Ocular Perfusion Pressure and Choroidal Thickness in Early Age-Related Macular Degeneration Patients With Reticular Pseudodrusen

Cheolmin Yun,[1] Jaemoon Ahn,[1] Minjung Kim,[1] Soon-Young Hwang,[2] Seong-Woo Kim,[1] and Jaeryung Oh[1]

[1]Department of Ophthalmology, Korea University College of Medicine, Seoul, Korea
[2]Department of Biostatistics, Korea University College of Medicine, Seoul, Korea

Correspondence: Jaeryung Oh, Department of Ophthalmology, Korea University College of Medicine, 126-1 Anam-dong 5-ga, Sungbuk-gu, Seoul, 136-705, Korea; ojr4991@korea.ac.kr.

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Purpose. The purpose of this study was to investigate the relationship between the ocular perfusion pressure (OPP) and subfoveal choroidal thickness (CT) in eyes with early age-related macular degeneration (AMD) with or without reticular pseudodrusen (RPD).

Methods. We evaluated the clinical history, blood pressure parameters, fundus photography, and optical coherence tomography images of consecutive patients with early AMD. We calculated the mean OPP from blood pressure and intraocular pressure.

Results. We included 103 eyes from 103 patients, classifying 45 as the RPD group and 58 as the non-RPD group. The mean OPP of the RPD group (46.1 ± 6.5 mm Hg) did not differ from that of the non-RPD group (45.1 ± 5.1 mm Hg, $P = 0.325$), but the RPD group showed a thinner mean subfoveal CT (158.3 ± 73.0 μm) than the non-RPD group (220.9 ± 67.0 μm, $P < 0.001$). Among 64 patients who underwent follow-up examination, the rate of change in subfoveal CT in the RPD group (−4.74 ± 0.86 μm/y) was greater than that in the non-RPD group (−2.46 ± 0.75 μm/y, $P = 0.028$). In the RPD group, a history of systemic hypertension and lower baseline OPP were associated with a higher rate of change in subfoveal CT ($P = 0.019$ and $P = 0.010$, respectively).

Conclusions. Subfoveal CT was thinner in early AMD patients with RPD than in those without RPD. Lower baseline mean OPP and a history of systemic hypertension could be risk factors associated with the progression of choroidal thinning in early AMD patients with RPD.

Keywords: age-related macular degeneration, choroidal thickness, ocular perfusion pressure, optical coherence tomography, pseudodrusen

Age-related macular degeneration (AMD) is a leading cause of legal blindness worldwide.[1] The pathogenic mechanisms of AMD are not entirely clear, but the choroid is of particular interest in AMD because it provides an important blood supply for the outer retina, and impairment of the blood flow from the choroid to the retina could cause AMD.[2–4] Recently, advances in imaging have enabled better visualization of the choroid, and many studies have examined choroidal thickness (CT) in various chorioretinal diseases.[5] In AMD, it is unclear whether CT is associated with the progression of dry AMD to late AMD or visual prognosis. However, reduced CT was suggested to have a role in the natural history of AMD.[4,6]

Recently, reticular pseudodrusen (RPD) has been introduced as a strong risk factor for late AMD.[7–10] Reticular macular disease is a process that can be visualized on multiple en face imaging modalities, such as infrared reflectance, indocyanine green angiography, and autofluorescence, and has also more recently been expanded to a two-compartment model that includes both RPD and choroidal alterations.[11,12] The pathogenic mechanism of RPD formation has not been clearly defined.[9] However, several studies reported finding choroidal changes in eyes with RPD and that overall CT was reduced when compared with early AMD.[4,9,13–16] It is unclear whether decreased CT is a cause or consequence of RPD. Several studies have suggested that choroidal insufficiency, vasculopathy, and hypoxia are involved in RPD pathogenesis.[9,13–17]

Choroidal thickness is affected by age, refractive error, axial length, diurnal variations, ocular perfusion pressure (OPP) and several other factors.[5,18,19] In the eye, OPP has been estimated using the systemic blood pressure and intraocular pressure (IOP) and has been considered an indirect indicator of choroidal blood flow.[20] Low OPP might cause a reduction in ocular blood flow, followed by choroidal blood flow insufficiency and hypoxia.[20] Recently, OPP has been investigated in ocular diseases.[20,21] Because OPP originates from systemic vascular status and some studies have linked cardiovascular disease to AMD and reticular macular disease, OPP status might be important for understanding the pathogenesis of reticular macular disease.[22–24] However, in eyes with RPD, the status of OPP has not been reported.

