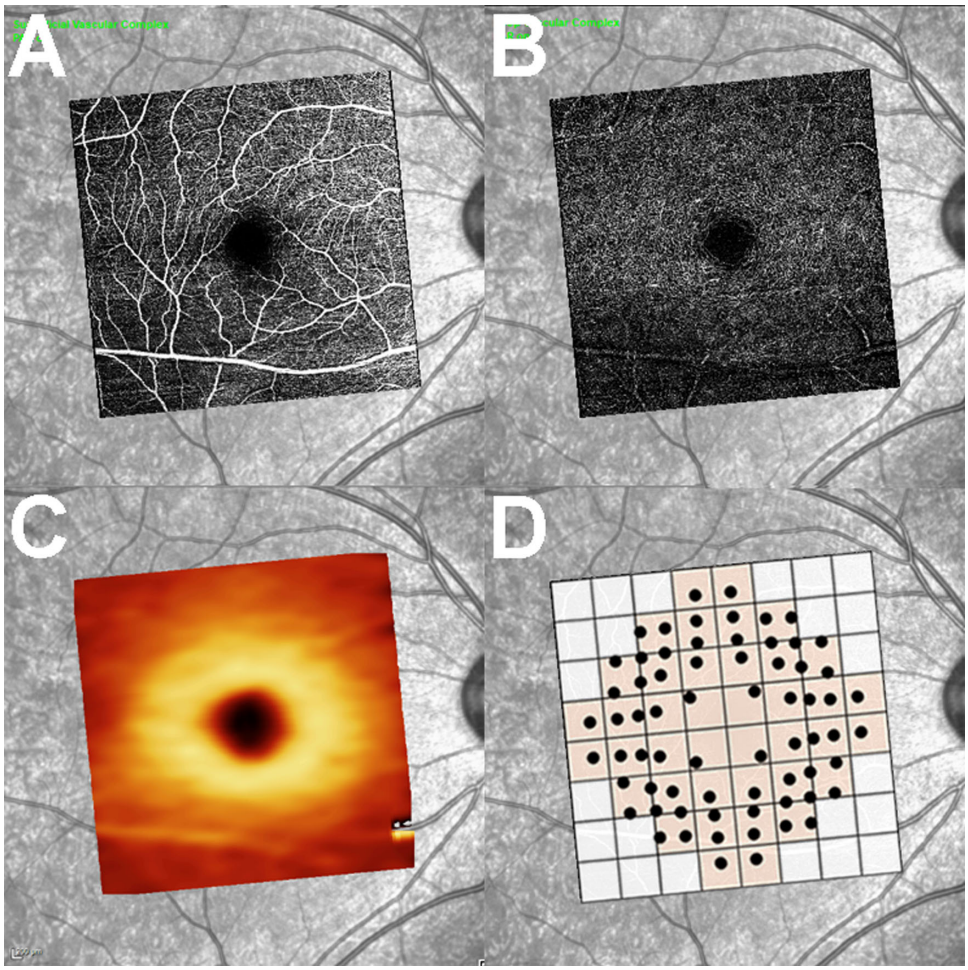

Figure 1. En-face OCTA images of (**A**) an SVC, (**B**) a DVC, and (**C**) an OCT macular thickness map of the ganglion cell layer. Macular OCTA and OCT images were acquired during the same session, using a raster scan pattern of Spectralis, parallel to the fovea-Bruch's membrane opening axis centered on the fovea, using a 20° × 20° scan angle. (**D**) Anatomic overlay of the test locations from the 10-2 visual field onto the macular OCTA/OCT images, after adjusting for retinal ganglion cell displacement.

be exported as .xls files using Spectralis software. In the present study, ganglion cell layer (GCL) thickness was used to assess macular structural thickness. An 8 × 8 grid of thickness measurements was created from the 512 × 512 pixel thickness data in the central 20° × 20° of the macula (Fig. 1).[24] The analysis included 40 of the 64 sections that corresponded to the area of VF assessment.

