PLOS ONE

RESEARCH ARTICLE

Characteristics of the inner retinal layer in the fellow eyes of patients with unilateral exudative age-related macular degeneration

Seong Eun Lee[1☯], Hyung Bin Lim[1☯], Yong Il Shin[1,2], Cheon Kuk Ryu[1], Woo Hyuk Lee[1], Jung-Yeul Kim[1]*

1 Department of Ophthalmology, Chungnam National University College of Medicine, Daejeon, Republic of Korea, **2** Rhee's Eye Hospital, Daejeon, Republic of Korea

☯ These authors contributed equally to this work.
* kimjy@cnu.ac.kr

Citation: Lee SE, Lim HB, Shin YI, Ryu CK, Lee WH, Kim J-Y (2020) Characteristics of the inner retinal layer in the fellow eyes of patients with unilateral exudative age-related macular degeneration. PLoS ONE 15(9): e0239555. https://doi.org/10.1371/journal.pone.0239555

Editor: Demetrios G. Vavvas, Massachusetts Eye & Ear Infirmary, Harvard Medical School, UNITED STATES

Received: March 27, 2020

Accepted: September 8, 2020

Published: September 23, 2020

Data Availability Statement: All relevant data are within the manuscript and its Supporting Information files.

Funding: The authors received no specific funding for this work.

Competing interests: The authors have declared that no competing interests exist.

Abstract

Objective

To investigate the thicknesses of the ganglion cell-inner plexiform layer (GC-IPL) and retinal nerve fiber layer (RNFL) of the fellow eyes of patients with unilateral exudative age-related macular degeneration (AMD).

Methods

A total of 107 patients with unilateral exudative AMD [34 of typical choroidal neovascularization (tCNV), Group A; 73 of polypoidal choroidal vasculopathy (PCV), Group B] and 73 normal control eyes (Group C) were included. Drusen and subretinal drusenoid deposits were assessed in all participants using fundus photography, autofluorescence, and optical coherence tomography (OCT). The GC-IPL and RNFL thicknesses were measured using Cirrus HD-OCT and compared among groups. Linear regression analyses were used to evaluate the factors associated with GC-IPL thicknesses.

Results

The average GC-IPL thicknesses of Groups A, B, and C were 77.09 ± 3.87, 80.10 ± 6.61, and 80.88 ± 6.50 μm, respectively ($p = 0.022$). Sectoral GC-IPLs and central macular thicknesses (CMTs) were significantly different among groups (all, $p < 0.05$), whereas none of the RNFL parameters differed significantly (all, $p > 0.05$). Multivariate linear regression analyses revealed that age ($p < 0.001$), CMT ($p < 0.001$), and tCNV ($p = 0.013$) were significantly associated with average GC-IPL thickness, and the rate of reduction of GC-IPL thickness with increasing age in the fellow eyes of tCNV patients was higher than those in the PCV and control groups.

Conclusions

Unilateral tCNV patients exhibited statistically significant reduction of the GC-IPL thickness in the fellow eyes, compared to values of the fellow eyes of unilateral PCV patients or control patients. RNFL values trended to be lower but did not reach statistical significance.

Introduction

Age-related macular degeneration (AMD) is a leading cause of irreversible blindness in elderly people in industrialized countries, and the third-most common cause of blindness worldwide [1, 2]. Regarding subtypes of neovascular AMD, occult choroidal neovascularization is the most common in Western populations [3], whereas polypoidal choroidal vasculopathy, which is a variant of neovascular AMD, is the predominant form in Asian populations [2, 4]. Although these subtypes share some clinical features, they have different epidemiological and pathophysiological characteristics, as well as different treatment outcomes.

Although it is well-known that the outer retinal layers are mainly affected in AMD, several studies have reported that thinning of the inner retinal layers, including the ganglion cell-inner plexiform layer (GC-IPL) and retinal nerve fiber layer (RNFL), are also observed in dry type [5–7] and exudative AMD [8, 9]. Several mechanisms have been recently introduced to explain the damage observed in the inner retinal layers, such as transneuronal degeneration or chronic ischemia [10–12]. In addition, it has also been reported that the ganglion cell layer thickness decreases as AMD progresses [8]. These findings suggest that AMD is a risk factor that should be considered in the analysis of the inner retinal layer.

In many cases, bilateral involvement of exudative AMD was observed, and it was reported that approximately 43% of unilateral exudative AMD patients develop typical fellow eye choroidal neovascularization (tCNV) within 5 years [13]. In addition, Baek et al. also reported that 84% of the fellow eyes of unilateral polypoidal choroidal vasculopathy (PCV) or aneurysmal type 1 neovascularization patients have outer retinal abnormalities [14]. Considering these results, analyses of the fellow eyes of unilateral exudative AMD patients could provide important clues relevant to the analyses of AMD progression and its clinical characteristics. In the present study, we therefore assessed the inner retinal layer characteristics of the fellow eyes in unilateral exudative AMD patients. Our aim was to compare thicknesses of the inner retinal layers, including the GC-IPL and RNFL, among subtypes of exudative AMD patients, to identify factors associated with inner retinal layer damage.

Methods

This was a retrospective, observational, comparative study. The study protocol was approved by the institutional review board of Chungnam National University Hospital (Daejeon, Republic of Korea) and adhered to the tenets of the Declaration of Helsinki.

Participants

This study included patients with treatment-naive unilateral tCNV and PCV who visited the Chungnam National University Hospital retinal clinic from June 2016 to December 2018. Patients who met the inclusion and exclusion criteria were consecutively included. Patients with unilateral tCNV were placed in Group A (Fig 1A–1F), and patients with unilateral PCV were placed in Group B (Fig 1G–1L). Age- and sex-matched normal subjects were placed in