In this study of patients with early AMD, we compared CT and OPP between patients with and without RPD, and we investigated the relationship between OPP and change in CT.

Methods

The Institutional Review Board at Korea University approved this study protocol. The data collection and research of this study followed the tenets of the Declaration of Helsinki.

We conducted this retrospective, cross-sectional, and observational study by reviewing the medical records of patients who were diagnosed with early AMD between March 2010 and September 2015 at Korea University Medical Center. All patients underwent comprehensive ophthalmic exam, including fundus photography and red-free photography with a 30-degree angle centered on the macula, spectral-domain optical coherence tomography (SD-OCT), and IOP measurement. We collected medical information about history of hypertension, diabetes, and blood pressure parameters.

We excluded cases with high myopia (axial length $\geq$ 26.0 mm or refractive error $\geq$ –6.0 diopters), choroidal neovascularization, geographic atrophy (GA), and other retinal or choroidal disorders, including vascular disease and uveitis. We also excluded cases with a history of vitreoretinal surgery, anti–vascular endothelial growth factor treatment, photodynamic therapy, or other laser treatment. Because of potential bias from biological correlation between two eyes from one patient, we chose the right eye for analysis. If the right eye was unsuitable for the inclusion criteria, we chose the left eye for analysis.

Definition of AMD and Identification of RPD

We defined early AMD as an early or intermediate stage of AMD based on the classification guidelines of the Age-Related Eye Disease Study.[25] Reticular lesions on color fundus photos or red-free photos were defined as yellow interlacing networks ranging from 125 to 250 μm.[26,27] Reticular lesions on SD-OCT were defined as five or more hyperreflective mounds or triangular lesions located above the RPE in at least one B-scan from the 6 × 6-mm macula cube scan.[28,29] Comparisons among color fundus photos, red-free photos, and SD-OCT images were performed using the point-to-point correlation built into the software of the SD-OCT (3D OCT-1000 Mark II software, version 4.21; Topcon Corp., Tokyo, Japan). Patients with RPD were diagnosed with a peculiar yellowish reticular pattern at the macula in the color fundus or red-free photos and by subretinal deposits confirmed by SD-OCT.[9,26–30] Two independent retinal specialists (C.Y. and J.A.) graded AMD status and confirmed the presence of RPD. In cases with disagreement, a final decision was made upon further review by two other observers. The drusen area (mm^2) was obtained from the 6 × 6-mm cube scan centered on the fovea and built-in software of the SD-OCT. The square root transformation of the drusen area was used for statistical analysis.[31]

We defined progression to late AMD as the new development of neovascular AMD or GA under the center of the macula, defining GA as the presence of well-marginated regions at least 175 μm in diameter.[32]

Estimation of OPP

Intraocular pressure was measured using a noncontact tonometer (CT-80A computerized tonometer; Topcon Corp.) at least two times, and we used the mean value for analysis. Blood pressure was measured on the upper arm with the patient in a sitting position after a rest of at least 15 minutes using an automated oscillometric machine. Mean OPP was calculated using the following formula: Mean OPP = 2/3 × mean arterial pressure (MAP) − IOP.[33] Mean arterial pressure was calculated from systolic blood pressure (SBP) and diastolic blood pressure (DBP) as follows: MAP = DBP + 1/3(SBP − DBP).