Vascular data were acquired from the same volumetric scans that assessed thickness information. En face OCTA images of the SVC and DVC were generated using the segmentation algorithm by the built-in software. En face OCTA images were exported from the image viewer software (Heidelberg Eye Explorer, software version 1.21; Heidelberg Engineering, Heidelberg, Germany) after projection artifact removal.[30] All OCTA scans were processed to reduce noise (filtering) and enhance vessel detection, as described previously.[31] The images were imported into an automated customized MATLAB (The MathWorks, Natick, MA, USA) program for image analysis.[32] Specifically, a locally adaptive image thresholding algorithm was used to generate binarized images by distinguishing regions with and without blood flow.[33] VD was calculated from the resulting binarized images and defined as sum of the pixels with flow. An 8 × 8 grid of VD measurements was created from the 512 × 512 pixel data in the central 20° × 20° of the macula (Fig. 1). The analysis included 40 locations on the 8 × 8 grid that corresponded to the area of VF assessment. Any errors in the layer segmentation were addressed by inspecting all B-scan images and correcting the errors manually.

Mapping of Macular GCL Thickness, VD, and Central VFS

The correlations of GCL thickness and VDs in the central 20° macular region, with the central VF 10-2 threshold results were assessed both globally and in the 40 individual macular grids. The VF locations were flipped vertically to match the corresponding superpixels of the displayed images.

The VF locations were correlated with individual macular grids after adjusting for RGC displacement (Fig. 1).[25,26] Because some grids corresponded to more than one VF location, the average linear scale VFS values were calculated for those locations, and the logarithms of these averages were analyzed.

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Statistical Data Processing

Correlations of central VFS with macular GCL thickness, SVC density and DVC density were assessed using Pearson's correlation analysis. Meng's test was used to evaluate differences in the correlation coefficients of central VFS with GCL thickness, SVC density and DVC density. Except when indicated otherwise, all data are presented as mean ± SD. Continuous variables were compared using Student's *t*-tests, and categorical variables were compared using χ^2 tests. Correlation analyses were performed using R statistical software (version R.4.1.2). Other statistical analyses were performed using SPSS version 22.0 software (SPSS, Inc., Chicago, IL, USA), with $P < 0.05$ considered statistically significant.

Results

The study included 100 eyes of 100 patients with POAG who met the eligibility criteria. The population consisted of 52 eyes with early and 48 eyes with advanced VF damage. Table 1 compares the clinical characteristics of eyes in the early and advanced groups. There were no between-group differences in age, sex distribution, history of trabeculectomy, number of IOP lowering drug, prevalence of diabetes mellitus, prevalence of systemic hypertension, axial length, central corneal thickness, baseline IOP and ocular hypertension treatment study classification of VF defect pattern. Baseline VF MD and pattern standard deviation were significantly worse and baseline global RNFL thickness was significantly lower in the advanced than in the early group (all $P < 0.001$). Although global SVC density was significantly higher in the early group ($P = 0.011$), global DVC density did not differ in the two groups. Global GCL thickness was significantly greater in the early than in the advanced group ($P < 0.001$).

Global Correlations Between the VD and GCL Thickness in the Macula and Central VFS

The global SVC ($R = 0.407$, $P < 0.001$) and DVC ($R = 0.343$, $P < 0.001$) densities and the global GCL thickness ($R = 0.357$, $P < 0.001$) were all significantly correlated with central VFS in the entire patient population. In the early glaucoma group, global SVC ($R = 0.506$, $P < 0.001$) and DVC ($R = 0.483$, $P < 0.001$) densities correlated significantly with central VFS, but global GCL thickness did not correlate with central VFS ($R = 0.109$, $P = 0.445$). In the advanced glaucoma group, however, global SVC ($R = 0.334$, $P = 0.020$) and DVC ($R = 0.293$, $P = 0.043$) densities and global GCL thickness ($R = 0.375$, $P = 0.009$) were all significantly correlated with central VFS.