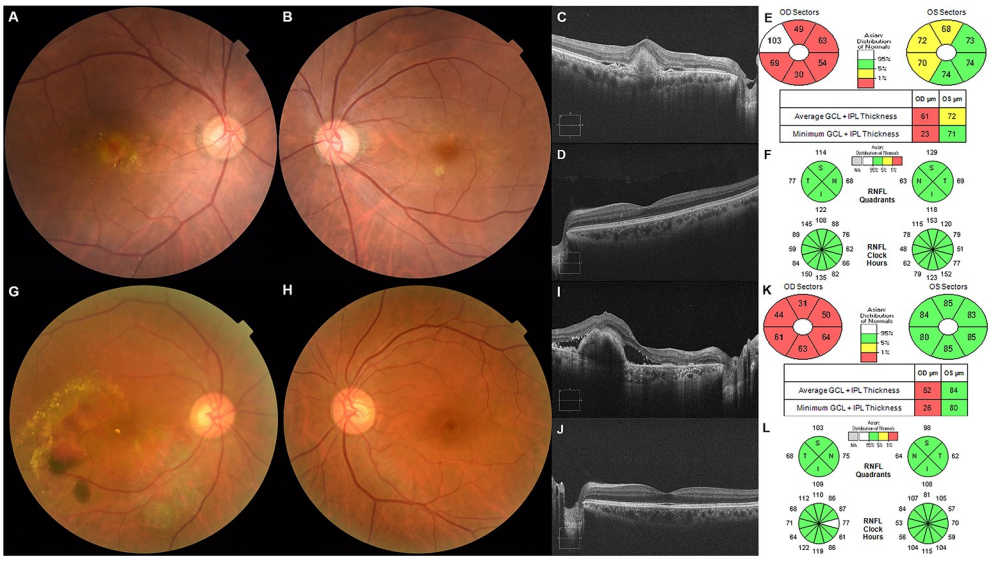

Fig 1. Fundus photography (A, B, G, H), optical coherence tomography images including line scan (C, D, I, J), ganglion cell—inner plexiform layer (GC-IPL) analysis map (E and K), and retinal nerve fiber layer (RNFL) analysis map (F and L) of representative cases showing unilateral exudative age-related macular degeneration. Typical choroidal neovascularization (tCNV) was observed in the right eye (A and C), and drusen and the focal depigmented lesion were noted in the left eye (B and D). The left eye (G and I) was diagnosed with polypoidal choroidal vasculopathy (PCV), and there was no abnormal finding in the right eye (H and J). The average GC-IPL and RNFL thickness was 72μm and 95μm in the fellow eye with tCNV, and 84μm and 97μm in the fellow eye with PCV, respectively.

https://doi.org/10.1371/journal.pone.0239555.g001

Group C (control). Exudative typical CNV was diagnosed when there was evidence of CNV associated with nondrusenoid retinal pigment epithelium (RPE) detachment, serous or hemorrhagic retinal detachment, subretinal hemorrhage, or subretinal exudation [15]. Inclusion criteria for PCV in this study were based on the EVEREST study criteria-the presence of early subretinal hyperfluorescent lesions upon analysis using indocyanine green angiography (ICGA) and other features including the nodular appearance of polyps when viewed stereoscopically, hypofluorescent halos around the nodule, pulsatile filling of polyps, branching vascular networks, and an orange appearance of nodules corresponding to ICGA lesions upon color imaging [16].

Comprehensive ophthalmic examinations, including slit-lamp microscopy; fundus examination; and measurements of uncorrected visual acuity, best-corrected visual acuity (BCVA) using the Snellen chart, refraction using an automatic refractometer, and intraocular pressure (IOP) and axial length (AXL) using an IOL Master (Carl Zeiss, Jena, Germany); fundus photography; fluorescein angiography (FA) and ICGA using the Heidelberg Retina Angiograph 2 (Heidelberg Engineering, Heidelberg, Germany); and optical coherence tomography (OCT; Carl Zeiss Meditec, Dublin, CA, USA), were performed. All fundus photographs and FA, ICGA and OCT images were reviewed by two independent investigators (H.B.L. and S.E.L.) to categorize them into groups. If there was any disagreement, a senior investigator (J.Y.K.) was invited for discussion until a consensus was reached.

Patients presenting only unilateral tCNV or PCV were included in the study. Patients with conditions that could affect the RPE and choroid status of both eyes (e.g., history of systemic steroid use and other concurrent diseases such as diabetic retinopathy, hypertensive retinopathy, uveitis, or tumors) or those with a history of anti-vascular endothelial growth factor treatment, prior laser or photodynamic therapy, or retina or choroid trauma were excluded.

Patients with other ocular diseases of either eye that could affect the GC-IPL thickness, such as glaucoma, or retinal or neuro-ophthalmic diseases, or those treated with intraocular surgery other than cataract surgery, were excluded. The fellow eyes with CMT <200 μm were considered as having macular atrophy [17, 18] and were excluded from the study. The fellow eyes with BCVA <20/25 or high myopia (AXL ≥26.0 mm or spherical equivalent ≤ –6.0 diopters) were also excluded. Normal subjects (Group C)) were also enrolled, and they had no history of ocular disease, normal anterior segment, BCVA ≥ 20/25, IOP in the normal range, and a spherical equivalent within ± 3.0 D.

The presence of soft drusen, pachydrusen, and subretinal drusenoid deposits (SDD) was evaluated using fundus photography, autofluorescence, and OCT. The definition of soft drusen and SDD followed that described in a previous report [19]. Pachydrusen were considered present if there were isolated or scattered yellowish-white deposits on fundus photography that corresponded to the presence of homogenous material accumulation under RPE on OCT images [20].

OCT

The OCT parameters were measured by an experienced examiner with a 512 × 128 macular cube and a 200 × 200 optic cube scanning protocol using a Cirrus HD-OCT instrument (Carl Zeiss Meditec, Dublin, CA, USA). The macular cube scan was assessed using ganglion cell analysis, which automatically measured the GC-IPL thickness by identifying the layer between the outer boundaries of the RNFL and the inner plexiform layer in three dimensions. The elliptical annulus was defined by the vertical radii (outer radius and inner radius of 2.0 and 0.5 mm, respectively) and horizontal radii (outer radius and inner radius of 2.4 and 0.6 mm, respectively) The average, minimum, and six sectoral (superior, superotemporal, superonasal, inferior, inferonasal, and inferotemporal) GC-IPL thicknesses were measured. The CMT was measured using retinal map analysis. The average and four sectoral (superior, temporal, inferior, and nasal) RNFL thicknesses were also evaluated. Optic nerve head parameters, such as the rim area, disc area, average cup/disc ratio, and cup volume were measured as well. The CMT and GC-IPL thicknesses were measured with the image centered on the fovea. Two researchers (H.B.L. and S.E.L.) reviewed the image, and if there were problems such as signal strength < 7, segmentation error, motion artifact or misalignment, they were excluded from the study.

Statistical analyses

Statistical analyses were performed using SPSS statistical software for Windows (ver. 21.0; IBM Corporation, Armonk, NY, USA). The GC-IPL, central macula, and RNFL thicknesses were compared among the three groups using analysis of variance, followed by a post hoc test (the Bonferroni test). The chi-square test and Fisher's exact test was used to compare categorical data. Analyses of covariance (ANCOVA) were also used to control the effects of covariate values such as sex, CMT, disc area, and cup volume. Univariate and multivariate linear regression analyses were used to evaluate the factors affecting GC-IPL thickness. In all analyses, a value of $p < 0.05$ was considered statistically significant.

