



Hyperreflective foci distribution in eyes with dry age-related macular degeneration with subretinal drusenoid deposits

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Abstract

Purpose To investigate the distribution of hyperreflective foci (HRF) in eyes with dry age-related macular degeneration (AMD).

Methods We retrospectively reviewed optical coherence tomography (OCT) images of 58 dry AMD eyes presenting HRF. The distribution of HRF according to the early treatment diabetic retinopathy study area was analyzed according to the presence of subretinal drusenoid deposits (SDDs).

Results We classified 32 eyes and 26 eyes into the dry AMD with SDD group (SDD group) and dry AMD without SDD group (non-SDD group), respectively. The non-SDD group had higher prevalence and density of HRF at the fovea (65.4% and 1.71 ± 1.48) than the SDD group (37.5% and 0.48 ± 0.63 , $P=0.035$ and $P < 0.001$, respectively). However, the prevalence and density of HRF in the outer circle area of the SDD group (81.3% and 0.11 ± 0.09) were greater than those of the non-SDD group (53.8% and 0.05 ± 0.06 , $p=0.025$ and $p=0.004$, respectively). The SDD group showed higher prevalence and mean densities of HRF in the superior and temporal area than in the non-SDD group (all, $p < 0.05$).

Conclusion HRF distributions in dry AMD varied according to the presence of SDDs. This might support that the degenerative features may be different between dry AMD eyes with and without SDDs.

Key messages

What is known

- The hyperreflective foci (HRF) have been suggested to be an important biomarker for the progression of early AMD to advanced AMD.
- HRF are typically detected in the neurosensory retina in areas with RPE atrophy and outer retinal atrophy associated with drusen.

What is new

- Hyperreflective foci distribution in dry age-related macular degeneration varied according to the presence of subretinal drusenoid deposits (SDDs).
- Diffuse and superotemporal distribution of HRF in AMD eyes with SDDs might support that the degenerative features may be different between dry AMD eyes with and without SDDs.

Keywords Hyperreflective foci · Age-related macular degeneration · Drusen · Subretinal drusenoid deposit

Introduction

Age-related macular degeneration (AMD) is a disease characterized by drusen and associated degenerative changes in retinal pigment epithelium (RPE), photoreceptors, Bruch's membrane, and choriocapillaris [1]. The pathogenesis of AMD is not entirely understood; however, previous studies suggested that RPE integrity is essential for photoreceptor function and RPE degeneration have an essential role during development and progression of the disease in most AMD cases [1].

Among the various optical coherence tomography (OCT) biomarkers for AMD, hyperreflective foci (HRF) have been suggested to be an important risk factor for the progression of early AMD to advanced AMD [2, 3]. HRF are typically detected in the neurosensory retina in areas with RPE atrophy and outer retinal atrophy associated with drusen, which has been suggested as an indicator of overall disease activity [4]. Several studies suggested that the HRF on OCT and hyperpigmentation on color fundus photography had highly specific spatial correlation [5, 6].

With the development of ophthalmic imaging techniques, subtypes of drusen had been classified into several categories and different clinical features according to subtype have been suggested [7]. Subretinal drusenoid deposits (SDDs), also known as reticular pseudodrusen, have different features when compared with soft drusen [7–9]. Eyes with SDDs have different degenerative features during disease progression manifested by outer retina degeneration and RPE in the absence of drusen [10]. In addition, these eyes also exhibit greater risk of development of type 3 macular neovascularization (MNV) and multifocal geographic atrophy (GA) [11–13]. These different clinical features support the idea that soft drusen and SDDs might have different underlying pathogenesis [14, 15].

Based on recent studies supporting the role of varied degenerative features during AMD progression according to subtype in early AMD, we proposed that the features of RPE migration into the retina may be different according to drusen type [10, 11, 13, 14]. In this study, we investigated HRF distribution in eyes with early AMD with or without SDDs and its associated characteristics.

Methods

This study was performed following the Declaration of Helsinki after the approval of the Institutional Review Board of Korea University Medical Center. We retrospectively reviewed the medical records of consecutive patients who were diagnosed with early or intermediate

AMD between January 2018 and June 2021 at Korea University Medical Center. To investigate the features of HRF, we included early or intermediate AMD eyes with HRF in the macular area and excluded patients with bilateral late AMD including neovascular AMD or GA [16]. Eyes with a history of vitreoretinal surgery, laser treatment, retinal vascular disease including retinal vein occlusion, diabetic retinopathy or retinal arterial occlusion, and/or high myopia with an axial length greater than 26.0 mm were excluded.

