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The Relationship Between Reticular Macular Disease and Choroidal Thickness

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Abstract

Purpose/Aim—Subretinal drusenoid deposits (SDD) are the main structural lesion of reticular macular disease (RMD), a phenotype of age-related macular degeneration (AMD). We aim to demonstrate spatiotemporal relationships between SDD and choroidal thickness alterations in RMD+ and RMD– eyes.

Materials and Methods—33 eyes (26 subjects) with early AMD/no SDD (RMD–) and 18 eyes (16 subjects) with early AMD/SDD (RMD+) underwent enhanced depth imaging spectral domain optical coherence tomography for choroidal thickness (CTh) measurements at 11 points per scan, in 5 horizontal B scans, creating a grid of 55 points/eye. The 55 points were treated as a cluster, controlling within-subject correlation. Marginal generalized estimating equation modeling was used to estimate the association between CTh and RMD status. All eyes were divided by their median age (<82 and >82 years) for stratified analyses.

Results—CTh was not significantly reduced in RMD+ eyes compared to RMD– eyes (mean difference [MD] –16.84 μm , $P=0.24$). Among younger subjects, mean CTh was significantly reduced in RMD+ vs. RMD– eyes (MD –53.72 μm , $P=0.01$). Conversely, among older subjects, there was no significant difference in CTh between RMD+ and RMD–.

Conclusions—In RMD, the association of SDD and choroidal thickness alterations varies with age but not by macular region. Among younger subjects (<82 years old), CTh was significantly thinner in RMD+ vs. RMD– eyes.

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Keywords

reticular macular disease; subretinal drusenoid deposits; choroidal thickness; age-related macular degeneration

INTRODUCTION

Age-related macular degeneration (AMD) is a degenerative disease of the macula affecting central vision [1]. AMD is the leading cause of blindness in developed nations, with approximately 1.75 million patients affected with advanced AMD in the United States alone [2]. While drusen have been considered the hallmark lesion of AMD [3], a different lesion type, subretinal drusenoid deposits (SDD), also known as reticular pseudodrusen (RPD), has recently been investigated as a different phenotype of AMD. This paper will use the term SDD, acknowledging that various authors have used different terminology. First described in 1990 by Mimoun et al. as a yellowish reticular pattern [4], Arnold et al. demonstrated in 1995, in a histopathologic study, that SDD are not associated with drusen [5], thus differentiating this new entity from classic descriptions of AMD. Since then, SDD lesions have been correlated in various imaging modalities [6-8]. Spectral domain optical coherence tomography (SD-OCT) imaging has allowed noninvasive characterization of SDD lesions in cross-section; Zweifel et al., and later Querques et al., showed that SDD appear as triangular hyperreflective drusenoid deposits which are localized between the retinal pigment epithelium (RPE) below and the EZ above, as opposed to typical drusen localization below the RPE [9, 10].

Until recently, SD-OCT had limited sensitivity in choroidal imaging. A new approach, termed enhanced depth imaging SD-OCT (EDI SD-OCT), provides reliable full-thickness choroidal cross-sectional images and allows for investigation of choroidal alterations in AMD [11, 12]. The technique behind EDI SD-OCT has been described previously [13, 14], but briefly, by bringing the machine closer to the eye than in regular scans, a stable inverted image of the retina is produced, with greater sensitivity in the deeper layers, including the choroid. Studies utilizing EDI SD-OCT images have found that normal physiologic aging is associated with decreasing choroidal thickness (CTh) [12, 15], and late AMD (both geographic atrophy and choroidal neovascularization) is associated with further decreases in CTh [16, 17]. Querques et al. demonstrated an overall thinned choroid in eyes with SDD than in eyes with early AMD but without SDD, except at 3000 μm superior to the fovea, where the choroid was actually thicker in SDD eyes [14]. Similarly, Garg et al. demonstrated that SDD lesions are associated with choroidal thinning in patients with early AMD [18].

Previous work by our group has defined this AMD phenotype with SDD/RPD, as reticular macular disease (RMD) [8]. RMD is a leading risk factor for progression from early to late AMD [19, 20] and is thus a phenotype that warrants further study. To this point, only a few studies have analyzed the effects of age on choroidal thickness, or the specific localization of choroidal alterations. Thus, the purpose of this study was to further elucidate the association between the main lesion of RMD (SDD) and CTh in early AMD.