SD-OCT and Measurement of CT

We used SD-OCT and obtained a 6-mm horizontal line scan centered on the fovea thorough the choroidal mode. Even with localized reticular RPD, CT is diffusely decreased; thus, we measured subfoveal CT as a representative value.[13,16] We measured the subfoveal CT manually at the center of the fovea with a caliper tool built into the SD-OCT image viewer program.[19] We defined the CT as the perpendicular distance between the RPE and the inner surface of the sclera. Two retinal specialists (C.Y. and J.A.) performed all of the measurements, and we used the mean for analysis.

Statistical Methods

The baseline characteristics of the two groups were compared using χ^2 tests to test for categorical variables and Student's *t*-tests or the Mann-Whitney *U* test for continuous variables. Analysis of covariance (ANCOVA) was employed to compare the subfoveal CT between the two groups to adjust for different baseline parameters.

Longitudinal changes of subfoveal CT were evaluated in cases with follow-up evaluations at an interval of at least 6 months. Because of the repeated measurement of subfoveal CT at each patient visit and variations in visit time, we used the linear mixed model to determinate the rate of changes in subfoveal CT. We modeled subfoveal CT as a function of time, baseline factors, and an interaction term for group with time and represented it as the average rate of change in subfoveal CT per year. The baseline factors were age, sex, group, history of systemic hypertension, history of diabetes, baseline OPP, and square root of baseline drusen area. The time and intercept were random factors, and we considered the other factors as fixed factors. In a set of subanalyses, we investigated factors that could potentially affect the rate of change in subfoveal CT in the RPD and non-RPD groups, respectively. In those tests, we modeled the subfoveal CT as a function of time, baseline factors, and interaction terms for baseline factors with time. We chose the final models after selecting the factors that showed a significant association with time.

A multivariate Cox proportional hazard model with a stepwise selection process was used to analyze the risk factors, age, sex, history of hypertension, history of diabetes, OPP, lens status, initial subfoveal CT, presence of RPD, and square root of initial drusen area. We obtained the hazard ratio and 95% confidence intervals for development of late AMD using that model. Statistical analyses were performed using analysis software (SAS 9.2; SAS Institute, Cary, NC, USA).

Results

We included 103 eyes from 103 patients in this study. Mean age was 72.4 ± 8.0, and 34 males and 69 females were included (Table 1). Twenty-one eyes had early stage AMD, and 82 had intermediate stage AMD. Their mean drusen area was 1.61 ± 2.40 mm^2.

Baseline Subfoveal CT and OPP

The mean subfoveal CT was 194.2 ± 75.6 μm (Table 2). Mean SBP, DBP, MAP, and IOP were 123.9 ± 13.6 mm Hg, 75.6 ± 8.7 mm Hg, 91.9 ± 8.4 mm Hg, and 15.4 ± 2.7 mm Hg, respectively (Table 2). The mean OPP was estimated to be 45.7 ± 5.9 mm Hg.

In univariate analyses, subfoveal CT had a statistically significant relationship with the square root of the drusen area ($P = 0.017$) and borderline significant relationships with age and refractive error ($P = 0.063$ and $P = 0.057$, respectively; see Supplementary Table S1 for univariate analyses). However, the relationship between baseline subfoveal CT and OPP was not statistically significant ($P = 0.151$).

Table 1. Baseline Characteristics of Early AMD Patients With and Without RPD

Characteristics	Total, $n = 103$	RPD Group, $n = 45$	Non-RPD Group, $n = 58$	*P* Value
Age, years	72.4 ± 8.0	75.1 ± 7.5	70.0 ± 7.7	<0.001†
Sex, male : female	34 : 69	10 : 35	24 : 34	0.040‡
Lens status, phakia : pseudophakia	86 : 17	35 : 10	51 : 7	0.169‡
Refractive error*	0.46 ± 1.42	0.18 ± 1.62	0.65 ± 1.28	0.092†
Hypertension, *n*, %	49, 47.6%	23, 51.1%	26, 44.8%	0.527‡
Diabetes, *n*, %	27, 26.2%	14, 31.1%	13, 22.4%	0.319‡
AMD classification, early stage : intermediate stage	21 : 82	8 : 37	13 : 45	0.562‡
Drusen area, mm²	1.61 ± 2.40	1.99 ± 2.51	1.32 ± 2.28	0.161†
Square root of drusen area	0.99 ± 0.80	1.15 ± 0.82	0.86 ± 0.77	0.107†

P values were obtained by comparing the RPD and non-RPD groups.
* Refractive errors were obtained from phakic eyes in each group and presented by the spherical equivalent (diopters).
† *P* value based on the Student's *t*-test.
‡ *P* value based on the χ^2 test.