Pointwise Correlations Between the VD and GCL Thickness in the Macula and Central VFS After Adjustment for RGC Displacement

Pointwise correlation analysis after adjusting for RGC displacement showed that the SVC and DVC densities and the GCL thickness were all significantly correlated with central VFS in both the early and advanced groups (Table 2, Fig. 2). In both groups, SVC density showed a higher correlation with central VFS than did GCL thickness (all $P < 0.001$) and DVC density ($P = 0.049$ in the early group, $P < 0.001$ in the advanced group). DVC density showed a higher correlation coefficient than GCL thickness ($P < 0.001$) in the early group, whereas the correlations were comparable in the advanced group ($P = 0.254$). The early and advanced groups showed comparable correlations of SVC density ($P = 0.927$) and GCL thickness ($P = 0.095$) with central VFS. In contrast, DVC density showed a significantly higher correlation with central VFS in the early than in the advanced group ($P < 0.001$).

Table 1. Comparison of Clinical Characteristics Between Early and Moderate to Advanced Group

	Early Group ($n = 52$)	Advanced Group ($n = 48$)	*P* Value
Age (y)	53.02 ± 15.50	58.33 ± 18.00	0.116*
Male/Female	34/18	18/10	0.125†
History of trabeculectomy	5.77%	25.00%	**0.007***
Number of IOP-lowering drugs	1.65 ± 1.19	2.25 ± 1.42	**0.025***
Diabetes mellitus	13.46%	18.75%	0.471†
Hypertension	21.15%	25.00%	0.648†
Axial length (mm)	25.51 ± 1.86	25.29 ± 1.92	0.577*
Central corneal thickness (µm)	524.20 ± 49.08	523.09 ± 46.86	0.911*
Baseline IOP (mm Hg)	17.72 ± 7.51	19.84 ± 9.41	0.214*
Baseline Visual field MD (C 24-2, dB)	−2.51 ± 1.71	−15.34 ± 6.70	—
Baseline Visual field PSD (C 24-2, dB)	3.44 ± 2.06	11.13 ± 2.74	**<0.001***
Baseline Visual field MD (C 10-2, dB)	−2.29 ± 2.91	−13.95 ± 8.31	**<0.001***
Baseline RNFL thickness (µm)	76.98 ± 12.17	58.33 ± 13.14	**<0.001***
Global SVC density	897.26 ± 378.75	710.70 ± 337.10	**0.011***
Global DVC density	1266.57 ± 509.46	1142.94 ± 447.02	0.202*
Global GCL thickness	29.35 ± 3.35	26.52 ± 3.50	**<0.001***
Visual field sensitivity	30.77 ± 3.00	19.70 ± 7.68	**<0.001***
Visual field classification			0.297†
Paracentral scotoma	17.31%	14.58%	
Nasal step	30.77%	43.75%	
Others	51.92%	41.67%	

PSD, pattern standard deviation.
* Student's *t*-test, significant *P* values are shown in bold.
† χ^2 test, significant *P* values are shown in bold.

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Table 2. Comparison of the Correlation Coefficients of the Vascular-Function and Structure-Function Relationships in POAG Eyes in the Early and Advanced Groups

	All (n = 100)		Early Group (n =52)		Advanced Group (n = 48)		P Value† (Early vs. Advanced Groups)
	R	P Value*	R	P Value*	R	P Value*	
SVC density	0.316	**<0.001**	0.327	**<0.001**	0.325	**<0.001**	0.927
DVC density	0.220	**<0.001**	0.311	**<0.001**	0.199	**<0.001**	**<0.001**
GCL thickness	0.234	**<0.001**	0.212	**<0.001**	0.176	**<0.001**	0.095
Strength of correlations with VFS†	SVC > DVC = GCL		SVC > DVC > GCL		SVC > DVC = GCL		

R, Pearson's correlation coefficient.
* Pearson's correlation analysis, significant P values are shown in bold.
† Meng's test, significant P values are shown in bold.

