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Peripapillary choroidal thickness in untreated normal-tension glaucoma eyes with a single-hemifield retinal nerve fiber layer defect

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Abstract

The aim of this study was to evaluate the regional variations of peripapillary choroidal thickness (PCT) in normal-tension glaucoma (NTG) patients with a retinal nerve fiber layer (RNFL) defect localized to a single superior or inferior hemifield. This is a retrospective, cross-sectional study.

Ninety-five NTG patients and 53 normal subjects were divided into 3 groups: 34 eyes with a superior RNFL defect (group A), 61 eyes with an inferior RNFL defect (group B), and 53 normal eyes (group C). The average, quadrant, and clock-hour RNFL thickness (RNFLT) and PCT were measured using spectral-domain optical coherence tomography. Choroidal thickness ratio (CTR) was defined as the ratio of the measured PCT at a quadrant or a clock-hour position to the average PCT of an individual. The PCT, CTR, and RNFLT were compared among 3 groups.

The average PCT of NTG patients was thinner compared to that of healthy subjects (154.17 vs. 180.65 μm, $P < .001$). Although the average, quadrant, and clock-hour PCTs were not different between groups A and B, the CTR at 11 o'clock was significantly lower in group A compared to that of group B. The 11 o'clock CTR was an independent factor for the initial location of a RNFL defect ($P = .03$).

Eyes with NTG showed regional differences in CTR according to the hemisphere location of their initial RNFL damage. Therefore, CTR may be more useful than the absolute PCT value to assess regional PCT differences in eyes with NTG.

Abbreviations: BCVA = best corrected visual acuity, CCT = central corneal thickness, CTR = choroidal thickness ratio, IOP = intraocular pressure, IT = inferotemporal, MD = mean deviation, NTG = normal-tension glaucoma, OCT = optical coherence tomography, ONH = optic nerve head, PCT = peripapillary choroidal thickness, PPA = peripapillary atrophy, RNFL = retinal nerve fiber layer, RNFLT = retinal nerve fiber layer thickness, ST = superotemporal, VF = visual field.

Keywords: choroid, normal-tension glaucoma, open-angle glaucoma, peripapillary choroidal thickness, retinal nerve fiber layer thickness

1. Introduction

Glaucoma is a progressive optic neuropathy characterized by structural loss and corresponding visual field (VF) defects, and it is one of the leading causes of blindness.[1] Although the exact mechanism of glaucomatous damage is unknown, increased intraocular pressure (IOP) is the main risk factor for glaucoma.[2] However, glaucomatous optic neuropathy can develop or progress in untreated eyes with normal IOP, or in eyes with an IOP lowered by glaucoma treatment. Hence, IOP-independent factors have been studied in the pathogenesis of glaucoma; reduced blood flow to the optic nerve head (ONH) has been reported to be implicated in the pathogenesis of normal-tension glaucoma (NTG).[3–6]

In addition to an insufficient blood flow to the retinal arterioles, an abnormal blood supply to the peripapillary choroid has also been hypothesized to play a role in the pathogenesis of glaucoma.[6,7] Several studies have indicated thinner peripapillary choroidal thickness (PCT) in glaucomatous eyes following post-mortem histologic examination, or by in vivo imaging using optical coherence tomography (OCT).[8–12] However, other studies have failed to report an association between choroidal thickness and the incidence of glaucoma.[13–15] Such conflicting outcomes among the past studies may be attributed to the differences in the methodology, patient characteristics, or inclusion of confounding factors. Age, axial length, IOP, myopia, and the presence of peripapillary atrophy (PPA) were found to influence the choroidal thickness.[15,16] Previous studies have mostly compared the direct measurements of global or regional choroidal thicknesses between glaucomatous and normal eyes. However, regional variations in PCT have been demonstrated, with the thickest PCT observed superiorly, and the thinnest PCT inferiorly.[16,17]

Therefore, we speculated that the choroidal thickness ratio (CTR), which is the ratio of the measured choroidal thickness of each quadrant, or clock-hour to the patient's individual average choroidal thickness, might be useful to evaluate the differences in PCT between glaucomatous and healthy subjects. We hypothesized that a reduced CTR at a specific area may be associated with

Editor: Michael Smolek.

Supplemental Digital Content is available for this article.

The authors report no conflicts of interest.

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Medicine (2018) 97:23(e11001)

Received: 6 January 2018 / Accepted: 14 May 2018

http://dx.doi.org/10.1097/MD.0000000000011001

the retinal nerve fiber layer (RNFL) damage at the corresponding area in glaucoma patients.

In this study, we investigated the regional variations of the PCT and CTR in NTG patients with a RNFL defect localized to a single hemifield. We compared these parameters with those measured from the healthy subjects, and also within the NTG patients.

2. Methods

We reviewed the database of NTG patients who visited the glaucoma clinic at Korea University Anam Hospital from October 2010 to September 2014, and we retrieved the data of those who had not been treated with IOP-lowering medication when they were first diagnosed as NTG in both eyes. We reviewed the patient medical records for medical history and ophthalmic examinations, including best corrected visual acuity (BCVA), refraction, axial length, gonioscopy, central corneal thickness (CCT), Goldmann applanation tonometry, dilated stereoscopic examination of the optic disc, color disc and red-free fundus photography (model FF 450 Plus; Carl Zeiss Meditec AG, Jena, Germany), spectral-domain OCT (SD-OCT; 3D OCT-1000 Mark II, software version 3.20, Topcon, Tokyo, Japan), and 30–2 Swedish interactive threshold algorithm standard automated perimetry (Carl Zeiss Meditec, Dublin, CA). This study was approved by the Institutional Review Boards and Ethics committee of Korea University Anam Hospital and was performed according to the tenets of the Declaration of Helsinki.