Comparison of Baseline CT and OPP Between Eyes With and Without RPD

Among the 103 patients, we classified 45 patients into the RPD group and 58 patients into the non-RPD group (Table 1). The RPD group was older and more female dominant than the non-RPD group. We found no differences in lens status, refractive error, IOP, AMD stage, mean square root of drusen area, or prevalence of hypertension or diabetes between the two groups.

The mean subfoveal CT at baseline for the RPD group (163.3 ± 74.2 μm) was smaller than that for the non-RPD group (218.2 ± 68.0 μm), adjusting for the age and sex differences between the two groups (ANCOVA test, $P = 0.002$). Hemodynamic parameters (SBP, DBP, MAP, and OPP) did not differ between the two groups (Table 2).

In the RPD group, we found no factors associated with subfoveal CT (see Supplementary Table S1 for univariate analysis). However, in the non-RPD group, subfoveal CT was negatively associated with age ($P = 0.028$) and the square root of the drusen area ($P = 0.020$); however, it was positively associated with refractive error ($P = 0.005$, see Supplementary Table S1 for univariate analyses). Multiple regression linear analyses revealed that refractive error ($P = 0.005$, ß ± SE = 18.68 ± 6.39, 95% confidence interval [CI] from 5.84 to 31.53) and age ($P = 0.052$, ß ± SE = –2.01 ± 1.05, 95% CI from –4.190 to 0.014) were associated independently with subfoveal CT in the non-RPD group.

Progression of AMD and Risk Factors

Among the 103 patients, we included 64 patients who had follow-up evaluations at an interval of at least 6 months in this analysis. The mean follow-up period was 30.5 ± 15.2 months. Mean age was 72.7 ± 5.7, with 22 males and 42 females. Twelve patients had early stage AMD, and 52 had intermediate stage AMD. The baseline subfoveal CT and OPP of 64 patients were 195.8 ± 56.2 μm and 45.4 ± 5.0 mm Hg, respectively. The mean baseline drusen area was 1.61 ± 2.40 mm². We classified 28 patients into the RPD group and 36 into the non-RPD group.

During the follow-up period, seven cases and four cases of late AMD developed in the RPD and non-RPD groups, respectively. Significant factors influencing the development of late AMD included large initial square root of the drusen area ($P = 0.005$, hazard ratio [HR] = 3.18, 95% CI: 1.41–7.18), and thin baseline subfoveal CT ($P = 0.020$, HR = 0.981, 95% CI: 0.965–0.997). Other factors (age, sex, RPD presence, history of hypertension, history of diabetes, OPP, and lens status) were removed from the final model.

Changes in Subfoveal CT and Risk Factors

During the 27.3 ± 11.7 months of the mean follow-up periods, we obtained a total of 190 subfoveal CT measurements from the 64 patients. The mean follow-up period was 29.0 ± 10.6 months for the RPD group and 26.0 ± 12.5 months for the non-RPD group. Our linear mixed model estimated the change rate in subfoveal CT for eyes with early AMD as –3.47 ± 0.58 μm/y. The rate of change in subfoveal CT was significantly faster in the RPD group (–4.74 ± 0.86 μm/y) than in the non-RPD group (–2.47 ± 0.76 μm/y, $P = 0.028$) (Table 3; Fig. 1).