Patients underwent comprehensive ophthalmic examination including wide-field fundus photography using Optos (Dunfermline, United Kingdom), optical coherence tomography (OCT), and near-infrared and blue reflectance images using the SPECTRALIS HRA system (Heidelberg Engineering, Heidelberg, Germany) [16]. The patients were diagnosed with early or intermediate AMD based on previously suggested criteria on fundus photograph and OCT [17]. SDDs were defined if reticular lesions within the macular area identified on fundus photos and near-infrared or blue reflectance images and the corresponding area showed 5 or more hyper-reflective triangular lesions above the RPE based on OCT [12, 16, 18]. Drusen volume (mm^3) was calculated from the thickness map using built-in OCT software. The mean volume of the area between the outer border of the RPE and Bruch's membrane was obtained after a manual adjustment of segmentation lines. Then, the mean macular drusen volume of each sector of the early treatment of diabetic retinopathy study (ETDRS) grid was used to calculate the total drusen volume in the macular area. The mean ganglion cell-inner plexiform layer (GCIPL) thickness and retinal thickness were obtained from the ETDRS grid. The mean choroidal thickness was defined as the mean of measurements at five points (fovea, 1,500 and 3,000 μm both nasally and temporally from the fovea) using horizontal line scans acquired using a previously described enhanced-depth imaging technique [18].

Based on previous studies, HRF is defined as a discrete, well-circumscribed lesion with a size greater than 15 μm of which reflectivity is similar to or greater than that of the RPE band on OCT and located above the RPE band [6, 19, 20]. Using volume scan images of the OCT, which covers at least a 6- \times 6-mm area with a 120- μm interscan distance, two retinal specialists (D. K. and K. N.) independently identified HRF in the retina manually by reviewing the B-scans at 400% magnification and identified the HRF location in the 6-mm zone of the ETDRS area: 1) fovea, 2) superior, nasal, inferior, and temporal sectors of the inner ring 1–3 mm zone, and 3) superior, nasal, inferior, and temporal sectors of the outer ring 3–6 mm zone. Cases with HRF not separated by hyporeflectivity were counted as one HRF [20]. The mean densities of

HRF in the superior, nasal, inferior, and temporal sectors were calculated as total number of HRF / area (mm²). If disagreement between the two investigators was present, a third reviewer (C. Y.) reviewed the case and made the final decision.

Considering biological correlations of two eyes from a single patient, one eligible eye was chosen for the analysis. If both eyes were eligible, the right eye was chosen. The kappa coefficient and intraclass correlation coefficients were used to evaluate the interobserver reliabilities for the categorical and continuous variables, respectively. Statistical Package for the Social Sciences version 20.0 for Windows software program (IBM Corporation, Armonk, NY, USA) was used for statistical analyses. Independent *t*-tests were used for the analysis of continuous variables and chi-squared tests or Fisher's exact tests were used for categorical variables. A *p*-value less than 0.05 was considered statistically significant.

Results

A total of 58 eyes from 58 patients were included and 26 eyes and 32 eyes were classified into the non-SDD and SDD groups based on the presence of SDDs, respectively. Mean age, sex, and history of hypertension or diabetes did not differ between the two groups (all *p* > 0.05; Table 1). The mean choroidal thickness of the non-SDD group (155.39 ± 54.15 μm) was greater than that of the SDD group (129.10 ± 25.80 μm; *p* = 0.018). Mean visual acuity, retinal thickness, ganglion cell-inner plexiform layer (GCIPL) thickness, AMD stage, and drusen volume were not different between the two groups (all *p* > 0.05).