The subjects included in this study met the following criteria: glaucomatous optic neuropathy with rim thinning, notching, and RNFL defect; baseline IOP of less than 21 mmHg; at least 2 reliable glaucomatous VF test results with false-positive and false-negative errors less than 15%, and a fixation loss less than 20%; presence of a normal anterior chamber and an open angle; BCVA >20/40; and an axial length <26 mm. Subjects were excluded if they presented the following: history of ocular trauma or ocular surgery; history of retinal diseases, such as diabetic retinopathy, retinal vessel occlusion, or epiretinal membrane; media opacity that could affect the quality of photography; optic nerve disease other than glaucoma; eyes with PPA; or history of a cerebrovascular event or systemic medication use that could affect the VF. If both eyes were eligible for inclusion, 1 eye was randomly selected for analysis.

Age-matched healthy subjects were selected from a cohort of patients who had visited the Korea University Anam Hospital for regular check-ups of incipient cataract, dry eyes, or myopia, and showed no glaucomatous optic disc appearance, no RNFL defect on red-free fundus photography, and had normal standard automated perimetry results.

2.1. Definition of superior and inferior RNFL group

We analyzed the overall pattern of RNFL defects in eyes with NTG using red-free fundus photographs in a blinded fashion by 2 independent observers (JHP and CY). RNFL defects were diagnosed as described elsewhere,[18,19] based on consensus between 2 independent observers on the red-free fundus photographs. The RNFL defects were localized to a single superior or inferior hemifield and were also confirmed by comparison with the OCT RNFL thickness profile using the 1% value of the normative data as a cut-off. Eyes with a diffuse RNFL defect, ambiguous lesions, and bihemispheric RNFL defects were excluded from further analysis. Subsequently, the glaucomatous eyes were divided into the following 2 groups based on the presence of a RNFL defect either in the superior or in the inferior hemisphere: group A for eyes with a superior hemispheric RNFL defect, and group B for eyes with an inferior hemispheric RNFL defect.

2.2. Measurements of RNFL thickness and PCT

A standard protocol for RNFL assessment using a 360-degree 3.4-mm diameter circle scan around the optic disc was used to investigate the RNFL and peripapillary choroid. The circle scan image provides 12 sectors around the disc, and each sector was numbered from 1 o'clock to 12 o'clock in a clockwise direction in the right eye, and a counterclockwise direction in the left eye.

RNFL thicknesses (RNFLT; average, quadrants, and clock-hours) were derived automatically from a scan using the in-built automated software for segmentation. The PCT was measured manually by using a previously reported method.[18] Briefly, using the modification tool in the OCT image viewer program, we modified the segmentation line presenting retinal pigment epithelium to the choriosclera junction. With the modification, we obtained the chorioretinal thickness between the internal limiting membrane and the choriosclera junction. PCT was calculated by subtracting the retinal thickness from the chorioretinal thickness. The measurements were performed by 2 independent observers (JHP and CY), and the mean of these observations was used for the analysis. In addition, we defined CTR as the ratio of the measured PCT at each quadrant or clock-hour to the patient's average PCT, and evaluated whether the CTRs were different among the 3 groups.

2.3. Association between PCT and CTR with RNFL thickness and the location of the initial RNFL defect

We evaluated the association of PCT or CTR with RNFL thickness at the corresponding locations. In addition, we investigated the differences in CTR and RNFL thickness according to the location of the RNFL defects. As most of the RNFL defects were located at either inferotemporal (IT) or superotemporal (ST) areas, the PCT and CTR at the 7 to 8 o'clock sectors and the 10 to 11 o'clock sectors were used specifically for analysis.

2.4. Statistical analysis

A statistical analysis was performed using SPSS software (version 21.0; SPSS, Chicago, IL). The baseline characteristics, RNFLT, PCT, and CTR were compared among groups with χ^2 tests for categorical variables, and with analysis of variance with post hoc analysis (Tukey method) for continuous variables. To investigate the association of PCT with RNFLT, we performed a linear regression analysis. Factors associated with the location of the initial RNFL defect were evaluated by logistic regression analysis. A P value $<.05$ was considered statistically significant.

3. Results

A total of 53 healthy eyes and 95 glaucomatous eyes were included in this cross-sectional study (Table 1). Thirty-four glaucomatous eyes had a superior RNFL defect, and 61 glaucomatous eyes had an inferior RNFL defect. There were no significant differences in the age, sex distribution, axial length, CCT, and refraction parameters between the control and glaucoma groups (all $P > .05$). Baseline IOP was similar between

Table 1

Comparison of baseline characteristics between glaucomatous eyes with a superior or inferior RNFL defect and non-glaucomatous control eyes.