MATERIALS AND METHODS

This cross-sectional study was performed after approval from the Institutional Review Board of New York University Langone Medical Center, in accordance with the tenets of the Declaration of Helsinki. All 42 patients were consecutively recruited from an outpatient retinal specialist clinic (KBF) between July 2012 and February 2013. Informed consent was obtained from all participants. All subjects completed a detailed questionnaire regarding their medical history and underwent a complete ophthalmologic examination, including infrared (IR) and EDI SD-OCT imaging, with methods described previously [13]. IR and EDI SD-OCT images were obtained using a confocal scanning laser ophthalmoscope (Spectralis, Heidelberg Engineering, Inc., Carlsbad, California, USA).

For inclusion, subjects needed to have early AMD with or without evidence of SDD. Patients were diagnosed with early AMD based on absence of GA or CNV, as well as presence on EDI SD-OCT of at least one large soft drusen ($>125\text{ }\mu\text{m}$) or more than five intermediate drusen ($63\text{--}125\text{ }\mu\text{m}$) below the RPE, or the presence of SDD, with or without pigment abnormalities. SDD were identified as hyper-reflective deposits above the RPE on EDI SD-OCT and as hyporeflectant lesions in well-defined reticular patterns, against a mildly hyperreflectant background, on IR. Based on these imaging findings, participants were divided into two study groups: (1) subjects with early AMD and SDD (RMD+), and (2) subjects with early AMD but without SDD (RMD-), the control group. Exclusion criteria were history of retinal detachment, retinal vascular occlusive disease, vitreoretinal or glaucoma surgery, central serous chorioretinopathy, macular hole, retinal pigment epithelium tear, media opacity resulting in poor image quality, or high myopia (spherical equivalent >-6 diopters).

EDI SD-OCT images were viewed and measured with Image J software (version 1.45, National Institutes of Health, Bethesda, MD, USA). Segmentation of the boundaries of the choroid were made manually, and then CTh was measured from the outer border of the RPE/Bruch's membrane complex to the inner scleral border as described previously by Margolis *et. al.* [15] using post-processing software with a ruler tool by a trained technician (CS), who was blinded to the subjects' age and RMD status. Measurements were made at 11 points per scan ($475\text{ }\mu\text{m}$ apart across 4.75 mm), in 5 horizontal B scans (1 mm apart), thus obtaining a grid of 55 points per eye (as demonstrated in **Fig 1**). These 55 data points were treated as a cluster, to control for within-subject correlation, in a generalized estimating equation (GEE) model of CTh also controlling for age, gender, eye (OD/OS), and fundus region. Three regions of the fundus were defined for localization analysis (nasal, subfoveal, and temporal). The nasal region was defined to include the 4 nasal-most of the 11 points and thus included 20 distinct points. The temporal region was defined similarly. The foveal region included the remaining 3 points and thus included 15 distinct points.

Statistical Analysis

Statistical analyses were performed with SAS 9.3 (SAS Institute, Cary, NC, USA), Excel 2007 software (Microsoft, Inc., Redmond, WA, USA), and SPSS 22.0 (IBM Corp., Armonk, NY, USA). For all tests, a P value less than 0.05 was considered statistically significant. Student's t-test and chi-square test were used for the descriptive analysis. Because each eye

had 55 distinct CTh measurement points, we considered each eye as a cluster and modeled the difference between CTh in RMD+ and RMD– groups assuming an exchangeable correlation structure using a GEE. Age, gender, eye (OD/OS), and region were controlled in the model. For the stratification analysis, we stratified all points by subjects' median age (≤ 82 years or >82 years) and their region (nasal, subfoveal, or temporal) in order to get subgroup specific CTh difference estimates. The SAS GENMOD procedure was used to perform all analyses and produced clustered robust standard errors that corrected for within-subject correlation and mis-specification of exchangeable correlation structure [22].

RESULTS

Subject Demographics

A total of 18 RMD+ eyes from 16 subjects (14 female [87.50%]; mean age 83.9 years, range 65-94 years) were included for analysis. A total of 33 RMD– eyes from 26 subjects (14 female [53.85%]; mean age 79.1 years, range 61-96 years) were included as the control group. Patient demographics are summarized in **Table 1**. Using student's t-test and Fisher's exact test, the two groups had a statistically significant difference in age, gender, and CTh.