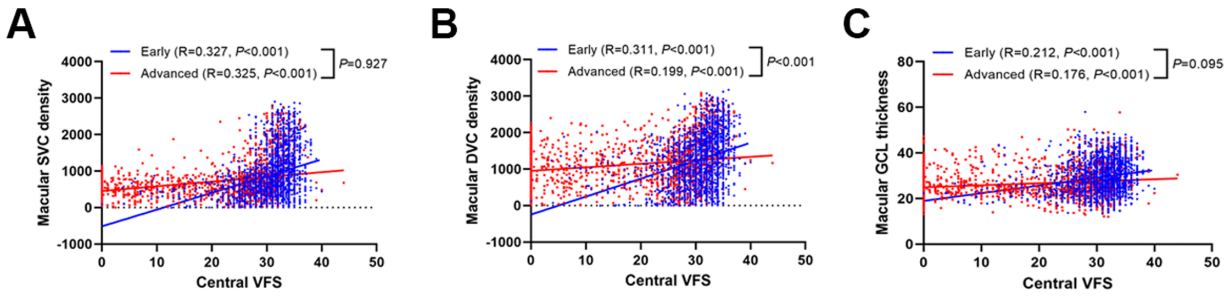

Figure 2. Correlations between (**A**) macular SVC density and central VFS, (**B**) macular DVC density and central VFS, and (**C**) macular GCL thickness and central VFS in eyes with early (*blue*) and advanced (*red*) glaucoma.

Figure 3 shows regional correlations of VFS with macular SVC density, macular DVC density and macular GCL thickness in the early (Fig. 3A) and advanced (Fig. 3B) groups. Locations with statistically significant correlations are shown in red scale, based on the correlation coefficients. SVC density showed good correlations with central VFS in almost all locations in both the early (Fig. 3A) and advanced (Fig. 3B) groups. However, fewer locations in the

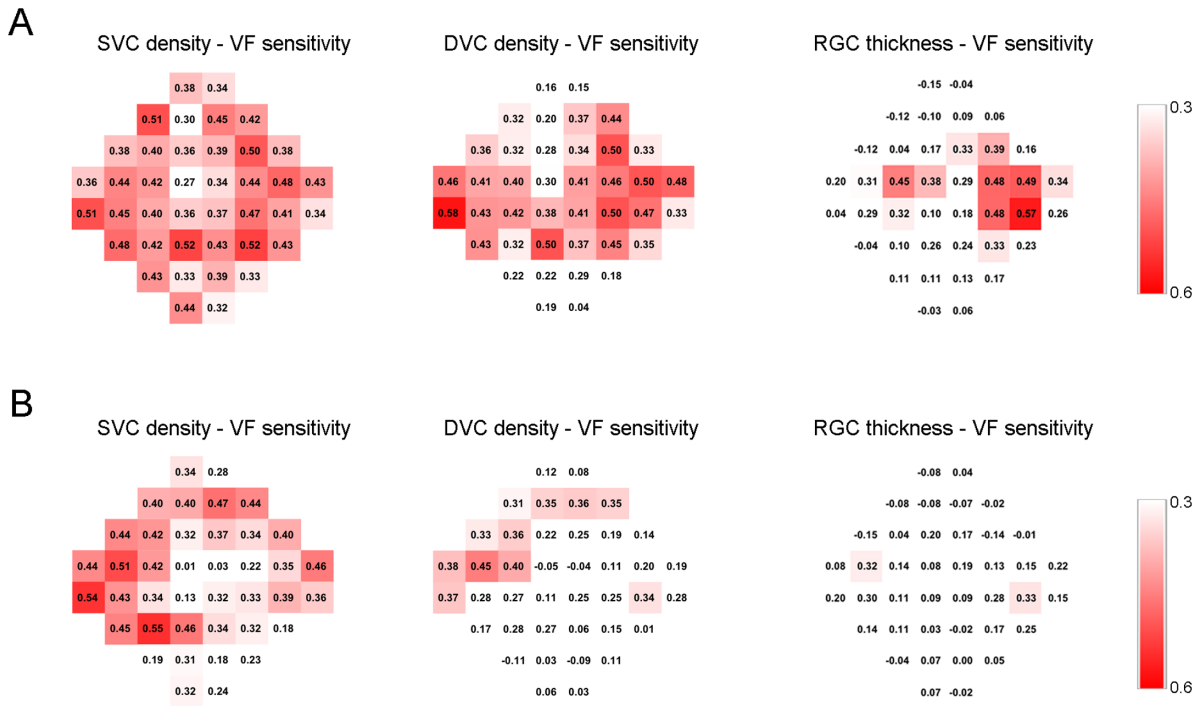

Figure 3. Sectoral correlation coefficients between SVC density and VFS, between DVC density and VFS and between GCL thickness and VFS in the macula of patients with (**A**) early and (**B**) advanced glaucoma. Locations with statistically significant correlations are shown in *red scale*.