Characteristics	Group A (mean ± SD, n = 34)	Group B (mean ± SD, n = 61)	Group C (mean ± SD, n = 53)	P^*	$P^\dagger_{A-B}$	$P^\dagger_{A-C}$	$P^\dagger_{B-C}$
Age, y	58.26 ± 12.87	56.54 ± 11.74	53.15 ± 13.77	.156			
Sex, female ratio (%)	55.9	42.6	45.3	.449‡			
Spherical equivalent (diopters)	0.11 ± 1.49	−0.64 ± 2.09	−0.83 ± 2.15	.148			
Axial length, mm	23.68 ± 1.05	23.93 ± 0.91	24.04 ± 1.01	.247			
Central corneal thickness, μm	516.76 ± 38.43	521.07 ± 31.48	523.04 ± 39.43	.730			
Untreated IOP, mmHg	15.5 ± 2.4	15.7 ± 2.6	14.6 ± 1.9	.042	.946	.183	.043
Mean deviation, dB	−3.78 ± 3.96	−4.08 ± 3.11	−0.93 ± 1.45	<.001	.882	<.001	<.001
Average RNFL thickness, μm	95.85 ± 16.81	93.56 ± 11.72	112.51 ± 8.67	<.001	.653	<.001	<.001

Group A = glaucomatous eyes with a superior RNFL defect, Group B = glaucomatous eyes with an inferior RNFL defect, Group C = non-glaucomatous eyes, IOP = intraocular pressure, RNFL = retinal nerve fiber layer, SD = standard deviation.

* Analysis of variance.

† Post-hoc analysis with Tukey method.

‡ χ^2 test.

glaucomatous eyes with superior RNFL defects and those with inferior RNFL defects (15.5 ± 2.4 vs. 15.7 ± 2.6 mmHg, $P = .95$), whereas it was significantly lower in the control group compared to the NTG eyes with an inferior RNFL defect (14.6 ± 1.9 vs. 15.7 ± 2.6 mmHg, $P = .04$). Although the mean deviation (MD) of VF was worse for glaucomatous eyes than for the control, it did not differ significantly between the 2 glaucoma groups ($P = .88$).

Except for the RNFL thicknesses at the nasal quadrant, and at the 3, 4, and 5 o'clock sectors, RNFLT significantly differed among the 3 groups (Table 2). Among the 95 glaucomatous eyes, the superior RNFLT was thinner in the superior RNFL defect group than in the inferior RNFL defect group, and vice versa in the inferior RNFL defect group. In addition, the temporal RNFLT was thinner in the superior RNFL defect group than in the inferior RNFL defect group ($P = .04$).

Table 3 shows a comparison of PCT between groups. The PCTs at the inferior quadrant and at the 6 o'clock sector showed the thinnest values in both glaucomatous and control eyes (Fig. 1A). The control group tended to have thicker PCT values compared to glaucoma patients. However, no significant difference was noted between glaucomatous eyes with a superior RNFL defect and those with an inferior RNFL defect in all meridians (all $P > .05$). Although the PCT measurements of the inferior RNFL defect group showed thinner values compared to those of the control group, the average PCT and PCTs at the temporal quadrant, and at 3, 8, 9, 10, and 11 o'clock sectors of the superior RNFL group were significantly thinner compared to those of the control group.

When the relative PCTs were compared, the CTR values at the 8 and 11 o'clock sectors were significantly different among the 3

Table 2

Comparison of peripapillary retinal nerve fiber layer thickness between glaucomatous eyes with a superior or inferior retinal nerve fiber layer defect and non-glaucomatous control eyes.

	Peripapillary RNFL thickness, μm						
Measurement location	Group A (n = 34) Mean ± SD	Group B (n = 61) Mean ± SD	Group C (n = 53) Mean ± SD	P^*	$P^\dagger_{A-B}$	$P^\dagger_{A-C}$	$P^\dagger_{B-C}$
Clock hours							
1	114.03 ± 23.02	116.33 ± 16.91	126.13 ± 20.98	.008	.852	.018	.026
2	96.06 ± 20.71	98.36 ± 18.20	107.00 ± 19.53	.016	.842	.029	.048
3	75.06 ± 15.65	76.70 ± 12.97	77.28 ± 12.05	.743			
4	81.94 ± 19.88	81.57 ± 16.41	82.17 ± 17.29	.983			
5	111.24 ± 20.61	106.49 ± 20.53	115.43 ± 22.75	.086			
6	136.97 ± 29.52	106.39 ± 26.80	144.40 ± 19.51	<.001	<.001	.373	<.001
7	133.41 ± 25.75	85.62 ± 28.49	147.21 ± 23.68	<.001	<.001	.047	<.001
8	82.74 ± 17.06	77.00 ± 15.56	87.66 ± 15.87	.002	.219	.344	.002
9	69.09 ± 13.98	78.56 ± 13.38	75.92 ± 11.62	.003	.002	.045	.525
10	81.97 ± 21.05	99.15 ± 18.38	102.23 ± 19.78	<.001	<.001	<.001	.679
11	94.15 ± 30.04	127.74 ± 21.55	144.45 ± 19.23	<.001	<.001	<.001	<.001
12	110.91 ± 25.87	116.67 ± 16.90	135.40 ± 20.80	<.001	.395	<.001	<.001
Quadrants							
Superior	106.44 ± 22.15	120.25 ± 12.45	135.28 ± 13.76	<.001	<.001	<.001	<.001
Nasal	84.88 ± 17.67	85.57 ± 13.93	88.74 ± 13.43	.393			
Inferior	127.12 ± 19.91	99.67 ± 19.25	135.57 ± 14.23	<.001	<.001	.081	<.001
Temporal	77.35 ± 15.82	84.84 ± 12.98	88.47 ± 13.74	.002	.035	.001	.349
Average	95.85 ± 6.81	93.56 ± 11.72	112.51 ± 8.67	<.001	.653	<.001	<.001

Group A = glaucomatous eyes with a superior RNFL defect, Group B = glaucomatous eyes with an inferior RNFL defect, Group C = non-glaucomatous eyes, SD = standard deviation.