In the RPD group, significant factors influencing the rate of change in subfoveal CT included a positive history of systemic hypertension ($P = 0.019$) and low baseline OPP ($P = 0.010$) (Table 4). A representative case is shown in Figure 2. Baseline square root of the drusen area ($P = 0.786$), sex ($P = 0.213$), and history of diabetes ($P = 0.118$) were not associated with changes over time, and we removed those factors from the

Table 2. Comparison of OPP and CT Between Groups With and Without RPD

Parameters	Total, $n = 103$	RPD Group, $n = 45$	Non-RPD group, $n = 58$	*P* value
Baseline mean subfoveal CT, μm	194.2 ± 75.6	163.3 ± 74.2	218.2 ± 68.0	0.002†
Baseline OPP, mm Hg*	45.7 ± 5.9	45.2 ± 5.5	46.0 ± 6.3	0.483‡
Baseline SBP, mm Hg	123.9 ± 13.6	122.2 ± 13.4	125.2 ± 13.7	0.271‡
Baseline DBP, mm Hg	75.6 ± 8.7	76.3 ± 8.4	75.1 ± 9.0	0.504‡
Baseline MAP, mm Hg	91.9 ± 8.4	91.6 ± 8.6	92.1 ± 8.4	0.741‡
Baseline IOP, mm Hg	15.4 ± 2.7	15.9 ± 2.6	15.0 ± 2.7	0.107‡

P values were obtained by comparing the RPD and non-RPD groups.
* OPP was calculated as OPP = 2/3 × MAP − IOP.
† *P* value based on the ANCOVA test with adjustment for differences in age and sex.
‡ *P* value based on the Student's *t*-test.

Table 3. Linear Mixed Model Estimating Factors Associated With Mean Subfoveal CT

Effect	Group	Estimate	SE	*P* Value
Age, y		−2.26	1.24	0.074
Sex, male		8.01	13.55	0.556
Hypertension		13.74	12.57	0.279
Diabetes		1.81	14.31	0.900
Group	Non-RPD group RPD group	28.18	13.90	0.047
Time, y		−4.74	0.86	<0.010
Time * group	Non-RPD group RPD group	2.27	1.14	0.028
OPP, mm Hg		5.16	1.25	0.100
Square root of drusen area		−5.04	8.12	0.540
Intercept		112.00	98.64	0.261

final model. We found no significant factors associated with changes over time in the non-RPD group.

We divided patients into two groups according to the median age of the follow-up group, using a cutoff of 73 years. Our linear mixed model based on this classification did not reveal significant differences in changes in CT according to age group (time * age group, $P = 0.803$) or age and RPD group (time * age group * RPD group, $P = 0.131$).

Interobserver Reproducibility

We obtained an intraclass correlation coefficient to assess the interobserver reproducibility of the CT measurements. The intraclass correlation coefficient was 0.958 (95% CI, 0.938–0.972), indicating good agreement.

Discussion

In this study, we found that the mean subfoveal CT was significantly thinner in the RPD group than in the non-RPD group. This result is consistent with those of previous studies.[9,13–16] This result suggests that CT is one of the factors involved in the development of RPD. We also found that the rate of change in subfoveal CT was greater in the RPD group than in the non-RPD group. Previous studies predicted the annual change of CT in the normal population to be 1.97 μm/y.[19] We found the change rate in the non-RPD group to be

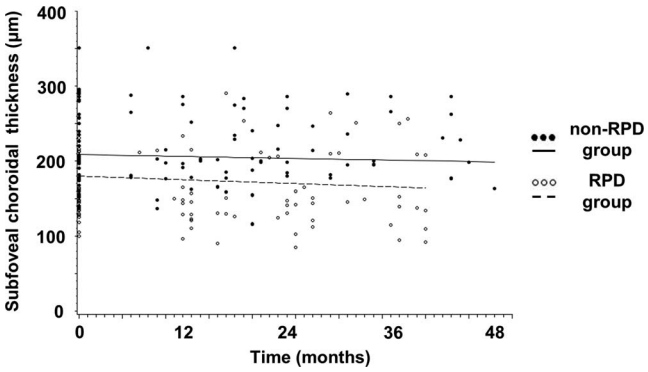

Figure 1. Scatter plots of subfoveal CT from the non-RPD and RPD groups. *Black dots* represent the non-RPD group, and *white dots* represent the RPD group. Regression lines estimated from the linear mixed model are continuous for the non-RPD group and dashed for the RPD group. The rate of change in subfoveal CT for the RPD group (*dashed line*, −4.74 ± 0.86 μm/y) was greater than that for the non-RPD group (*continuous line*, −2.47 ± 0.76 μm/y, $P = 0.028$).