Results

Patient demographics

This study enrolled a total of 180 subjects, including 34 tCNV patients (Group A), 73 PCV patients (Group B), and 73 control subjects (Group C). The mean ages in Groups A, B, and C

were 70.74 ± 8.70, 69.18 ± 7.86, and 70.60 ± 7.54 years, respectively (p = 0.473; Table 1). The proportion of female patients in Group B was lower than those of the other groups (p = 0.019). Histories of diabetes and hypertension, BCVA, spherical equivalents, IOP, and AXL did not differ significantly among groups (all, p >0.05). There were no significant differences in rim area (p = 0.417) and cup/disc ratio (p = 0.201), whereas disc area (p = 0.003) and cup volume (p = 0.008) were significantly different among groups. The mean CMTs in Groups A–C were 246.03 ± 18.09, 253.30 ± 22.31, and 257.11 ± 20.26 μm, respectively (p = 0.039), and the mean value for Group A was significantly lower than that for Group C (p = 0.033, post hoc test). Soft drusen and SDD were found more frequently in Group A (soft drusen: 82.4%, p <0.001; SDD: 29.4%, p = 0.004) than in Group B (soft drusen: 6.8%, SDD: 4.1%). However, pachydrusen were more common in Group B (21 eyes; 28.8%, p = 0.015) than in Group A (2 eyes; 5.9%).

Comparison of GC-IPL and RNFL thicknesses

The average GC-IPL thicknesses in Groups A–C were 77.09 ± 6.87, 80.10 ± 6.61, and 80.88 ± 6.50 μm, respectively. The average and all subfields of GC-IPL thickness differed significantly among the three groups (all, p <0.05). In the post hoc analyses, all GC-IPL measurements in Group A were significantly lower than those in Group C (all, p <0.05, Table 2), and no statistically significant differences were observed for all GC-IPL measurements between groups A and B and between groups B and C. For the RNFL, no significant differences were observed for the average and all sectors among all groups both in ANOVA and post hoc analyses (p >0.05).

ANCOVA was performed by adjusting sex, CMT, disc area, and cup volume among the three groups. The estimated average GC-IPL thicknesses in Groups A–C after compensating for covariants were 77.60, 79.83, and 80.90 μm, respectively (p = 0.042; Table 3). Post hoc analyses revealed that differences were only significant between Groups A and C (p = 0.039). The estimated average RNFL thickness did not differ significantly among groups (p = 0.107).

Determination of factors associated with GC-IPL thickness

Univariate linear regression analyses revealed that age (p <0.001), BCVA (p = 0.011), CMT (p <0.001), and tCNV (p = 0.008) were associated with average GC-IPL thickness (Table 4). Multivariate linear regression analyses that included four variables from the univariate linear regression analyses showed that age (β = –0.253 ± 0.061, p <0.001), CMT (β = 0.078 ± 0.022, p <0.001), and tCNV (β = –2.864 ± 1.138, p = 0.013) were significant factors. Age was significantly correlated with average GC-IPL thickness in Groups A–C, with slopes of –0.405 (p = 0.001), –0.297 (p = 0.002), and –0.292 (p = 0.003), respectively (Fig 2).

Discussion

Studies on GC-IPL thickness have reported observations of various ocular disorders, including glaucoma, neuro-ophthalmic diseases, and macular diseases [21–24]. Approximately half of the retinal ganglion cells are concentrated in the macula [25, 26]. Measurement of these large cell bodies in the macular ganglion cell complex has therefore been useful for the detection of many ocular disorders [21–24, 27, 28].

Studies of the inner retinal layers in AMD patients have been reported even before the development of OCT [29–31]. Clarke et al. [31] detected almost complete loss of macular granule cell layer neurons in AMD patients. With the development of OCT, numerous studies have evaluated GC-IPL and RNFL thicknesses in AMD patients. Many studies showed that ganglion cell damage was significantly associated with both dry and exudative AMD, whereas there has been controversy regarding the significance of RNFL thickness [5–9, 32].

Table 1. Demographic and clinical characteristics of the study subjects.

	Group A (n = 34)	Group B (n = 73)	Group C (n = 73)	p-value	p-value[a]	p-value[b]	p-value[c]
Age (mean ± SD; years)	70.74 ± 8.70	69.18 ± 7.86	70.60 ± 7.54	0.473*	1.000	1.000	0.832
Sex ratio (male/female)	16/18	52/21	38/35	**0.019**†			
Diabetes (n, %)	5 (14.7)	10 (13.7)	13 (17.8)	0.782‡			
Hypertension (n, %)	14 (41.2)	31 (42.5)	35 (47.9)	0.732†			
BCVA (mean ± SD; logMAR)	−0.02 ± 0.04	−0.01 ± 0.03	−0.02 ± 0.04	0.092*	0.428	1.000	0.115
Spherical equivalent (mean ± SD; diopters)	−0.10 ± 1.17	0.23 ± 1.05	0.52 ± 2.51	0.241*	1.000	0.297	0.993
Intraocular pressure (mean ± SD; mmHg)	14.85 ± 2.68	14.23 ± 2.46	14.38 ± 2.59	0.512*	0.752	1.000	1.000
Axial length (mean ± SD; mm)	23.57 ± 1.06	23.62 ± 0.85	23.69 ± 0.92	0.804*	1.000	1.000	1.000
Rim area (mean ± SD; mm^2)	1.31 ± 0.25	1.25 ± 0.27	1.25 ± 0.22	0.417*	0.674	0.677	1.000
Disc area (mean ± SD; mm^2)	1.92 ± 0.37	2.00 ± 0.38	1.81 ± 0.27	**0.003***	0.848	0.286	**0.002**
Cup/disc ratio (mean ± SD)	0.53 ± 0.16	0.57 ± 0.16	0.52 ± 0.15	0.201*	0.606	1.000	0.290
Cup volume (mean ± SD; mm^3)	0.14 ± 0.12	0.22 ± 0.17	0.15 ± 0.16	**0.008***	**0.048**	1.000	**0.016**
Central retinal thickness (mean ± SD; μm)	246.03 ± 18.09	253.30 ± 22.31	257.11 ± 20.26	**0.039***	0.280	**0.033**	0.807
Soft drusen (n, %)	28 (82.4)	5 (6.8)	N.A.	**<0.001**‡			
Pachydrusen (n, %)	2 (5.9)	21 (28.8)	N.A.	**0.015**‡			
Subretinal drusenoid deposit (n, %)	10 (29.4)	3 (4.1)	N.A.	**0.004**‡			

Group A, fellow eyes of choroidal neovascularization patients; Group B, fellow eyes of polypoidal choroidal vasculopathy patients; Group C, control group; SD, standard deviation; BCVA, best-corrected visual acuity; logMAR, logarithm of the minimum angle of resolution; N.A., not applicable.