* ANOVA.

† Post-hoc analysis with Tukey method.

Table 3

Comparison of peripapillary choroidal thickness between glaucomatous eyes with a superior or inferior retinal nerve fiber layer defect and non-glaucomatous control eyes.

	Peripapillary choroidal thickness, μm						
Measurement location	Group A (n = 34) Mean ± SD	Group B (n = 61) Mean ± SD	Group C (n = 53) Mean ± SD	P^*	$P^{\dagger}_{A-B}$	$P^{\dagger}_{A-C}$	$P^{\dagger}_{B-C}$
Clock hours							
1	175.41 ± 35.45	165.70 ± 52.87	189.98 ± 50.99	.032	.622	.364	.024
2	178.56 ± 38.78	165.02 ± 43.16	191.30 ± 52.14	.010	.352	.415	.007
3	165.79 ± 33.59	155.21 ± 39.68	189.21 ± 50.92	<.001	.483	.037	<.001
4	163.71 ± 41.72	148.75 ± 40.82	177.74 ± 43.48	.002	.223	.284	.001
5	150.41 ± 34.98	136.75 ± 34.95	166.72 ± 40.84	<.001	.202	.117	<.001
6	140.47 ± 34.53	127.87 ± 35.87	155.25 ± 40.01	.001	.255	.169	<.001
7	144.74 ± 31.92	131.11 ± 33.99	163.25 ± 41.08	<.001	.189	.056	<.001
8	153.00 ± 32.74	139.02 ± 39.50	184.75 ± 44.81	<.001	.237	.001	<.001
9	165.97 ± 34.21	158.46 ± 45.70	192.47 ± 45.97	<.001	.699	.017	<.001
10	161.47 ± 31.05	158.00 ± 42.83	191.53 ± 47.59	<.001	.922	.004	<.001
11	158.03 ± 34.48	160.18 ± 44.62	185.72 ± 47.45	.003	.971	.012	.006
12	170.47 ± 38.32	160.51 ± 42.95	184.47 ± 45.69	.014	.526	.302	.010
Quadrants							
Superior	167.94 ± 32.88	160.62 ± 42.21	186.23 ± 45.09	.005	.687	.113	.004
Nasal	167.71 ± 33.20	156.08 ± 39.77	186.09 ± 47.24	.001	.389	.110	<.001
Inferior	148.76 ± 32.71	134.57 ± 33.73	159.91 ± 39.11	.001	.152	.330	.001
Temporal	163.62 ± 34.01	154.49 ± 44.53	189.64 ± 44.21	<.001	.572	.016	<.001
Average	160.67 ± 29.56	150.55 ± 36.26	180.65 ± 40.82	<.001	.402	.037	<.001

Group A = glaucomatous eyes with a superior RNFL defect, Group B = glaucomatous eyes with an inferior RNFL defect, Group C = non-glaucomatous eyes, SD = standard deviation.

* Analysis of variance.

† Post-hoc analysis with Tukey method.

groups (Table 4). The CTR at the 8 o'clock position for the control group was proportionally larger compared to that of glaucoma patients, whereas the difference was not significant between the 2 glaucoma groups. Moreover, the superior RNFL defect group showed a smaller value for CTR at the 11 o'clock meridian compared to the inferior RNFL defect group (Fig. 1B). When the average CTRs of IT (7–8 o'clock) and ST (10–11 o'clock) areas were compared (Table 5), the CTRs of the IT area were smaller in all 3 groups compared to those of the ST area. However, the difference in CTR between the IT and ST areas was largest in the inferior RNFL defect group.

Linear regression analysis was performed to assess the association between PCT and the corresponding RNFLT (Table 6). The average PCT and PCT at the superior and inferior quadrants, and at the 7, 8, and 11 o'clock meridians were significantly associated with the corresponding RNFL thicknesses ($P < .05$). After adjusting for age, IOP, and axial length, a thinner PCT was shown to be independently associated with a thinner RNFL thickness globally, in the inferior quadrant, and at the 7 o'clock meridian. In addition, the average PCT was negatively correlated with age ($\beta = -0.370$, $P < .001$) and positively correlated with average RNFLT ($\beta = 0.192$, $P = .01$) (see supplementary table, http://links.lww.com/MD/C284).

Multivariate logistic regression analysis was also performed to determine the factors associated with the hemispheric location of the RNFL defect in glaucoma patients (Table 7). The CTR at the 11 o'clock position was found to be independently associated with the presenting location of the RNFL defect in untreated eyes with NTG ($P = .03$).