Table 4. Linear Mixed Model for Estimating Factors Associated With Subfoveal CT and Its Mean Change Rate in the RPD Group

Effect	Estimate	SE	*P* Value
Age, y	1.06	2.15	0.626
Sex, male	34.80	27.76	0.258
Hypertension	−13.10	24.76	0.600
Diabetes	29.23	21.70	0.187
OPP, mm Hg	−0.13	2.64	0.963
Square root of drusen area	−41.64	15.48	0.011
Time, y	−25.38	6.45	<0.001
Time * hypertension	−3.12	1.27	0.019
Time * OPP	0.49	0.14	0.010
Intercept	39.08	171.5	0.822

similar, but in the RPD group in our study the change appeared to be greater. The small number of cases in the RPD group might have influenced that result, but it nonetheless suggests the possibility of a different pathogenic mechanism underlying the two groups.

In our study, OPP was not associated with the mean subfoveal CT in either of the two groups with AMD, which differs from the result of a previous study.[34] This discrepancy might result from differences in the study population; our study examined patients who were old (range, 52–93) and had early AMD, whereas the previous study examined healthy young persons (range, 20–25).[34] Another possibility could be that the relationship between OPP and subfoveal CT could be reduced by aging or AMD-related choroidal changes. In eyes with RPD, baseline OPP significantly influenced the rate of change in subfoveal CT. Previous studies suggested that relatively thicker choroids might need a lower OPP to maintain blood flow, whereas a relatively thinner choroid could require a higher OPP to compensate for possible reductions and maintain blood flow.[34,35] Because eyes with RPD have a thinner choroid, they might need higher OPP to maintain blood flow than those without RPD, which have a relatively thicker choroid. In addition to thin CT, eyes with RPD are thought to exhibit vasculopathy of the choroid.[9,15,36] The altered choroid in eyes with RPD could have an altered circulatory system and autoregulatory reserve. Thus, normal OPP in eyes without RPD could be lower than the lower limit of the autoregulatory reserve (and therefore inadequate) in eyes with RPD. The choroid in patients with AMD might not be able to compensate for the change in OPP, leaving those with RPD unable to endure the reduced OPP. Eyes with RPD and low baseline OPP might therefore be especially vulnerable to choroidal thinning or atrophy.

Hypertension, which has been suggested to be a risk factor for neovascular AMD and RPD, affected the rate of change in subfoveal CT in the RPD group in this study.[37,38] Age-related changes in blood vessels have characteristic features, including vascular endothelial dysfunction, inflammation, and vascular remodeling.[39] Hypertension augments age-related vascular dysfunction and remodeling.[39,40] The choroid is a vascular layer, and eyes with RPD might have vasculopathy in the choroid with atrophy and fibrotic changes.[15,36] Although the exact pathogenesis of RPDs is unknown, considering choroidal vasculopathy as one cause of RPD formation suggests the possibility that vascular changes from aging and hypertension could affect or aggravate the choroidal vasculopathy already present in eyes with RPD.

A previous study also suggested that the rate of change in subfoveal CT was greater in the RPD group than in the non-RPD group.[11] Additionally, they found that the rate of CT change might vary according to age and that choroids in the RPD group became thinner with each additional year of age