Table 1 Baseline characteristics of patients with age-related macular degeneration (AMD) with or without subretinal drusenoid deposits (SDDs)

	Non-SDD group (<i>n</i> = 26)	SDD group (<i>n</i> = 32)	<i>p</i> -value
Age (years)	76.00 ± 6.98	75.19 ± 5.82	0.631*
Sex (male:female)	12: 14	11: 21	0.362 [†]
Hypertension (<i>n</i> , %)	12 (46.2%)	12 (37.5%)	0.956 [†]
Diabetes (<i>n</i> , %)	10 (38.5%)	8 (25.0%)	0.270 [†]
Visual acuity (LogMAR) [§]	0.33 ± 0.21	0.34 ± 0.19	0.912*
Retinal thickness (μm)	284.55 ± 16.03	281.97 ± 16.30	0.549*
GCIPL thickness (μm)	62.77 ± 6.52	62.16 ± 6.95	0.731*
Choroidal thickness (μm)	155.39 ± 54.15	129.10 ± 25.80	0.018*
AMD stage (early: intermediate)	0: 26	2: 30	0.195 [†]
Drusen volume (mm ³)	0.12 ± 0.10	0.08 ± 0.07	0.094*
Drusen cube root volume (mm)	0.44 ± 0.16	0.38 ± 0.14	0.160*

LogMAR logarithm of minimum angle of resolution, GCIPL ganglion cell-inner plexiform layer

*Independent *t*-test

[†]Chi-square test or fisher's exact test

[§]Uncorrected visual acuity

Prevalence of HRF

The distribution of HRF in the non-SDD group showed 65.4% at the fovea; 34.6%, 42.3%, 30.8%, and 26.9% at the respective superior, nasal, inferior, and temporal sectors of the inner circle; and 19.2%, 19.2%, 26.9%, and 15.4% at superior, nasal, inferior, and temporal sectors of the outer circle. The SDD group showed HRF of 37.5% at the fovea; 62.5%, 25.0%, 18.8%, and 56.3% at the superior, nasal, inferior, and temporal sectors of the inner circle, respectively; and 59.4%, 40.6%, 12.5%, and 40.6% at the superior, nasal, inferior, and temporal sector of outer circle (*p* = 0.035, 0.035, 0.163, 0.287, 0.025, 0.002, 0.080, 0.163 and 0.036, respectively) (Fig. 1). At the inner circle (< 3 mm area) area, the non-SDD group showed HRF of 88.5%, similar to the 84.4% of the SDD group (*p* = 0.654). However, the SDD group showed a higher prevalence of HRF at the outer circle (3 to 6 mm area) area, with 81.3% relative to 53.8% in the non-SDD group (*p* = 0.025). The kappa coefficients for the presence of HRF in each area ranged from 0.668 to 0.931. Representative cases are presented in Figs. 2 and 3.

Number and density of HRF

The mean number of HRF in the SDD group (5.28 ± 2.16) was not different from that of the non-SDD group (4.42 ± 1.30, *p* = 0.081). The mean number and density of HRF at the fovea of the non-SDD group (1.35 ± 1.16 and 1.71 ± 1.48) were greater than those of the SDD group (0.38 ± 0.49, 0.48 ± 0.63, *p* < 0.001) (Table 2). The mean number and density of HRF at the inner circle of the SDD group (2.50 ± 1.74 and 0.40 ± 0.28) were not different from those of the non-SDD group (2.00 ± 1.20 and 0.32 ± 0.19, *p* = 0.219). However, the mean number and density of HRF at the outer circle of the SDD