4. Discussion

The advancement of spectral-domain OCT has allowed for the in vivo measurement of choroidal thickness, which has been extensively investigated in the pathogenesis of various retinal diseases and glaucoma. Nonetheless, the association between PCT and the incidence of glaucoma remains unclear.[10,11,13,14,19–21] Unlike previous studies, where only the absolute PCT values were evaluated, the present study investigated the differences in both CTR and absolute PCT between NTG patients and healthy subjects, to determine the relationship between glaucomatous damage and the peripapillary choroid. We found that the CTR at the 11 o'clock position was significantly lower in patients with a superior RNFL defect compared to those with an inferior RNFL defect, and that PCT did not differ between patients with either a superior or inferior RNFL defect. We demonstrated that the relatively reduced CTR at the 11 o'clock position was associated with the hemisphere location of a presenting RNFL defect. To our knowledge, this is the first study to investigate the differences in CTR in untreated NTG eyes with respect to the initial location of RNFL defect.

Recently, Lee et al[11] compared the relative choroidal thicknesses of treated NTG eyes and healthy subjects. In agreement with our observations, they demonstrated that there was a thinner juxtapapillary choroidal thickness in NTG eyes than in healthy control eyes, and that a correspondingly smaller choroidal thickness was evident at the location of the dominant RNFL defect in NTG eyes. However, unlike our study, wherein we defined PCT as the measurement of choroidal thickness at a 3.4-mm diameter peripapillary circle scan, Lee et al used a different OCT instrument to evaluate the juxtapapillary choroidal thickness, which was defined as the average choroidal thickness within a 500-μm area from the border tissue of Elschnig. They also defined the relative choroidal thickness as the ratio of the measured juxtapapillary choroidal thickness at each meridian to the average value of the corresponding value for the age-matched normal controls. Another notable difference between these 2 studies is that their study included treated

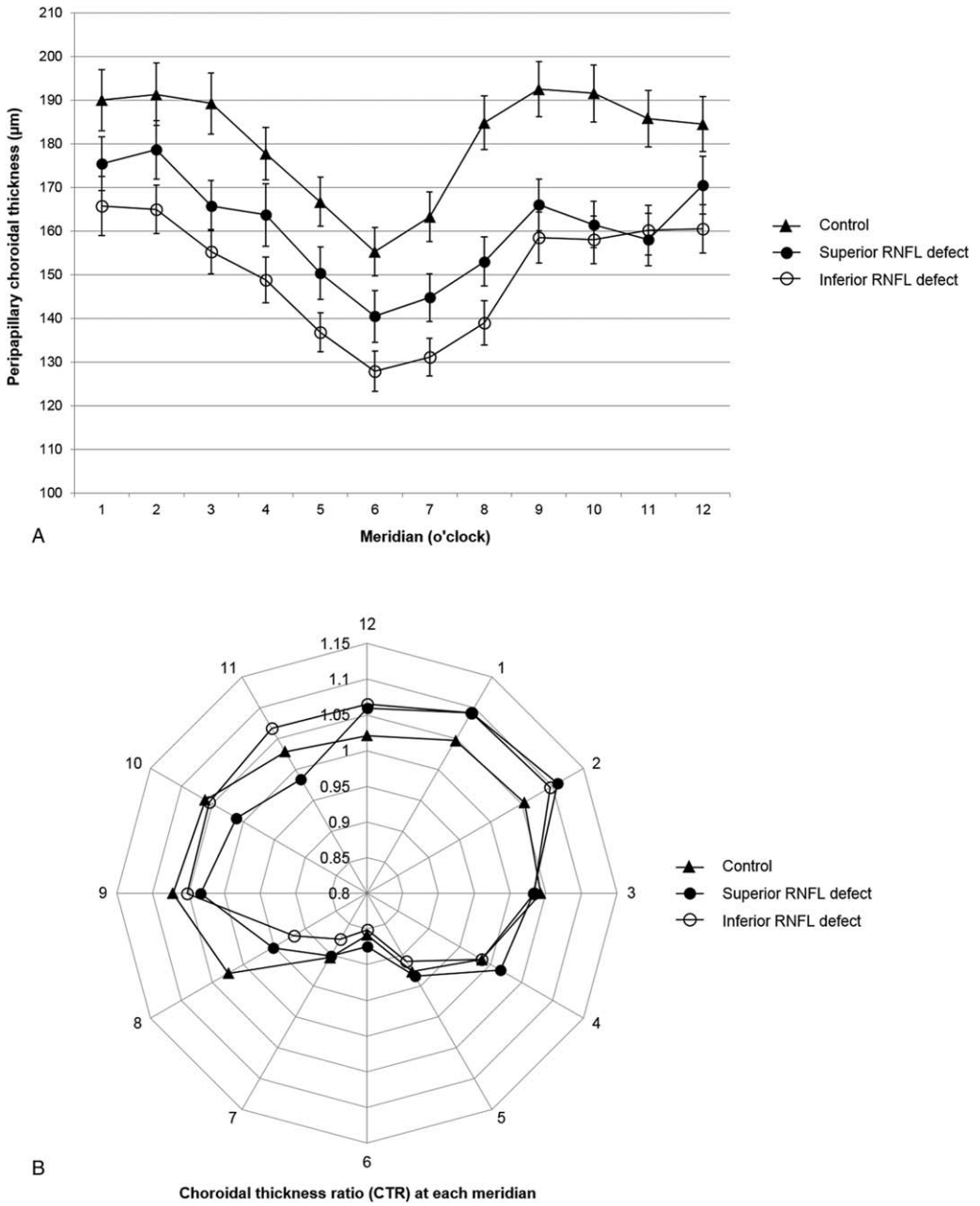

Figure 1. Comparison of the peripapillary choroidal thickness (A) and CTR (B) in all meridians of the control group and the 2 glaucoma patient groups. CTR = choroidal thickness ratio, RFNL = retinal nerve fiber layer.