Comparisons by Age Groups and Fundus Regions

GEE model analysis found that the mean choroidal thickness was not significantly reduced in the RMD+ group overall, as compared to the RMD– group (mean difference $-16.84 \mu\text{m}$, $P=0.24$). Similarly, there was no difference in CTh in any of the fundus regions (nasal, subfoveal, or temporal) between RMD+ and RMD– eyes. However, after we stratified all subjects by the median age (82 years), choroids in the younger age group (≤ 82 years) were significantly thinner in eyes with RMD compared to those without (mean difference $-53.72 \mu\text{m}$, $P=0.01$). (See **Table 2**.)

We further investigated how age affected this relationship by determining the yearly change in CTh within the age groups. Though subgroup analysis did not yield statistically significant results, trends suggest that RMD+ choroids became thinner with each additional year of age in the ≤ 82 years age group (7 eyes; $-1.61 \mu\text{m}$ per year, $p=0.67$) and became thicker with each additional year of age in the >82 years age group (11 eyes; $+4.37 \mu\text{m}$ per year, $p=0.33$). In RMD– eyes, the choroid became thinner with each additional year of age in the ≤ 82 years age group (21 eyes; $-2.72 \mu\text{m}$ per year, $p=0.79$) and in the >82 years age group (12 eyes; $-0.33 \mu\text{m}$ per year, $p=0.39$), though again these results are not statistically significant.

Finally, when analyzing the combined sample of RMD+ and RMD– eyes, CTh decreases $-2.63 \mu\text{m}$ per year ($P=0.01$). Similarly, in RMD– subjects, CTh decreases $-2.75 \mu\text{m}$ per year ($P=0.03$) (See **Table 3**).

DISCUSSION

The present study examined CTh in eyes with early AMD, with and without SDD. SDD is a risk factor for progression to late AMD [23]. As our group described in a recent review, SDD may be considered one component of reticular macular disease (RMD) is a phenotype

of AMD with SDD in the subretinal space, often accompanied by alterations in the choroid. Together, these findings are known as the two compartment hypothesis of RMD [24]. With the present work, we aimed to further elucidate the differences in choroidal thickness between subjects with and without SDD in early AMD.

There were significant differences found in the baseline demographics between the RMD+ (with SDD) and RMD- (control) groups. The RMD+ group was older and composed of more females when compared to the RMD- control group. Previous studies of patients with SDD have found similar gender disparity [5, 8, 19, 23, 25], and older ages [26].

Margolis et al., in a pilot study using EDI-OCT, found that foveal CTh decreased over time in normal eyes [15]. In eyes with AMD, a study utilizing light microscopic computer-aided morphometric analysis found no changes in CTh with age [27]. In our study, age had an important impact on the thickness of the choroid in early AMD subjects, both in RMD+ eyes and in RMD- controls. Utilizing a GEE model, which controlled for intra-class correlation within the 55-point grid cluster, all subjects together demonstrated decreased CTh with each additional year of age ($-2.63 \mu\text{m}/\text{yr}$, $P=0.01$).

Using a t-test, mean CTh was significantly thinner in RMD+ eyes, but this result was no longer significant in the GEE model. In order to investigate further the influence of age on CTh, we dichotomized the groups by the median age of all subjects, 82 years. Among subjects ≥ 82 years old, eyes with RMD had significantly thinner choroids than control eyes without RMD (mean difference $-53.72 \mu\text{m}$, $P=0.01$), suggesting that the effects of RMD on CTh occur earlier in the AMD process. There was no difference in CTh in the older group, suggesting that the choroids of RMD+ eyes thickened to match those of RMD- controls. Indeed, CTh correlated *positively* with age in the >82 years RMD+ group, whereas in the other three groups, CTh correlated negatively with age (non-statistically significant results). To illustrate this, in **Fig 2** we present EDI SD-OCT images from two subjects with RMD: the first from the ≥ 82 years age group, with thin choroid, and the second from the >82 years age group, with thick choroid. Further, **Fig 3** shows CTh measurements vs. Age, for RMD+ and RMD- subjects. Another goal of our study was to compare choroidal thickness in nasal, subfoveal, and temporal regions; we found no difference in CTh between RMD+ and RMD- eyes, in any of the three regions.

Our results support the two-compartment theory of RMD, in which patients with SDD also have choroidal alterations, and expands our knowledge of the temporal nature of these changes. The pathophysiology of RMD is still unclear, possibly vascular, either preceded or followed by SDD. Querques and colleagues showed loss of choroidal vessels in subjects with RMD and speculated that fibrosis of the choroidal stroma contributed to the reticular pattern seen on fundus imaging and that RMD pathology begins with diffuse loss of small choroidal vessels and diffuse choroidal thinning, later followed by fibrotic replacement and thus a slight thickening, [14] consistent with our findings.