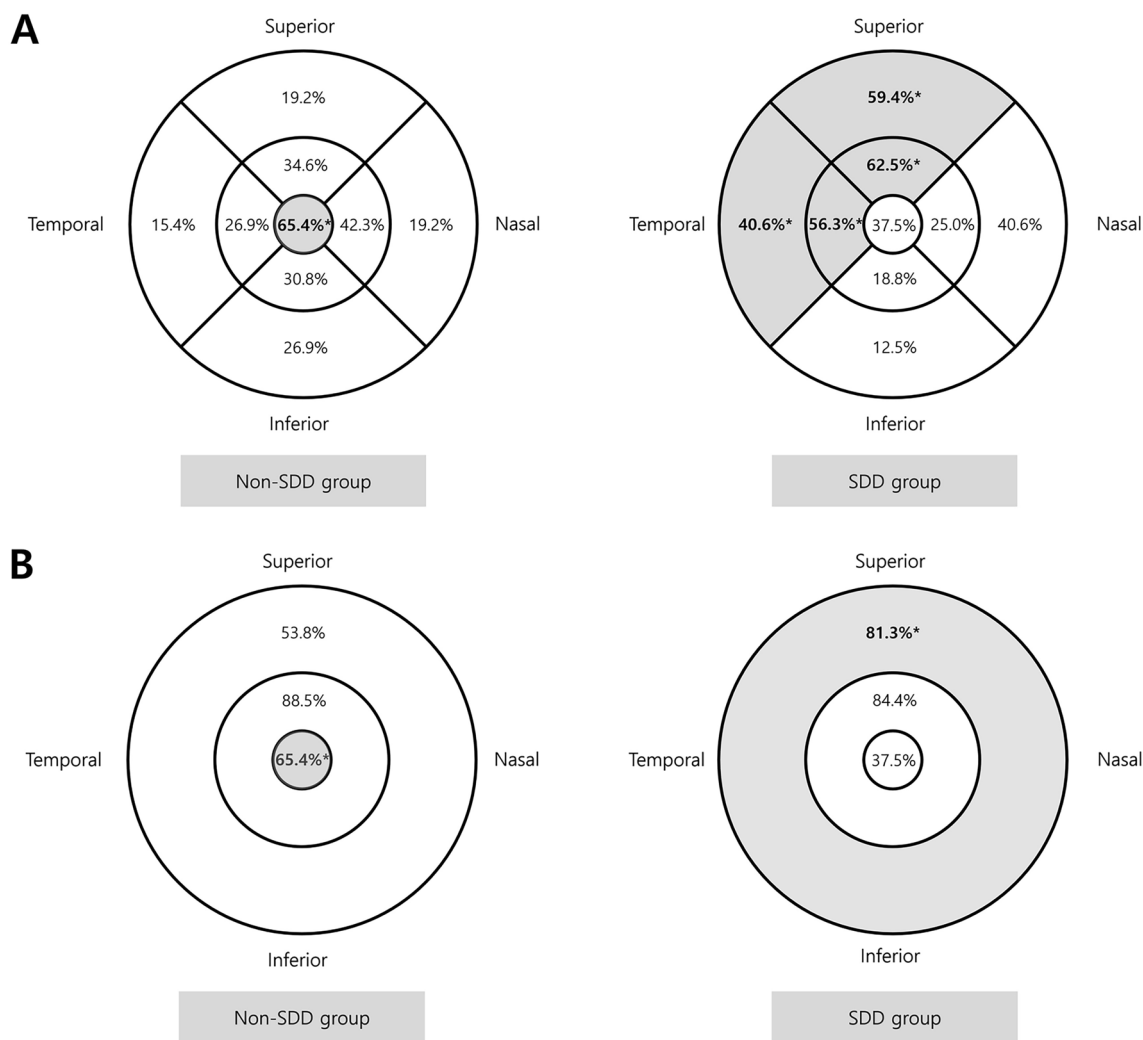


Fig. 1 Distribution of hyperreflective foci (HRF) in the macula according to the early treatment diabetic retinopathy study (ETDRS) area between age-related macular degeneration (AMD) eyes with and without subretinal drusenoid deposits (SDDs). **(A)** The non-SDD group (AMD eyes without SDDs) showed a higher prevalence of HRF at the fovea while the the SDD group (AMD eyes with SDDs)

showed a higher prevalence of HRF in the superior and temporal sectors of the inner and outer circle areas. **(B)** The SDD group showed higher prevalence of HRF at the outer circle area. Gray-colored areas with an asterisk (*) indicate significant difference of prevalence between the two groups, with a p -value < 0.05

group (2.41 ± 1.92 and 0.11 ± 0.09) were greater than those of the non-SDD group (1.08 ± 1.29 and 0.05 ± 0.06 , $p = 0.004$). The mean numbers and densities of HRF at superior and temporal areas of the inner and outer circles of SDD group were greater than those of non-SDD group (all, $p < 0.05$). The intra-class correlation coefficients for the mean number of HRF in each area ranged from 0.682 to 0.965.

Discussion

In this study, distributions of HRF differed according to the presence of SDDs. The non-SDD group showed higher prevalence of HRF at the fovea, while the SDD group showed

higher prevalence of HRF in outer circle and superior and temporal areas. These different features suggest that the features of RPE degeneration vary in eyes with AMD according to the presence of SDDs.