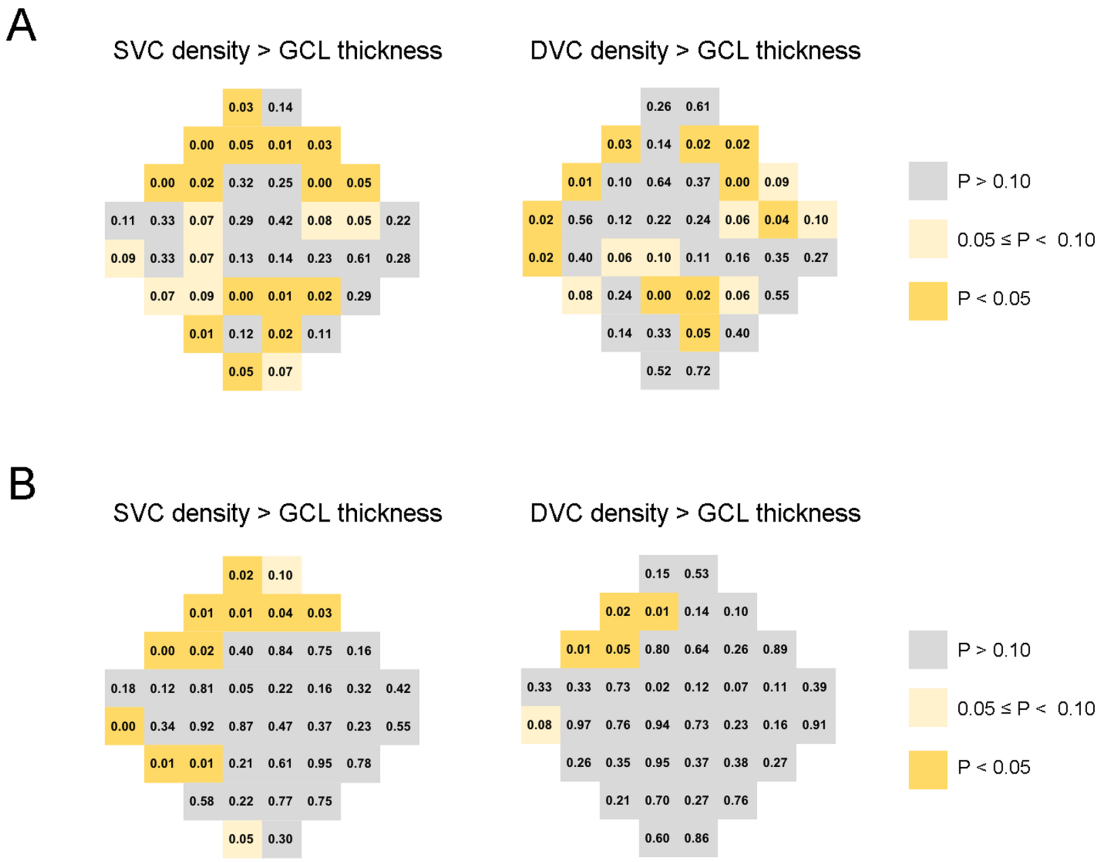

Figure 4. Sectors in which macular vessel density showed stronger correlation with VFS than macular GCL thickness in patients with (**A**) early and (**B**) advanced glaucoma. *Yellow* sectors indicate the locations at which vascularity-function correlations were significantly better than structure-function correlations ($P < 0.05$), and *light yellow* sectors indicate marginally better correlations ($0.05 \leq P < 0.10$).

advanced than in the early group showed significant correlations between DVC density and VFS. Although significant correlations between GCL thickness and VFS were observed at perifoveal locations of the early group (Fig. 3A), these locations were rare in the advanced group (Fig. 3B). Figure 4 shows the locations at which the correlation coefficient of VFS with SVC or DVC density was larger than the correlation coefficient of VFS with GCL thickness in the early (Fig. 4A) and advanced (Fig. 4B) groups. Locations at which the vascularity-function correlations were better than the structure-function correlations are indicated in yellow scale, based on the probability of type 1 errors.