Our study has several limitations, such as the absence of choroidal thickness measurements beyond 2mm superior and inferior in the macula. However, our fundus grid included 55 points 5mm along the nasal-temporal axis, providing multiple measurements in the nasal,

foveal, and temporal zones. Additionally, the series presented here is relatively small, and included both eyes from the same subject if images were available, which could potentially have led to biased results. On the other hand, this study has several strengths. First, our statistical model accounted for 55 discrete CTh measurement points per eye, a total of 2,805 separate measurements, while fully adjusting for the intra-class correlation within subjects. Additionally, we utilized EDI SD-OCT, an advanced imaging technique with good visualization of the choroidal boundaries.

In conclusion, data from this study confirm earlier work that showed choroidal thinning in patients with SDD, the basis for the two-compartment phenotype of RMD. We have also notably shown significantly thinned choroids in patients with RMD compared to controls without RMD 82 years old, but no significant difference in CTh between study groups >82 years old. This is potentially new information compared to the general finding in the literature that RMD+ eyes overall have thinner choroids than RMD– eyes. In future work, we will investigate the hypothesis that RMD+ choroids initially thin and subsequently thicken, perhaps due to fibrotic changes as the disease progresses.

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Figure 1. 55-point grid and choroidal thickness (CTh) measurements

A: Shown is the 55 point grid, defined by 5 horizontal B scans (1 mm apart) with 11 points per scan (475 μ m apart). CTh measurements were made at each of these points. SDD lesions are outlined by a black crescent. **B:** CTh measurements were obtained from the outer border of the RPE/Bruch's membrane complex to the inner scleral border (red lines); the yellow line shows an example measurement. White arrows point to SDD lesions.

Figure 2. Choroidal thickness changes in subjects with RMD

A: Shown is an example of a younger subject (80 years old) with thin choroid (135 μm subfoveal CTh). **B:** Shown is an example of an older subject (94 years old) with thicker choroid (235 μm subfoveal CTh) than the younger subject. Note the greater proportion of reflective areas (choroidal stroma and/or fibrosis) in this image relative to the lucent areas (vasculature), compared to that in the choroid in the younger subject (top). White arrows point to SDD lesions.

Figure 3. Choroidal thickness (CTh) changes with Age

Scatter plots of Choroidal Thickness (μm) vs. Age (years) in RMD+ (A) and RMD– (B) eyes. Each vertical bar represents one or more eyes at a particular age, with circles representing individual choroidal thickness measurements. Note extended y-axis scale in (B) for thicker choroids overall in RMD– eyes. However, CTh was significantly greater *only* in RMD– eyes ≤ 82 years of age (see Results).

Table 1

Demographics of the Study Subjects; Comparison Using Student's T-Test and Fisher's Exact Test

	RMD+[*]	RMD–	P Value
Number of Eyes/Patients	18/16	33/26	--
Mean Age (Years)	83.9 ± 7.9	79.1 ± 7.9	0.05
Gender (% Female)	87.50%	53.85%	0.01
Mean Choroidal Thickness (μm)	149.47 ± 23.00	161.64 ± 20.22	<0.001

^{*} RMD+ is a phenotype of age-related macular degeneration, which features SDD and choroidal pathology.

Table 2

Choroidal Thickness (CTh) Comparisons by Fundus Region and Subject Age

RMD+ vs. RMD–	CTh Difference (μm) *	95% CI		P Value
All Subjects	–16.84	11.53	–45.20	0.24
Fundus Region				
Nasal	–15.72	12.16	–43.60	0.27
Subfoveal	–26.41	6.38	–59.21	0.11
Temporal	–10.89	20.43	–42.21	0.50
Age				
Age 82 Years	–53.72	–11.83	–95.60	0.01
Age>82 Years	–3.32	32.04	–38.68	0.85

* Assuming an exchangeable correlation structure using a generalized estimating equation.

Table 3

Choroidal Thickness (CTh) Change Trends Within Different Age Groups

	Mean CTh change with each additional year of age (μm) *	95% CI		P Value
All Ages				
All subjects	−2.63	−4.69	−0.57	0.01
RMD+	−2.71	−5.97	0.56	0.10
RMD−	−2.75	−5.17	−0.32	0.03

^{*} Assuming an exchangeable correlation structure using a generalized estimating equation.