NTG patients and eyes with bihemisphere RNFL defects, comparing the relative choroidal thicknesses between the hemispheres according to the extensiveness of the RNFL defect. Despite these methodological differences, our observations were concordant, supporting the hypothesis that relative choroidal thinning may be relevant in the pathogenesis of optic nerve damage in NTG patients.

The significance of PCT for the evaluation of glaucomatous damage is debated. Li et al[13] reported no significant difference in the PCT of glaucomatous eyes with unilateral VF loss compared to perimetrically unaffected fellow eyes or healthy controls. They found no correlation between PCT and ONH damage, as determined by the RNFL thickness or VF MD. Nonetheless, Park et al[10] showed that PCT was thinner in NTG patients compared to normal controls, whereas the PCT did not differ between patients with primary open angle glaucoma (OAG) with high IOP and those with normal eyes. The PCT was found to be associated with the type of glaucoma, but not with RNFLT or MD. Recently, Song et al[12] used swept-source OCT to evaluate the PCT between 114 OAG patients and normal controls. They reported that PCT, globally and at all 12 clock-hour positions, except for the 10 o'clock position, was thinner in OAG patients compared to normal subjects. However, they found no correlation between glaucoma severity and PCT. In the present study, we found significantly thinner average PCT in overall NTG patients (n = 95) compared to healthy subjects (154.17 vs. 180.65 μm, $P < .001$). When the NTG patients were grouped according to their initial RNFL defect location, those with

Table 4

Comparison of peripapillary choroidal thickness ratio between glaucomatous eyes with a superior or inferior retinal nerve fiber layer defect and non-glaucomatous control eyes.

	Peripapillary choroidal thickness ratio						
Measurement location	Group A (n = 34) Mean ± SD	Group B (n = 61) Mean ± SD	Group C (n = 53) Mean ± SD	P^*	$P^\dagger_{A-B}$	$P^\dagger_{A-C}$	$P^\dagger_{B-C}$
Clock hours							
1	1.09 ± 0.11	1.09 ± 0.15	1.05 ± 0.13	.151			
2	1.11 ± 0.10	1.10 ± 0.11	1.05 ± 0.12	.052			
3	1.03 ± 0.11	1.03 ± 0.13	1.04 ± 0.11	.899			
4	1.02 ± 0.15	0.99 ± 0.10	0.99 ± 0.11	.452			
5	0.93 ± 0.11	0.91 ± 0.10	0.93 ± 0.13	.547			
6	0.87 ± 0.13	0.85 ± 0.13	0.86 ± 0.08	.646			
7	0.90 ± 0.11	0.87 ± 0.10	0.90 ± 0.10	.247			
8	0.95 ± 0.10	0.92 ± 0.10	1.02 ± 0.10	<.001	.278	.005	<.001
9	1.03 ± 0.10	1.05 ± 0.14	1.07 ± 0.13	.399			
10	1.01 ± 0.13	1.05 ± 0.15	1.06 ± 0.12	.215			
11	0.98 ± 0.13	1.07 ± 0.17	1.03 ± 0.14	.045	.036	.392	.391
12	1.06 ± 0.13	1.06 ± 0.11	1.02 ± 0.10	.095			
Quadrants							
Superior	1.05 ± 0.10	1.07 ± 0.11	1.03 ± 0.08	.148			
Nasal	1.04 ± 0.07	1.04 ± 0.09	1.03 ± 0.09	.697			
Inferior	0.93 ± 0.11	0.90 ± 0.94	0.88 ± 0.07	.109			
Temporal	1.02 ± 0.96	1.03 ± 0.14	1.05 ± 0.09	.333			

Group A = glaucomatous eyes with a superior RNFL defect, Group B = glaucomatous eyes with an inferior RNFL defect, Group C = non-glaucomatous eyes, SD = standard deviation.
* Analysis of variance.
† Post-hoc analysis with Tukey method.

inferior RNFL defects had lower PCT values compared to the control group, whereas the average PCT, and PCTs at the temporal quadrant, and at the 3, 8, 9, 10, and 11 o'clock positions were significantly thinner in those with superior RNFL defects. The average PCT, and PCTs at the inferior quadrant, and at the 7 o'clock meridian, were correlated with the corresponding RNFLT. Moreover, the age and average RNFLT were found to be associated with the average PCT.