Figure 5 shows correlations of central VFS with SVC density and DVC density in the early (Fig. 5A) and advanced (Fig. 5B) groups, as well as the locations at which the correlation coefficients of SVC density were significantly higher than those of DVC density in the early (Fig. 5C) and advanced (Fig. 5D) groups. In both groups, SVC density was better correlated with central VFS than was DVC density ($P \leq 0.049$). Figure 6 shows OCT, OCTA, and C10-2 VF results of the eyes in the early (Figs. 6A–E) and advanced (Figs. 6F–J) glaucoma groups.

Discussion

The present study describes the results of pointwise analyses of vascularity-structure-function correlations in the macula after adjustments for RGC displacement. Generally, VD performed better than structural thickness in diagnosing functional loss in the macula in both early and advanced glaucoma. In addition, SVC density was more highly correlated with central VFS than GCL thickness in both early- and advanced-stage glaucoma patients. In contrast, DVC density showed a higher correlation with VFS than did GCL thickness in patients with early, but not advanced, glaucoma.

Macular RGC damage has been shown to correlate well with central 10° VF damage.[26,34,35] However, significant structure-function correlations were found to be present at only some test points in the macula after adjusting for RGC displacement,[4] findings comparable to those of the present study. Although average macular GCL thickness showed good correlation with central VFS in the present study, significant correlations were observed at only some perifoveal locations, with fewer locations present in advanced than in early glaucoma. RGC displacement can affect measurements of GCL thickness, making them appear thicker and underestimating the degree of structural damage. Also, the macular GCL thickness has a peak in the narrow annuls-shaped rage, which may weaken the correlation with the wider 10-2 VF region.[36] In fact, in the present study, a correlation peak between GCL thickness and central VFS was observed slightly inside the outermost periphery of 10-2 VF, and the degree of correlation was relatively low in other regions. VD, however, is less affected by such displacement, suggesting that this parameter may more accurately represent functional damage in the macula.

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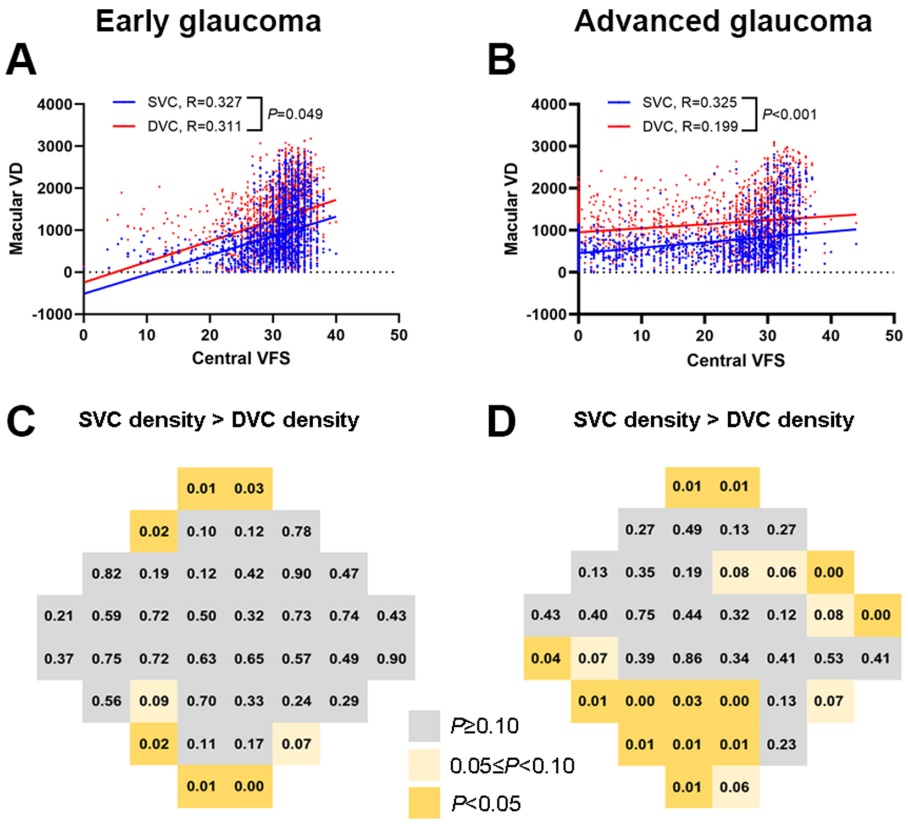