RPE dysfunction has an important role in AMD disease progression and several lines of evidence suggest that phenotypic characteristics of AMD may come from the RPE dysfunction or degeneration [1, 3, 4, 6, 21]. Among these features, migrating RPE associated with drusen has been shown as HRF in OCT and these features are suggested to be a biomarker for AMD progression [1, 2, 4–6, 22]. Previous studies reported presence of HRF over drusen as a sign of RPE atrophy, and that HRF usually occurs in and around the fovea [21–23]. In this study, 65.4% and 88.5% of cases in

Fig. 2 Representative fundus and optical coherence tomography (OCT) scan images of a 79-year-old male patient with dry age-related macular degeneration (AMD) without subretinal drusenoid deposit. (A to B) Soft drusen are located at the fovea. (C) The hyperreflective foci are located at and around the fovea, and the locations are indicated as black dots. (D to G) The hyperreflective foci are indicated with arrows on each OCT scan

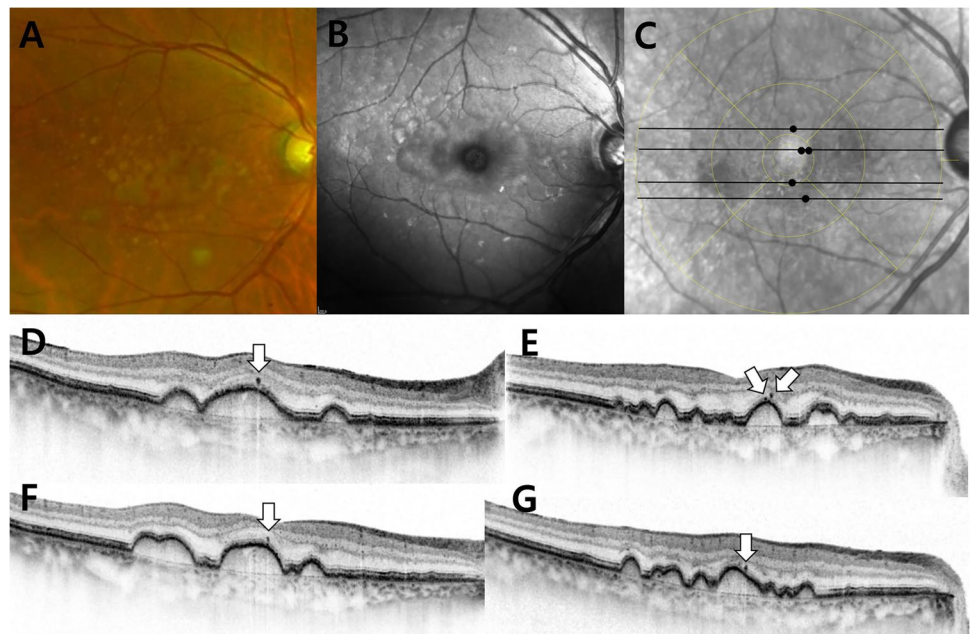
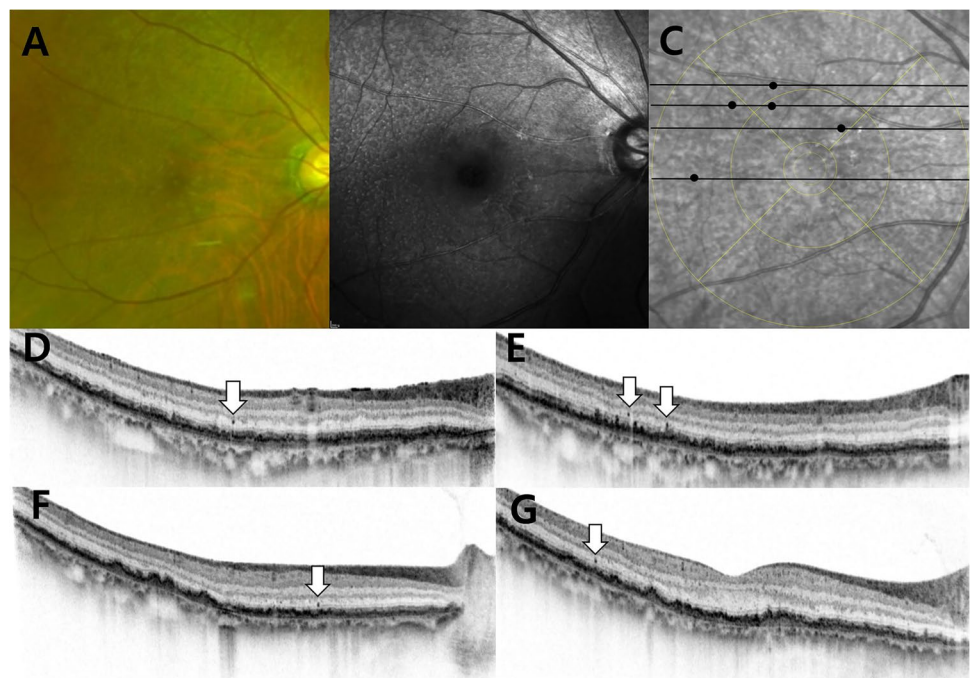