Values in boldface are statistically significant ($p < 0.05$).

*P-value from one-way analysis of variance among the three groups followed by post hoc multiple comparison.

†P-value from the chi-square test.

‡P-value from Fisher's exact test.

[a]P-value from post hoc test (Bonferroni) between Groups A and B.

[b]P-value from post hoc test (Bonferroni) between Groups A and C.

[c]P-value from post hoc test (Bonferroni) between Groups B and C.

https://doi.org/10.1371/journal.pone.0239555.t001

There are several mechanisms that can explain thinning of the GC-IPL in AMD patients. First, apoptosis of ganglion cells may be caused by transneuronal degeneration, which is induced from chronically reduced input to the inner retinal layer secondary to photoreceptor damage [10, 33–35]. Second, longstanding outer retinal degeneration in AMD patients may lead to vascular abnormalities in the inner retinal layers, which can affect the thickness of the GC-IPL, with reduced blood flow as identified by OCT angiography [12, 36]. Toto et al. [36] separately analyzed the severity of AMD in individual patients and reported that as dry AMD progressed, vascular abnormalities were induced from the outer to inner retinal layers. In their study, deep vessel density decreased significantly in both early and intermediate dry AMD patients compared to normal controls.

In the present study, the GC-IPL was significantly thinner in the fellow eyes of tCNV patients than in those of normal controls, but no significant differences were found between the fellow eyes of tCNV and PCV patients or PCV patients and controls. Additionally, soft drusen and SDD were found in 82.4% and 29.4% of the fellow eyes of tCNV patients, respectively, and these values were higher than those observed for the fellow eyes of PCV patients, which were 6.8% and 4.1%, respectively. Previous studies have reported that the prevalence of SDD in the fellow eyes of unilateral neovascular AMD patients was 19.4%–41% [37–40], which was consistent with the results of the present study.

The retinal and choroidal vascular characteristics in the fellow eyes of AMD patients showed differences according to the type of wet AMD. Abdolrahimzadeh et al. [41] recently

Table 2. Comparison of ganglion cell-inner plexiform layer and retinal nerve fiber layer thicknesses among Groups A–C.

		Group A (n = 34) (mean ± SD; μm)	Group B (n = 73) (mean ± SD; μm)	Group C (n = 73) (mean ± SD; μm)	p-value*	p-value†	p-value‡	p-value§
GC-IPL	Average	77.09 ± 6.87	80.10 ± 6.61	80.88 ± 6.50	**0.022**	0.089	**0.019**	1.000
	Minimum	71.21 ± 11.83	75.26 ± 11.65	76.67 ± 8.24	**0.043**	0.189	**0.038**	1.000
	Superior	75.09 ± 9.64	78.44 ± 7.02	80.68 ± 7.76	**0.002**	0.104	**0.002**	1.000
	Superotemporal	76.47 ± 7.46	79.96 ± 7.95	79.82 ± 5.91	**0.043**	0.057	**0.072**	1.000
	Inferotemporal	77.91 ± 5.81	81.29 ± 7.23	81.90 ± 6.71	**0.016**	0.052	**0.015**	1.000
	Inferior	75.12 ± 6.85	78.00 ± 7.32	78.96 ± 7.14	**0.037**	0.162	**0.032**	1.000
	Inferonasal	76.65 ± 6.46	78.64 ± 8.43	80.67 ± 7.80	**0.041**	0.664	**0.043**	0.360
	Superonasal	77.82 ± 7.79	81.75 ± 6.65	83.45 ± 8.59	**0.003**	0.054	**0.002**	0.553
RNFL	Average	91.24 ± 9.34	94.81 ± 9.11	93.40 ± 9.07	0.170	0.184	0.768	1.000
	Superior	116.68 ± 12.42	117.44 ± 18.29	118.23 ± 15.97	0.894	1.000	1.000	1.000
	Temporal	66.53 ± 12.04	70.95 ± 9.84	68.18 ± 10.89	0.101	0.146	1.000	0.361
	Inferior	116.62 ± 17.45	120.22 ± 15.13	118.26 ± 17.09	0.543	0.874	1.000	1.000
	Nasal	66.38 ± 8.07	70.18 ± 8.75	68.48 ± 8.55	0.097	0.101	0.716	0.694

Group A, fellow eyes of choroidal neovascularization patients; Group B, fellow eyes of polypoidal choroidal vasculopathy patients; Group C, control group.

Ganglion cell-inner plexiform layer, GC-IPL; retinal nerve fiber layer, RNFL; SD, standard deviation.

*P-value from one-way analysis of variance among the three groups. SD.

†P-value from post hoc test (Bonferroni) between Groups A and B.

‡P-value from post hoc test (Bonferroni) between Groups A and C.

§P-value from post hoc test (Bonferroni) between Groups B and C.

https://doi.org/10.1371/journal.pone.0239555.t002

reported that the GC-IPL was thinner in early AMD patients than in healthy controls and significantly thinner in eyes with SDD in respect to eyes with drusen alone. They speculated that SDD was associated with choroidal hypoperfusion [42, 43], which may have induced GC-IPL thinning. In addition, a previous study reported that microvascular perfusion as observed using OCT angiography was decreased further in the fellow eyes of unilateral classic AMD patients compared to unilateral PCV patients [44]. Soft drusen and SDD are uncommon in both unilateral PCV patients and their fellow eyes [45, 46]. Although outer retinal and choroidal abnormalities are commonly found in the fellow eyes of PCV patients [44], their effects on the inner retinal layer are thought to be minimal. Based on these observations, it is assumed that the presence of soft drusen and SDD is an important variable affecting the inner retinal layer.

Lee et al. [6] reported a 5.6% reduction in peripapillary RNFL thickness in dry AMD patients compared to that of the control group; mostly in the temporal sector, whereas no significant reduction in peripapillary RNFL thickness was observed in other studies [5, 8, 32]. On

Table 3. Average GC-IPL and RNFL thicknesses estimated after adjusting for covariants.

	Group A (n = 34)	Group B (n = 73)	Group C (n = 73)	p-value*	p-value†	p-value‡	p-value§
Average GC-IPL thickness (estimated range; μm)	77.60 (75.44–79.71)	79.83 (78.33–81.34)	80.90 (79.41–82.40)	**0.042**	0.294	**0.039**	1.000
Average RNFL thickness (estimated range; μm)	90.90 (87.94–93.86)	94.82 (92.76–96.87)	93.55 (91.50–95.59)	0.107	0.105	0.448	1.000

Group A, fellow eyes of choroidal neovascularization patients; Group B, fellow eyes of polypoidal choroidal vasculopathy patients; Group C, control group.

*P-value from analysis of covariance among the three groups, with adjustments for sex, central macular thickness, disc area, and cup volume.