Figure 5. Correlations between macular vessel densities of the superficial and deep vascular layers and central VFS in (**A, C**) early and (**B, D**) advanced glaucoma. Sectors in which the SVC density was significantly better correlated with VFS than DVC density ($P < 0.05$) are shown in *yellow*, whereas those with marginal significance ($0.05 \leq P < 0.10$) are shown in *light yellow*.

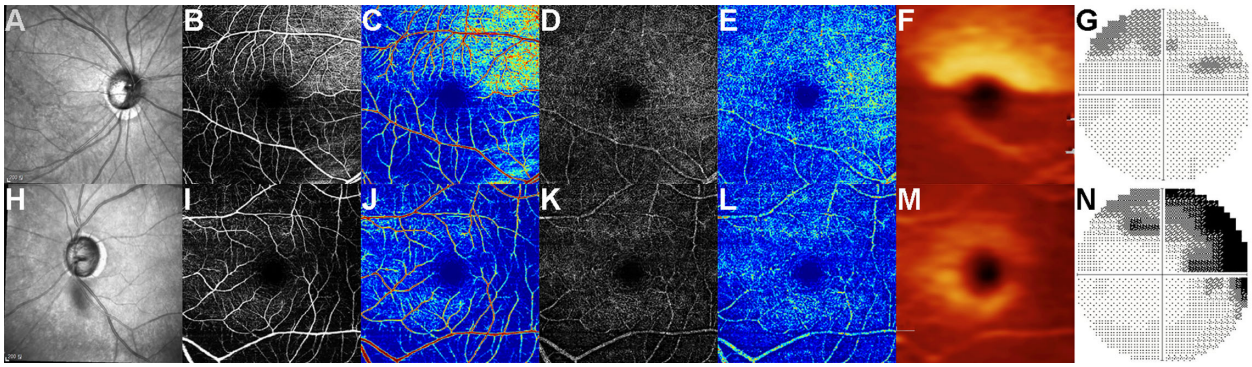

Figure 6. Representative cases of early (**A–G**) and advanced (**H–N**) groups. Infrared fundus images (**A, H**), en-face OCT angiography images of superficial vascular complex (**B, C, I, J**) and deep vascular complex (**D, E, K, L**), OCT macular thickness maps of the ganglion cell layer (**F, M**), and grayscales of central 10-2 visual field tests (**G, N**).

Structural loss can lead to a secondary decrease in vascular perfusion, whereas primary vascular compromise can also induce structural damage, suggesting a need to determine associations between structure, vascularity and function during different stages of glaucoma. Macular SVC density was found to better correlate with 24-2 VFS than macular structural thickness in advanced glaucoma.[11,12] Moreover, reduced SVC density in the macula was found to correlate significantly with central 10° VF defect, with SVC density being superior to GCL thickness in differentiating between glaucomatous and healthy eyes.[37] In the present study, SVC density was better correlated with central 10° VFS than macular GCL thickness in both the early and advanced glaucoma groups. Macular SVC supplies macular RNFL, GCL and part of the inner plexiform layer[38,39] and is most likely associated with glaucomatous changes. It is possible that reduced SVC perfusion precede the loss of macular RGC in early-stage glaucoma. In contrast, GCL thickness may be influenced by the floor effect, resulting in the better performance of SVC density.