Such inconsistent results between the previous studies and ours may be attributed to several reasons. First, the study populations were different. Age, axial length, CCT, myopia, optic disc appearance, and glaucoma type were reported to influence PCT.[15,16,22] A failure to properly standardize these factors during patient enrollment would have affected the choroidal thickness measurement. Moreover, the inclusion criteria for control group enrolment were also different. Ehrlich et al[14] selected glaucoma-suspect patients as the control group and compared their PCTs to established glaucoma patients. Suh et al[21] and Li et al[13] compared the PCT in a group of unilateral NTG patients and patients with unilateral VF loss, respectively, to evaluate the inter-eye difference in PCT. In addition, Gupta et al[17] evaluated the relationship between PCT and RNFL thickness in a population-based sample of nonglaucomatous eyes and reported a significant association in the inferior and superior quadrants, and globally. Second, the use of different OCT instruments could have influenced the results. Most studies investigating the relationship between PCT and glaucoma used the Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany). Recent studies by Lee et al[11] and Song et al[12] used swept-source OCT (DRI-OCT-1 system, Topcon, Tokyo, Japan). Different wavelength, repetition rate, and axial resolution may have different effects on the visualization of the choroid. Third, the measurement location was different. Some studies[14,15,22,23] used the 360-degree 3.4-mm diameter peripapillary circle scan to measure PCT, whereas others used the juxtapapillary area,[11] or a 3-mm area nasal to the fovea.[20] The lack of a standardized protocol for evaluating PCT in glaucoma patients makes direct comparison difficult between the studies.

Given that various factors can affect choroidal thickness, we speculated that comparing the relative choroidal thickness values obtained at different regions within the same eye might be helpful to evaluate the relationship between the choroid and glaucom-

Table 5

Differences in CTR and RNFLThickness According to the Location of the RNFL Defect.

	Group A (mean ± SD, n = 34)			Group B (mean ± SD, n = 61)			Group C (mean ± SD, n = 53)			
	Measurement location			Measurement location			Measurement location			
	ST	IT	P^*	ST	IT	P^*	ST	IT	P^*	$P^\dagger$
CTR	1.00 ± 0.12	0.93 ± 0.10	.023	1.06 ± 0.14	0.90 ± 0.08	<.001	1.05 ± 0.12	0.96 ± 0.09	<.001	
RNFL thickness	88.06 ± 23.32	108.07 ± 20.01	<.001	113.44 ± 18.15	81.31 ± 19.62	<.001	123.34 ± 17.37	117.43 ± 17.35	.200	
Δ CTR	0.07 ± 0.17			0.16 ± 0.18			0.08 ± 0.15			.009

Δ CTR = difference in CTRs between ST and IT areas, CTR = choroidal thickness ratio, Group A = glaucomatous eyes with a superior RNFL defect, Group B = glaucomatous eyes with an inferior RNFL defect, Group C = non-glaucomatous eyes, IT = inferotemporal area (at 7 to 8 o'clock), RFNL = retinal nerve fiber layer, SD = standard deviation, ST = superotemporal area (at 10 to 11 o'clock),.
* Paired *t* test.
† Analysis of variance (post-hoc analysis with Tukey method, group A vs. group B: *P* = .026; group A vs. group C: *P* = .955; group B vs. group C: *P* = .024).

Table 6

Association of PCT with peripapillary retinal nerve fiber layer thickness (n = 148).

	Model 1			Model 2		
	B (95% CI)	Beta	*P*	B (95% CI)	Beta	*P*
Average PCT	0.101 (0.040, 0.162)	0.262	.001	0.092 (0.026, 0.57)	0.237	.006
Superior PCT	0.075 (0.004, 0.147)	0.169	.040	0.049 (−0.029, 0.128)	0.111	.214
Nasal PCT	0.026 (−0.029, 0.082)	0.077	.355	0.063 (0.003, 0.123)	0.184	.051
Inferior PCT	0.158 (0.024, 0.233)	0.197	.016	0.143 (0.033, 0.253)	0.220	.011
Temporal PCT	0.025 (−0.028, 0.078)	0.078	.348	−0.003 (−0.055, 0.049)	−0.010	.898
7 o'clock PCT	0.269 (0.112, 0.425)	0.270	.001	0.232 (0.071, 0.393)	0.234	.005
8 o'clock PCT	0.063 (0.003, 0.123)	0.169	.039	0.037 (−0.024, 0.098)	0.100	.233
10 o'clock PCT	0.016 (−0.061, 0.092)	0.034	.683	−0.024 (−0.097, 0.049)	−0.051	.521
11 o'clock PCT	0.145 (0.040, 0.250)	0.221	.007	0.094 (−0.012, 0.200)	0.143	.082
Superior CTR	−8.920 (−40.257, 22.418)	−0.047	.575	−14.965 (−45.459, 16.068)	−0.077	.347
Inferior CTR	8.242 (−34.520, 51.004)	0.032	.704	10.893 (−30.933, 52.720)	0.042	.607
7 o'clock CTR	30.271 (−30.962, 91.504)	0.081	.330	40.769 (−18.535, 100.072)	0.109	.176
8 o'clock CTR	8.978 (−15.191, 33.147)	0.061	.464	14.504 (−9.020, 38.028)	0.098	.225
10 o'clock CTR	−21.017 (−45.501, 3.466)	−0.139	.092	−5.153 (−29.334, 19.028)	−0.034	.674
11 o'clock CTR	3.715 (−27.495, 34.924)	0.019	.814	11.862 (−18.026,41.750)	0.062	.434

CI = confidence interval, CTR = peripapillary choroidal thickness ratio, PCT = peripapillary choroidal thickness. Average, superior, nasal, inferior, temporal, 7 o'clock, 8 o'clock, and 11 o'clock PCT or CTR were regressed with average, superior, nasal, inferior, temporal, 7 o'clock, 8 o'clock, and 11 o'clock RNFLT, respectively. Model 1: Non-adjusted. Model 2: Adjusted for age, intraocular pressure, and axial length.

atous damage. Therefore, we compared the CTR in glaucomatous eyes with superior or inferior RNFL defects and healthy subjects. Compared to the control group, the CTR at the 8 o'clock meridian was significantly lower in 2 glaucomatous groups. However, it did not differ between glaucomatous eyes with a superior RNFL defect and those with an inferior RNFL defect. Moreover, the superior RNFL defect group had a lower CTR at the 11 o'clock position than the inferior RNFL defect group. Although absolute PCT did not differ between the 2 glaucoma groups, a reduced CTR showed correlativity with the location of the initial RNFL defect. The regional differences in PCT can potentially account for these findings.