†P-value from post hoc test (Bonferroni) between Groups A and B.

‡P-value from post hoc test (Bonferroni) between Groups A and C.

§P-value from post hoc test (Bonferroni) between Groups B and C.

https://doi.org/10.1371/journal.pone.0239555.t003

Table 4. Results of univariate and multivariate linear regression analyses to evaluate factors affecting GC-IPL thickness.

	Univariate analysis			Multivariate analysis		
Factors	**r**	**β ± SE**	**p-value**	**β ± SE**	**Partial r**	**p-value**
Age	0.342	−0.291 ± 0.060	**<0.001**	−0.253 ± 0.061	**−0.299**	**<0.001**
Sex (0 = male, 1 = female)	0.063	−0.860 ± 1.019	0.400			
BCVA	0.188	34.117 ± 13.334	**0.011**	6.150 ± 12.841	−0.015	0.633
Spherical equivalent	0.059	0.218 ± 0.277	0.434			
Intraocular pressure	0.030	0.078 ± 0.195	0.689			
Axial length	0.076	−0.552 ± 0.556	0.322			
Central macular thickness	0.295	0.094 ± 0.023	**<0.001**	0.078 ± 0.022	**0.194**	**<0.001**
Rim area	0.037	0.026 ± 0.052	0.618			
Disc area	0.130	2.521 ± 1.440	0.082			
C/D ratio	0.056	−2.374 ± 3.184	0.457			
Cup volume	0.008	0.341 ± 3.241	0.916			
tCNV	0.198	−3.398 ± 1.258	**0.008**	−2.864 ± 1.138	**−0.156**	**0.013**
PCV	0.031	0.423 ± 1.023	0.680			

SE, standard error; BCVA, best-corrected visual acuity; C/D, cup to disc; tCNV, typical choroidal neovascularization; PCV, polypoidal choroidal vasculopathy.
r represents the zero-order correlation; β represents the standardized regression weights; Partial r represents partial correlation coefficient which means the association between two variables after adjusting the effects of additional variables.
Boldface numbers indicate statistically significant associations ($p < 0.05$).

https://doi.org/10.1371/journal.pone.0239555.t004

the other hand, Yuda et al. [47] also reported that there was no difference in peripapillary RNFL thickness between disease eyes and fellow eyes in the patients with unilateral exudative AMD, which is consistent with our study. The reason for these results could be that the peripapillary RNFL reflected the entire retina, compared to the macula or GC-IPL thickness, which reflected only the macular area. Alternatively, there is the possibility that ganglion cell damage was not severe enough to cause changes in the RNFL.

Previous studies have reported aging effects on GC-IPL thickness in normal subjects [48–50]. More specifically, a prospective longitudinal study reported that the age-related reduction

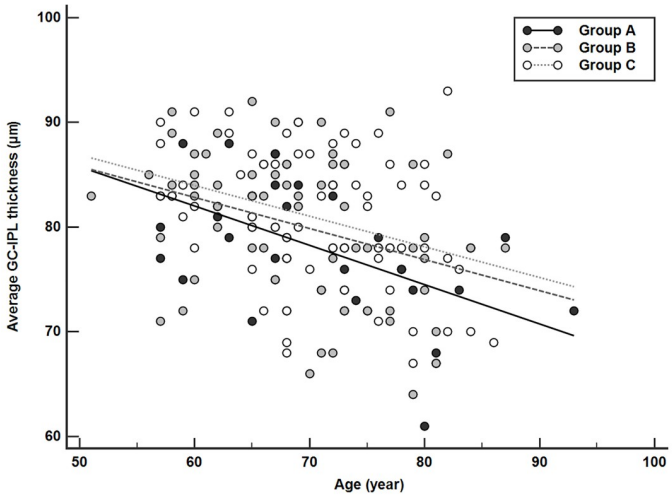

Fig 2. Scatter plot and results of linear regression analysis associating average GC-IPL thickness and age for the fellow eyes of Groups A, B, and C (control). The equations fitted to the regression lines for Groups A–C were: y = −0.405x + 104.504 (p = 0.001), y = −0.297x + 100.608 (p = 0.002), and y = −0.292x + 101.522 (p = 0.003), respectively.

https://doi.org/10.1371/journal.pone.0239555.g002

rate of the average GC-IPL thickness was –0.318 μm/year in normal eyes [50]. In the present study, age-related GC-IPL reductions in the fellow eyes of tCNV (–0.405 μm/year; linear regression analysis) patients were slightly greater than in the other two groups (fellow eyes of PCV patients: –0.297 μm/year, normal controls: –0.292 μm/year; linear regression analysis). This study is a cross-sectional study, and the age-related reduction rates obtained through linear regression may not be accurate. Therefore, it is difficult to directly compare these values with previous studies. However, the tCNV group had a higher reduction rate than the other two groups, and unilateral tCNV was found to be significantly associated with the GC-IPL thickness of fellow eyes using multivariate linear regression analysis, suggesting that unilateral tCNV is an important factor to be considered in the analysis of the GC-IPL.

Our study had some limitations. First, it had a retrospective design, which might have involved selection bias. Second, because tCNV is a less common subtype of exudative AMD than PCV in the Asian population, the number of patients with unilateral tCNV was small. Third, patients with comorbidities such as diabetes mellitus and hypertension were also included in the study. It has been reported that diabetes or hypertension affects GC-IPL and RNFL, and this change can occur even without retinopathy [21, 22, 51, 52]. However, there were no statistically significant differences among the three groups concerning diabetes and hypertension, as presented in Table 1, so it is considered that the effect of diabetes and hypertension would be small. Despite these limitations, the present study could report the inner retinal changes in the fellow eyes of unilateral exudative AMD according to the subtype of AMD, and we also found the factors affecting the inner retinal change, and these results would be helpful to physicians. Additional well-designed longitudinal studies will therefore be needed to investigate differences in the GC-IPL and RNFL using a larger number of patients.

In conclusion, the GC-IPL in the fellow eyes of tCNV patients was thinner than that of the normal control subjects, but no significant differences were found when the fellow eyes were compared between tCNV and PCV patients or PCV patients and controls. In addition, RNFL thickness did not differ among the three groups. In the fellow eyes of exudative AMD patients, drusen were thought to have a significant effect on the ganglion cell layer. The inner retinal layer of fellow eyes showed different characteristics depending on the subtype of AMD, and these results may be helpful in understanding the changes in the inner retinal layer in exudative AMD.

Supporting information

S1 Data.
(XLSX)

Author Contributions

Conceptualization: Jung-Yeul Kim.

Data curation: Seong Eun Lee, Hyung Bin Lim, Cheon Kuk Ryu.