In contrast to the results of the present study, a previous study reported that the correlation between VF and

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SVC density was low in early stage but high in advanced-stage glaucoma.[11] However, these studies may not be directly comparable, because of differences in the analyzed regions and glaucoma stages. In addition, the previous study reported the results of 24-2 VF tests rather than those of 10-2 VF tests, and RGC displacement was not considered.

Studies of macular DVC changes in glaucoma have yielded conflicting results. Several studies have reported that the DVC density is relatively conserved in glaucoma,[40–42] whereas other studies have reported evidence of impairment.[43–45] In the present study, macular DVC density was more highly correlated with central VFS than was GCL thickness during early-stage glaucoma. Decreased DVC density has been observed in several retinal diseases characterized by impaired autoregulation of retinal vessels[18–22] and associated with a greater risk of developing VF damage in patients with preperimetric normal-tension glaucoma.[46] Additional studies are required to determine the pathogenic importance of DVC perfusion in early glaucoma.

In contrast to early-stage glaucoma, DVC density did not correlate with central VFS in advanced glaucoma, with the correlation in the latter being comparable to that between GCL thickness and VFS. Given that DVC density reflects the autoregulatory function of the retinal vasculature, DVC density may decrease in early-stage glaucoma but be relatively well preserved compared with SVC density in advanced stage glaucoma. It is also possible that DVC density already reached at its lower limit in the early stage; thus it did not further decrease with progression toward advanced stage. Alternatively, vascular signals in the deeper layer may be affected by projection from the superficial retinal vessels, which are more abundant in early-stage glaucoma.[47] More advanced glaucoma with lower SVC density may allow more vessels to be visible in the deeper layer, resulting in a tendency of DVC density to increase with disease progression.[42] The likelihood of the latter is low, however, because any potential signal from the superficial vessels would be excluded by the subtraction algorithm from the determination of density in the evaluation of DVC.

The present study had several limitations. First, the macular scanning was performed based on the foveal-BM opening axis, which was manually determined by an examiner, not based on the automated algorithm in the Spectralis. The current version of Spectralis does not have an OCTA scanning algorithm for the fovea-BM opening axis. Because the Spectralis examiner in the present study had more than 10 years of experience, any errors that may have been caused by misalignment were likely minimal and not larger than the potential test-retest variability of an automated algorithm. Second, GCL thickness typically has lower values than the thickness of ganglion cell complex, rendering changes more difficult to detect. In the present study, we used the new Spectralis software providing structural and vascular information simultaneously in the same volumetric scans. Using the Spectralis software, the GCL thickness could be directly exported without processing. It has been previously shown that GCL thickness was equivalent to ganglion cell complex thickness in glaucoma diagnostic accuracy,[48] and a study using machine learning also showed that GCL thickness measurement was the most important predictor for early glaucoma detection.[49] Third, early and advanced VF damage was defined based on C 24-2 VF results, whereas the present study was mainly based on 10-2 test results.[28] Although central visual function is important in determining the quality of vision in glaucoma patients, the use of the central 10-2 field alone for glaucoma staging, while omitting peripheral VF, may not accurately represent glaucoma severity. This limitation may arise in other studies dealing with functional assessment of the macula and should be considered in the interpretation of the present results. Fourth, all study subjects were of Korean ethnicity, indicating a need to test the applicability of these results to subjects of other races and/or ethnicities. Finally, this study was retrospective in design and included a relatively small number of subjects.

In conclusion, SVC density in the macular area, as determined by OCTA, was better correlated with central VFS than was structural GCL thickness, as measured by OCT, in both early and advanced POAG. These findings indicated that the vascularity-function correlation was stronger than the structure-function correlation in the macula regardless of the stage of disease. Macular DVC density was superior to GCL thickness in representing the central VFS in early, but not in advanced, OAG. Further studies are needed to determine differential vascularity-function relationships in the macula according to vascular layers and the stage of glaucoma.

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Investigative Ophthalmology & Visual Science

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