The short posterior ciliary artery (PCA) supplies the ONH and the choroid up to the equator of the eye. As the ONH and the posterior choroid share the same blood supply, a reduction in blood supply from a branch of the short PCA may result in a thinner PCT and a structurally weaker lamina cribrosa (LC) at the corresponding area, leaving the ONH vulnerable to glaucomatous damage. As the thinner lamina in eyes with NTG may easily deform the LC and contribute to the development of retinal ganglion cell damage,[24] the reduced CTR may act as an inherent predisposing factor for the development of glaucomatous damage in patients with NTG. Further study comparing the CTRs before and after the development of a RNFL defect at a specific area may inform us about the role of CTR in the pathogenesis of NTG.

The present study has several limitations. First, since our study design was cross-sectional, we were unable to explain the

Table 7

Logistic regression analysis of factors associated with the hemispheric location of the presenting retinal nerve fiber defect in glaucomatous eyes (n = 95).

	Univariate		Multivariate	
	Exp (B) (95% CI)	*P*	Exp (B) (95% CI)	*P*
Age	0.988 (0.953, 1.024)	.504		
Gender	0.586 (0.252, 1.367)	.216		
Untreated IOP	1.023 (0.866, 1.215)	.768		
Axial length	1.321 (0.837, 2.086)	.232		
Mean deviation	0.974 (0.860, 1.104)	.684		
Average RNFLT	0.988 (0.957, 1.019)	.433		
Average PCT	0.991 (0.979, 1.004)	.168		
Superior PCT	0.995 (0.984, 1.006)	.381		
Inferior PCT	0.988 (0.975, 1.000)	.053	0.988 (0.962, 1.017)	.443
7 o'clock PCT	0.988 (0.975. 1.001)	.064	1.008 (0.973, 1.05)	.646
8 o'clock PCT	0.990 (0.979,1.001)	.085	0.993 (0.969, 1.019)	.598
10 o'clock PCT	0.998 (0.687, 1.008)	.675		
11 o'clock PCT	1.001 (0.991, 1.012)	.806		
Superior CTR	5.236 (0.097, 281.864)	.416		
Inferior CTR	0.056 (0.001, 3.942)	.184		
7 o'clock CTR	0.071 (0.001, 4.892)	.221		
8 o'clock CTR	0.036 (0.000, 2.757)	.133		
10 o'clock CTR	8.287 (0.413, 166.477)	.167		
11 o'clock CTR	75.432 (2.038, 2792.473)	.019	65.543 (1.49, 2985.300)	.032

IOP = intraocular pressure, RNFLT = retinal nerve fiber layer thickness, PCT = peripapillary choroidal thickness, CTR = choroidal thickness ratio. ariables with $P < .10$ were included in the multivariate analysis.

temporal relationship between the changes in PCT and glaucomatous damage. Further longitudinal study is required to verify this issue. Second, the choroidal thickness may not represent the actual blood flow of the choroid. Sogawa et al found no significant correlation between the subfoveal choroidal thickness and the total choroidal blood flow in healthy young subjects.[25] In contrast, a histologic study conducted by Kubotal et al[9] reported that decreased choroidal thickness was caused by a reduction in the diameter of the choroidal vessels, resulting in reduced choroidal blood flow. Recently, Lee et al[11] reported reduced juxtapapillary choroidal thickness and parapapillary vascular nonperfusion in NTG patients. Further study using OCT angiography may provide more information on the relationship between choroidal blood flow and choroidal thickness. Third, one may criticize lack of the blood pressure measurements or different time points of day when OCT scanning was performed for PCT measurements, because the PCT may be influenced by the systemic blood pressure and may have diurnal variations. Finally, the measurement of PCT was performed at a fixed 3.4-mm diameter peripapillary circle scan. Using Bruch membrane opening as a fiducial point to measure the choroidal thickness may have shown different results.

Nevertheless, the strength of the present study is that this is the first study to calculate the relative choroidal thickness at the quadrant and clock-hour sectors within an individual subject, and to compare it between NTG patients with a superior RNFL defect and those with an inferior RNFL defect. In addition, we only included NTG patients who had not received any treatment for glaucoma. Thus, the potential influences on PCT owing to IOP alterations induced by either medication or filtering surgery were excluded.[26,27]

In conclusion, PCT was thinner in untreated NTG patients compared to age-matched healthy subjects. Among the NTG patients, the CTR differed according to the hemisphere location of RNFL damage, whereas PCT did not. A reduced CTR at a specific clock-hour was topographically related to the incidence of a glaucomatous change. These findings suggest that the CTR, instead of the absolute choroidal thickness value, may help us to better understand the regional variation of PCT and its relationship to glaucomatous damage.

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