Formal analysis: Seong Eun Lee, Hyung Bin Lim, Cheon Kuk Ryu, Jung-Yeul Kim.

Investigation: Seong Eun Lee, Hyung Bin Lim, Yong Il Shin, Cheon Kuk Ryu, Woo Hyuk Lee, Jung-Yeul Kim.

Supervision: Yong Il Shin, Woo Hyuk Lee, Jung-Yeul Kim.

Writing – original draft: Seong Eun Lee, Hyung Bin Lim, Jung-Yeul Kim.

Writing – review & editing: Seong Eun Lee, Hyung Bin Lim, Yong Il Shin, Woo Hyuk Lee, Jung-Yeul Kim.

References

1. Resnikoff S, Pascolini D, Etya'le D, Kocur I, Pararajasegaram R, Pokharel GP, et al. Global data on visual impairment in the year 2002. Bulletin of the World Health Organization. 2004; 82(11):844–51. Epub 2005/01/11. /S0042-96862004001100009. PMID: 15640920.
2. Lim LS, Mitchell P, Seddon JM, Holz FG, Wong TY. Age-related macular degeneration. Lancet (London, England). 2012; 379(9827):1728–38. Epub 2012/05/09. https://doi.org/10.1016/s0140-6736(12)60282-7 PMID: 22559899.
3. Lim LS, Cheung CM, Wong TY. Asian Age-Related Macular Degeneration: Current Concepts and Gaps in Knowledge. Asia-Pacific journal of ophthalmology (Philadelphia, Pa). 2013; 2(1):32–41. Epub 2013/01/01. https://doi.org/10.1097/APO.0b013e31827ff5bc PMID: 26107866.
4. Laude A, Cackett PD, Vithana EN, Yeo IY, Wong D, Koh AH, et al. Polypoidal choroidal vasculopathy and neovascular age-related macular degeneration: same or different disease? Progress in retinal and eye research. 2010; 29(1):19–29. Epub 2009/10/27. https://doi.org/10.1016/j.preteyeres.2009.10.001 PMID: 19854291.
5. Muftuoglu IK, Ramkumar HL, Bartsch DU, Meshi A, Gaber R, Freeman WR. QUANTITATIVE ANALYSIS OF THE INNER RETINAL LAYER THICKNESSES IN AGE-RELATED MACULAR DEGENERATION USING CORRECTED OPTICAL COHERENCE TOMOGRAPHY SEGMENTATION. Retina (Philadelphia, Pa). 2018; 38(8):1478–84. Epub 2017/06/27. https://doi.org/10.1097/iae.0000000000001759 PMID: 28650925.
6. Lee EK, Yu HG. Ganglion Cell-Inner Plexiform Layer and Peripapillary Retinal Nerve Fiber Layer Thicknesses in Age-Related Macular Degeneration. Investigative ophthalmology & visual science. 2015; 56(6):3976–83. Epub 2015/06/19. https://doi.org/10.1167/iovs.15-17013 PMID: 26087362.
7. Ramkumar HL, Nguyen B, Bartsch DU, Saunders LJ, Muftuoglu IK, You Q, et al. REDUCED GANGLION CELL VOLUME ON OPTICAL COHERENCE TOMOGRAPHY IN PATIENTS WITH GEOGRAPHIC ATROPHY. Retina (Philadelphia, Pa). 2018; 38(11):2159–67. Epub 2017/11/09. https://doi.org/10.1097/iae.0000000000001867 PMID: 29117065.
8. Zucchiatti I, Parodi MB, Pierro L, Cicinelli MV, Gagliardi M, Castellino N, et al. Macular ganglion cell complex and retinal nerve fiber layer comparison in different stages of age-related macular degeneration. American journal of ophthalmology. 2015; 160(3):602–7.e1. Epub 2015/06/09. https://doi.org/10.1016/j.ajo.2015.05.030 PMID: 26052088.
9. Rimayanti U, Kiuchi Y, Yamane K, Latief MA, Mochizuki H, Hirata J, et al. Inner retinal layer comparisons of eyes with exudative age-related macular degeneration and eyes with age-related macular degeneration and glaucoma. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie. 2014; 252(4):563–70. Epub 2013/10/23. https://doi.org/10.1007/s00417-013-2496-z PMID: 24146272.
10. Hendrickson A, Warner CE, Possin D, Huang J, Kwan WC, Bourne JA. Retrograde transneuronal degeneration in the retina and lateral geniculate nucleus of the V1-lesioned marmoset monkey. Brain structure & function. 2015; 220(1):351–60. Epub 2013/11/01. https://doi.org/10.1007/s00429-013-0659-7 PMID: 24173617.
11. Feigl B, Brown B, Lovie-Kitchin J, Swann P. Functional loss in early age-related maculopathy: the ischaemia postreceptoral hypothesis. Eye (London, England). 2007; 21(6):689–96. Epub 2006/05/09. https://doi.org/10.1038/sj.eye.6702389 PMID: 16680100.
12. Arya M, Sabrosa AS, Duker JS, Waheed NK. Choriocapillaris changes in dry age-related macular degeneration and geographic atrophy: a review. Eye and vision (London, England). 2018; 5:22. Epub 2018/09/22. https://doi.org/10.1186/s40662-018-0118-x PMID: 30238015.
13. Bressler NM, Bressler SB, Congdon NG, Ferris FL 3rd, Friedman DS, Klein R, et al. Potential public health impact of Age-Related Eye Disease Study results: AREDS report no. 11. Archives of ophthalmology (Chicago, Ill: 1960). 2003; 121(11):1621–4. Epub 2003/11/12. https://doi.org/10.1001/archopht.121.11.1621 PMID: 14609922.
14. Baek J, Cheung CMG, Jeon S, Lee JH, Lee WK. Polypoidal Choroidal Vasculopathy: Outer Retinal and Choroidal Changes and Neovascularization Development in the Fellow Eye. Investigative ophthalmology & visual science. 2019; 60(2):590–8. Epub 2019/02/06. https://doi.org/10.1167/iovs.18-24244 PMID: 30721925.
15. Cheung CM, Bhargava M, Laude A, Koh A, Xiang L, Wong D, et al. Asian age-related macular degeneration phenotyping study: rationale, design and protocol of a prospective cohort study. Clinical &

experimental ophthalmology. 2012; 40(7):727–35. Epub 2012/02/04. https://doi.org/10.1111/j.1442-9071.2012.02765.x PMID: 22299650.

16. Tan CS, Ngo WK, Chen JP, Tan NW, Lim TH. EVEREST study report 2: imaging and grading protocol, and baseline characteristics of a randomised controlled trial of polypoidal choroidal vasculopathy. The British journal of ophthalmology. 2015; 99(5):624–8. Epub 2015/03/12. https://doi.org/10.1136/bjophthalmol-2014-305674 PMID: 25758601.