Fig. 3 Representative fundus and optical coherence tomography (OCT) scan images of a 70-year-old female patient with dry age-related macular degeneration (AMD) with subretinal drusenoid deposits. (A to B) Soft drusen are located at the fovea, and reticular pseudodrusen are found on the macula area (C) The hyperreflective foci are located at the inner and outer circles of the macula superotemporally, and the locations are indicated as black dots. (D to G) The hyperreflective foci are indicated with arrows on each OCT scan image



the non-SDD group showed HRF at the fovea and inside the 3 mm area, respectively. This feature is consistent with previous reported studies about HRF in dry AMD that showed that the distribution of drusen and relatively lower presence of HRF outside the 3 mm area may be associated with the topographic distribution of drusen, which are usually centered on the fovea [2, 15]. However, the SDD group showed HRF both inside and outside the 3 mm area in about 80% of cases, and this might be a distinguishing feature compared with those without SDDs.

Schuman et al. reported that HRF in AMD eyes were signs of outer retinal atrophy characterized by photoreceptor thinning and RPE atrophy associated with drusen, which are precursors of GA [23]. However, recent studies suggested that outer retinal atrophy can be developed in an area with SDDs during their progression and regression [10, 12]. This type of retinal atrophy was suggested to be a new late form of AMD in addition to classic GA and neovascular AMD [10, 12]. In addition to the outer retinal atrophy associated with SDDs, concurrent loss

Table 2 Mean numbers and densities of the hyperreflective foci (HRF) in patients with age-related macular degeneration (AMD) with or without subretinal drusenoid deposits (SDDs)

	Non-SDD group (<i>n</i> = 26)		SDD group (<i>n</i> = 32)		<i>p</i> -value*
	Number (<i>n</i>)	Density (n/mm ²)	Number (<i>n</i>)	Density (n/mm ²)	
Fovea	1.35 ± 1.16	1.71 ± 1.48	0.38 ± 0.49	0.48 ± 0.63	< 0.001
Inner circle (1 to 3 mm)	2.00 ± 1.20	0.32 ± 0.19	2.50 ± 1.74	0.40 ± 0.28	0.219
Superior	0.46 ± 0.71	0.29 ± 0.45	0.97 ± 0.93	0.62 ± 0.59	0.026
Nasal	0.58 ± 0.76	0.37 ± 0.48	0.28 ± 0.52	0.18 ± 0.33	0.085
Inferior	0.54 ± 0.91	0.34 ± 0.58	0.31 ± 0.74	0.20 ± 0.47	0.299
Temporal	0.42 ± 0.76	0.27 ± 0.48	0.94 ± 0.95	0.60 ± 0.60	0.029
Outer circle (3 to 6 mm)	1.08 ± 1.29	0.05 ± 0.06	2.41 ± 1.92	0.11 ± 0.09	0.004
Superior	0.31 ± 0.68	0.06 ± 0.13	0.94 ± 1.01	0.18 ± 0.19	0.009
Nasal	0.27 ± 0.60	0.05 ± 0.11	0.44 ± 0.56	0.08 ± 0.11	0.278
Inferior	0.27 ± 0.45	0.05 ± 0.09	0.22 ± 0.66	0.04 ± 0.12	0.741
Temporal	0.23 ± 0.59	0.04 ± 0.11	0.81 ± 1.31	0.15 ± 0.25	0.040