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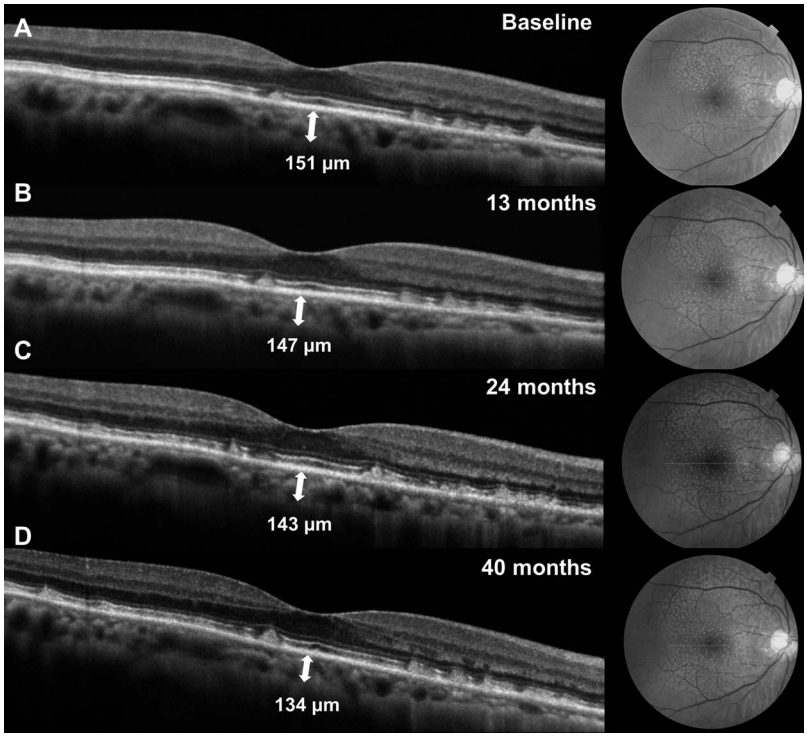

Figure 2. Representative case of a 73-year-old female patient with early AMD and RPD. The patient had a history of hypertension and a baseline ocular perfusion pressure of 36.1 mm Hg. The subfoveal CT was 151 μm at baseline (**A**), and it decreased to 134 μm at 40 months (**B–D**).

among participants ≤82 years old, while they became thicker with each additional year of age among participants >82 years age old.[11] However, our subanalysis according to age did not show a similar trend. This might be because of differences in our study population, which had a younger mean age than that of the previous study; thus, these two studies may not be comparable.

In this study, seven and four cases of late AMD developed in the RPD and non-RPD groups, respectively, during the follow-up period. The rate of conversion to late AMD in the RPD group was approximately twice that of the non-RPD group. This is consistent with previous reports that found that RPD was strongly associated with development of late AMD.[7,8,41] Furthermore, eyes with RPD developed late AMD more often than those without.[7,10,42] However, in this study, development of late AMD was associated with a larger initial drusen area and thinner baseline subfoveal CT but not with RPD status or OPP. The reason we did not find an association between late AMD development and RPD or OPP might be because of our small case sample size and the short follow-up period of this study. Thus, further investigations using a prospective design and with a larger case sample will improve our understanding of the roles that RPD and OPP play in late AMD development.

This study has several limitations. First, it is a retrospective study with a small sample size. There were cases with irregular follow-up and follow-up loss, although we adjusted for that using a statistical method. Because of short-term follow-up, CT changes might not have been detected in some cases. Second, blood pressure was measured only once. The blood pressure reading at the hospital might not represent the whole of a patient's blood pressure status over time. Third, we might have missed cases with drusen or RPD located outside the 30-degree area around the macula. Fourth, because we included aged persons and cases with RPD, the CT was thin in many cases. Because we measured CT manually, our results might not be entirely accurate, even though two independent observers measured all eyes, with good interobserver reliability. Fifth, we could not consider diurnal variation in CT and IOP.[18] In addition, because of a lack of normal age-matched controls, we could not compare the rate of changes in subfoveal CT directly.

In conclusion, the subfoveal CT was thinner in eyes with early AMD that had RPD than in those without RPD in spite of similar OPP. The rate of change in subfoveal CT in eyes with early AMD was greater in those with RPD than in those without RPD and was also greater in RPD cases with a history of systemic hypertension and lower baseline OPP. These results may suggest that OPP contributes to the age-related changes in eyes with RPD.

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