17. Lee HJ, Kim MS, Jo YJ, Kim JY. Ganglion Cell-Inner Plexiform Layer Thickness in Retinal Diseases: Repeatability Study of Spectral-Domain Optical Coherence Tomography. American journal of ophthalmology. 2015; 160(2):283–9.e1. Epub 2015/05/26. https://doi.org/10.1016/j.ajo.2015.05.015 PMID: 26004405.

18. Bhisitkul RB, Mendes TS, Rofagha S, Enanoria W, Boyer DS, Sadda SR, et al. Macular atrophy progression and 7-year vision outcomes in subjects from the ANCHOR, MARINA, and HORIZON studies: the SEVEN-UP study. American journal of ophthalmology. 2015; 159(5):915–24.e2. Epub 2015/02/03. https://doi.org/10.1016/j.ajo.2015.01.032 PMID: 25640411.

19. Khan KN, Mahroo OA, Khan RS, Mohamed MD, McKibbin M, Bird A, et al. Differentiating drusen: Drusen and drusen-like appearances associated with ageing, age-related macular degeneration, inherited eye disease and other pathological processes. Progress in retinal and eye research. 2016; 53:70–106. Epub 2016/05/14. https://doi.org/10.1016/j.preteyeres.2016.04.008 PMID: 27173377.

20. Warrow DJ, Hoang QV, Freund KB. Pachychoroid pigment epitheliopathy. Retina (Philadelphia, Pa). 2013; 33(8):1659–72. Epub 2013/06/12. https://doi.org/10.1097/IAE.0b013e3182953df4 PMID: 23751942.

21. Lim HB, Shin YI, Lee MW, Koo H, Lee WH, Kim JY. Ganglion Cell—Inner Plexiform Layer Damage in Diabetic Patients: 3-Year Prospective, Longitudinal, Observational Study. Scientific reports. 2020; 10 (1):1470. Epub 2020/02/01. https://doi.org/10.1038/s41598-020-58465-x PMID: 32001760.

22. Lim HB, Lee MW, Park JH, Kim K, Jo YJ, Kim JY. Changes in Ganglion Cell-Inner Plexiform Layer Thickness and Retinal Microvasculature in Hypertension: An Optical Coherence Tomography Angiography Study. American journal of ophthalmology. 2019; 199:167–76. Epub 2018/12/07. https://doi.org/10.1016/j.ajo.2018.11.016 PMID: 30502337.

23. Han J, Byun MK, Lee J, Han SY, Lee JB, Han SH. Longitudinal analysis of retinal nerve fiber layer and ganglion cell-inner plexiform layer thickness in ethambutol-induced optic neuropathy. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie. 2015; 253(12):2293–9. Epub 2015/09/08. https://doi.org/10.1007/s00417-015-3150-8 PMID: 26344730.

24. Sari ES, Koc R, Yazici A, Sahin G, Ermis SS. Ganglion cell-inner plexiform layer thickness in patients with Parkinson disease and association with disease severity and duration. Journal of neuro-ophthalmology: the official journal of the North American Neuro-Ophthalmology Society. 2015; 35(2):117–21. Epub 2014/12/09. https://doi.org/10.1097/wno.0000000000000203 PMID: 25485861.

25. Meshi A, Goldenberg D, Armarnik S, Segal O, Geffen N. Systematic review of macular ganglion cell complex analysis using spectral domain optical coherence tomography for glaucoma assessment. World Journal of Ophthalmology. 2015; 5(2):86–98.

26. Pazos M, Dyrda AA, Biarnés M, Gómez A, Martín C, Mora C, et al. Diagnostic Accuracy of Spectralis SD OCT Automated Macular Layers Segmentation to Discriminate Normal from Early Glaucomatous Eyes. Ophthalmology. 2017; 124(8):1218–28. Epub 2017/05/04. https://doi.org/10.1016/j.ophtha.2017.03.044 PMID: 28461015.

27. Ishikawa H, Stein DM, Wollstein G, Beaton S, Fujimoto JG, Schuman JS. Macular segmentation with optical coherence tomography. Investigative ophthalmology & visual science. 2005; 46(6):2012–7. Epub 2005/05/26. https://doi.org/10.1167/iovs.04-0335 PMID: 15914617.

28. Sato S, Hirooka K, Baba T, Tenkumo K, Nitta E, Shiraga F. Correlation between the ganglion cell-inner plexiform layer thickness measured with cirrus HD-OCT and macular visual field sensitivity measured with microperimetry. Investigative ophthalmology & visual science. 2013; 54(4):3046–51. Epub 2013/04/13. https://doi.org/10.1167/iovs.12-11173 PMID: 23580483.

29. Medeiros NE, Curcio CA. Preservation of ganglion cell layer neurons in age-related macular degeneration. Investigative ophthalmology & visual science. 2001; 42(3):795–803. Epub 2001/02/27. PMID: 11222543.

30. Humayun MS, de Juan E Jr., Dagnelie G, Greenberg RJ, Propst RH, Phillips DH. Visual perception elicited by electrical stimulation of retina in blind humans. Archives of ophthalmology (Chicago, Ill: 1960). 1996; 114(1):40–6. Epub 1996/01/01. https://doi.org/10.1001/archopht.1996.01100130038006 PMID: 8540849.

31. Clarke S. Modular organization of human extrastriate visual cortex: evidence from cytochrome oxidase pattern in normal and macular degeneration cases. The European journal of neuroscience. 1994; 6 (5):725–36. Epub 1994/05/01. https://doi.org/10.1111/j.1460-9568.1994.tb00984.x PMID: 8075817.

32. Savastano MC, Minnella AM, Tamburrino A, Giovinco G, Ventre S, Falsini B. Differential vulnerability of retinal layers to early age-related macular degeneration: evidence by SD-OCT segmentation analysis. Investigative ophthalmology & visual science. 2014; 55(1):560–6. Epub 2014/01/11. https://doi.org/10.1167/iovs.13-12172 PMID: 24408984.

33. Strettoi E, Porciatti V, Falsini B, Pignatelli V, Rossi C. Morphological and functional abnormalities in the inner retina of the rd/rd mouse. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2002; 22(13):5492–504. Epub 2002/07/05. 20026533. https://doi.org/10.1523/JNEUROSCI.22-13-05492.2002 PMID: 12097501.

34. Blanks JC, Adinolfi AM, Lolley RN. Photoreceptor degeneration and synaptogenesis in retinal-degenerative (rd) mice. The Journal of comparative neurology. 1974; 156(1):95–106. Epub 1974/07/01. https://doi.org/10.1002/cne.901560108 PMID: 4836657.