*Independent *t*-test

and degeneration of the RPE are key features in eyes with SDDs [12, 24]. Previous studies about the histologic features of the RPE and its associated in vivo imaging data showed that eyes with SDD are characterized by retinal changes from the RPE to the outer nuclear layer accompanied by the RPE damage [25, 26]. The aberrant displacement of the RPE toward the outer retina was supposed to be a sign of RPE abnormality or dysfunction and might suggest an advanced stage of degeneration [25, 26]. The different distribution of HRF in AMD eyes with SDDs might be associated with the different features of degeneration in eyes with SDDs [10, 12]. The SDDs usually develop at the perifoveal area, initially sparing the fovea, and propagate diffusely to the adjacent area of the macula, which is different from that of soft drusen [15, 27]. As the degenerative process associated with SDDs is supposed to start at the perifoveal area following the sequence of SDD development, the degeneration of RPE and HRF might also follow topographic features [13, 28]. In addition to those topographic features, the diffuse and multifocal chorioretinal degenerative features in eyes with SDDs, which have been suggested to be associated with underlying overall choroidal ischemia, might also contribute to diffuse HRF distribution in the macula [18, 29].

The SDD group showed a higher prevalence of HRF in the superior and temporal sector of the macula than the non-SDD group in this study. The HRF has been considered to be a precursor for late AMD and the topographic features of these HRF might be associated with the location of late AMD [2, 4–6]. In GA, previous studies reported that the location of GA has no predilection; however, these studies did not consider the presence of SDDs [30, 31]. Recently, GA in eyes with SDDs has also been reported to have different characteristics when compared with those without SDDs [8, 13]. These eyes show a higher prevalence of perifoveal

and multifocal GA [28, 31, 32]. However, the location of initial GA or nascent GA in eyes with SDDs have not been precisely reported.

Recently, Reiter et al. reported that the superior and temporal macular areas were associated with faster GA progression and photoreceptor degeneration in eyes with SDDs [28]. The authors suggested that these features might be associated with the distribution of SDDs, which are usually initially seen in the superior macula. Thus, the outer retina and RPE degeneration may start at the superior macula and follow the area with SDD propagation. This might contribute to the finding of the current study, which shows a higher prevalence of HRF in the superior and temporal macula in AMD eyes with SDDs.

In addition to GA, type 3 MNV is a neovascular form of late AMD that is strongly associated with SDDs [33, 34]. Type 3 MNV is likely associated with the migrated RPE in the inner retina and focally changed vascular endothelial growth factor concentration caused by the RPE [35]. These type 3 MNV have topographic characteristics with predilection for the superior and temporal macula and these features are supposed to be associated with similar topographic features of SDDs and type 3 MNV [36]. Overall, the topographic features of retinal degeneration and neovascularization in eyes with SDDs, which are predominantly located in the superior and temporal area, might also be associated with the topographic features of HRFs in eyes with SDDs in this study.

This study has several limitations. This study has a retrospective design and includes a small number of cases from one tertiary medical center. Lack of follow up data may limit the clinical importance of the study. Second, we did not investigate lesions outside the 6 × 6 mm ETDRS macular area. Thus, investigation of the limited area might not represent overall retinal changes. Third, even though three

investigators assessed the HRF, the identification of HRF may depend on the investigator's judgement and the lack of an objective method for assessment might have adversely affected data interpretation. Fourth, because the interscan distance of the OCT scans was 120 μm , there might be missing lesions between the scans.

In conclusion, dry AMD eyes showed different features of HRF according to the presence of SDDs. Diffuse and superotemporal distribution of HRF in eyes with SDDs might suggest that RPE degenerative features are different between dry AMD eyes with and without SDDs.

Authors' contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Dongwan Kang, Young Joo Lee, Ki Tae Nam, Mihyun Choi and Cheolmin Yun. The first draft of the manuscript was written by Dongwan Kang and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Code availability Not applicable.

Declarations

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the institutional review board of the Korea University Medical Center. This study does not contain contents about animals.

Consent to participate This type of study does not require informed consent.

Consent for publication This type of study does not require informed consent.

Conflicts of interest/Competing interests The authors declare that they have no conflict of interest.

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