35. Ramirez JM, Ramirez AI, Salazar JJ, de Hoz R, Trivino A. Changes of astrocytes in retinal ageing and age-related macular degeneration. Experimental eye research. 2001; 73(5):601–15. Epub 2001/12/19. https://doi.org/10.1006/exer.2001.1061 PMID: 11747361.

36. Toto L, Borrelli E, Di Antonio L, Carpineto P, Mastropasqua R. RETINAL VASCULAR PLEXUSES'CHANGES IN DRY AGE-RELATED MACULAR DEGENERATION, EVALUATED BY MEANS OF OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY. Retina (Philadelphia, Pa). 2016; 36 (8):1566–72. Epub 2016/01/26. https://doi.org/10.1097/iae.0000000000000962 PMID: 26807629.

37. Kim JH, Chang YS, Kim JW, Lee TG, Kim CG. PREVALENCE OF SUBTYPES OF RETICULAR PSEUDODRUSEN IN NEWLY DIAGNOSED EXUDATIVE AGE-RELATED MACULAR DEGENERATION AND POLYPOIDAL CHOROIDAL VASCULOPATHY IN KOREAN PATIENTS. Retina (Philadelphia, Pa). 2015; 35(12):2604–12. Epub 2015/06/08. https://doi.org/10.1097/iae.0000000000000633 PMID: 26049615.

38. Pumariega NM, Smith RT, Sohrab MA, Letien V, Souied EH. A prospective study of reticular macular disease. Ophthalmology. 2011; 118(8):1619–25. Epub 2011/05/10. https://doi.org/10.1016/j.ophtha.2011.01.029 PMID: 21550118.

39. Cohen SY, Dubois L, Tadayoni R, Delahaye-Mazza C, Debibie C, Quentel G. Prevalence of reticular pseudodrusen in age-related macular degeneration with newly diagnosed choroidal neovascularisation. The British journal of ophthalmology. 2007; 91(3):354–9. Epub 2006/09/16. https://doi.org/10.1136/bjo.2006.101022 PMID: 16973663.

40. Hogg RE, Silva R, Staurenghi G, Murphy G, Santos AR, Rosina C, et al. Clinical characteristics of reticular pseudodrusen in the fellow eye of patients with unilateral neovascular age-related macular degeneration. Ophthalmology. 2014; 121(9):1748–55. Epub 2014/05/27. https://doi.org/10.1016/j.ophtha.2014.03.015 PMID: 24856310.

41. Abdolrahimzadeh S, Parisi F, Marcelli M, Giustolisi R, Gharbiya M. Optical coherence tomography evidence of macular ganglion cell-inner plexiform layer thinning in eyes with subretinal drusenoid deposits. Eye (London, England). 2019. Epub 2019/03/31. https://doi.org/10.1038/s41433-019-0405-3 PMID: 30926911.

42. Sivaprasad S, Bird A, Nitiahpapand R, Nicholson L, Hykin P, Chatziralli I. Perspectives on reticular pseudodrusen in age-related macular degeneration. Survey of ophthalmology. 2016; 61(5):521–37. Epub 2016/03/21. https://doi.org/10.1016/j.survophthal.2016.02.005 PMID: 26994868.

43. Spaide RF, Ooto S, Curcio CA. Subretinal drusenoid deposits AKA pseudodrusen. Survey of ophthalmology. 2018; 63(6):782–815. Epub 2018/06/03. https://doi.org/10.1016/j.survophthal.2018.05.005 PMID: 29859199.

44. Lee B, Ahn J, Yun C, Kim SW, Oh J. Variation of Retinal and Choroidal Vasculatures in Patients With Age-Related Macular Degeneration. Investigative ophthalmology & visual science. 2018; 59(12):5246–55. Epub 2018/11/02. https://doi.org/10.1167/iovs.17-23600 PMID: 30383196.

45. Ciardella AP, Donsoff IM, Huang SJ, Costa DL, Yannuzzi LA. Polypoidal choroidal vasculopathy. Survey of ophthalmology. 2004; 49(1):25–37. Epub 2004/01/09. https://doi.org/10.1016/j.survophthal.2003.10.007 PMID: 14711438.

46. Kang SW, Lee H, Bae K, Shin JY, Kim SJ, Kim JM. Investigation of precursor lesions of polypoidal choroidal vasculopathy using contralateral eye findings. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie. 2017; 255 (2):281–91. Epub 2016/09/07. https://doi.org/10.1007/s00417-016-3452-5 PMID: 27596850.

47. Yuda K, Inoue Y, Tomidokoro A, Tamaki Y, Yanagi Y. Nerve fiber layer thickness in exudative age-related macular degeneration in Japanese patients. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie. 2010; 248 (3):353–9. Epub 2009/11/03. https://doi.org/10.1007/s00417-009-1222-3 PMID: 19882162.

48. Xu Q, Li Y, Cheng Y, Qu Y. Assessment of the effect of age on macular layer thickness in a healthy Chinese cohort using spectral-domain optical coherence tomography. BMC ophthalmology. 2018; 18 (1):169. Epub 2018/07/13. https://doi.org/10.1186/s12886-018-0842-y PMID: 29996804.

49. Zhang X, Francis BA, Dastiridou A, Chopra V, Tan O, Varma R, et al. Longitudinal and Cross-Sectional Analyses of Age Effects on Retinal Nerve Fiber Layer and Ganglion Cell Complex Thickness by Fourier-Domain OCT. Translational vision science & technology. 2016; 5(2):1. Epub 2016/03/12. https://doi.org/10.1167/tvst.5.2.1 PMID: 26966637.

50. Leung CKS, Ye C, Weinreb RN, Yu M, Lai G, Lam DS. Impact of age-related change of retinal nerve fiber layer and macular thicknesses on evaluation of glaucoma progression. Ophthalmology. 2013; 120 (12):2485–92. Epub 2013/09/03. https://doi.org/10.1016/j.ophtha.2013.07.021 PMID: 23993360.

51. Lim HB, Shin YI, Lee MW, Park GS, Kim JY. Longitudinal Changes in the Peripapillary Retinal Nerve Fiber Layer Thickness of Patients With Type 2 Diabetes. JAMA ophthalmology. 2019; 137(10):1125–32. Epub 2019/07/26. https://doi.org/10.1001/jamaophthalmol.2019.2537 PMID: 31343674.

52. Lee WH, Lee MW, Lim HB, Kim KM, Shin YI, Kim JY. Longitudinal changes in the thickness of the ganglion cell-inner plexiform layer in patients with hypertension: a 4-year prospective observational study. Acta ophthalmologica. 2020; 98(4):e479–e86. Epub 2019/10/29. https://doi.org/10.1111/aos.14291 PMID: 31658412.