Association between Decreased Renal Function and Reticular Macular Disease in Age-Related Macular Degeneration

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Purpose: To compare renal function in patients with age-related macular degeneration (AMD) with and without concurrent reticular macular disease (RMD).

Design: Retrospective cohort study.

Participants: Patients with documented AMD with and without RMD.

Methods: Via our electronic health record system, we retrospectively identified patients assigned an International Classification of Diseases, Ninth Edition, code associated with AMD between January 2012 and January 2016. Patients met inclusion criteria if they had at least 1 macular spectral-domain optical coherence tomography volume scan, 1 provider note, and 1 glomerular filtration rate (GFR) value in the electronic medical record. We evaluated images for the presence or absence of RMD; we defined RMD as the presence of at least 1 subretinal drusenoid deposit in at least 1 macular slice. Patients with RMD in at least 1 eye were deemed RMD positive. Patients with bilateral choroidal neovascularization were excluded from analysis.

Main Outcome Measure: Observation of renal function in RMD patients.

Results: Inclusion criteria were met by 119 patients (mean age, 75 years; range, 46−101 years). To account for the significant difference in RMD prevalence at extreme ages, we limited our study population to 107 patients 50 to 90 years of age. A GFR less than 60 ml/min/1.73 m^2 was found in 45.0% (27/60) of those with RMD compared with 12.8% (6/47) of those without RMD (odds ratio, 5.6; 95% confidence interval, 2.1−15). Multivariate logistic regression indicated that low GFR was a significant predictor for RMD, even after accounting for differences in age, diabetes, hypertension, hyperlipidemia, and other potential confounders. When comparing within classification subsets for RMD and GFR in patients with choroidal thickness data, significant choroidal thinning was associated with RMD (170 vs. 228 μm; $P = 0.01$) and GFR less than 60 ml/min/1.73 m^2 (144 vs. 219 μm; $P = 0.0008$).

Conclusions: Our analysis showed an association between RMD and renal dysfunction. Larger cross-sectional and longitudinal studies of the association of RMD with kidney function are warranted to better understand the nature and biological basis of this observed connection. *Ophthalmology Retina 2017;1:42-48 © 2016 by the American Academy of Ophthalmology*

Reticular pseudodrusen (RPD) have continued to be categorized and described since first being identified by their characteristic appearance in 1990.[1] The term *reticular macular disease* (RMD) has been suggested as a unifying term for a larger disease process presenting on multiple imaging methods with reticular lesions and including evidence of choroidal dysfunction.[2] These lesions, now recognized as subretinal drusenoid deposits (SDDs), were found to be located above the retinal pigment epithelium (RPE) and to contain refractile material.[3] More recent literature suggests that choroidal thinning, which is commonly associated with SDDs,[4,5] may be a second important feature of RMD.[6] Spectral-domain optical coherence tomography (SD OCT) has been used to describe 4 stages of SDD: stage 1, diffuse depositions of granular hyperreflective material above the RPE and below the ellipsoid zone; stage 2, increased accumulation of material causing an elevation to the ellipsoid zone; stage 3, penetration of the ellipsoid zone by the material; and stage 4,

fading of the material secondary to documented migration into the retinal layers.[3,7]

The prevalence of SDD varies by imaging technique. In the Beaver Dam Eye Study, a population-based epidemiologic study, SDD prevalence, as measured by color fundus photography, was 0.7% (0.1% in ages 43−54 years and 2.4% in ages 75−86 years).[8] A recent study found SDD prevalence, as measured by multimodal optic nerve and macular SD OCT, to be 23% in healthy participants 60 years of age and older and 49% and 79% in those with early and intermediate age-related macular degeneration (AMD), respectively.[9] Previous studies have demonstrated an SDD prevalence of 9.0% to 37.5% in AMD, depending on the severity of disease and imaging method.[10−12] Known risk factors for the development of SDD in the Beaver Dam Eye Study were older age, female gender, smoking, diabetes, and high body mass index.[8]

The Curcio model of the RPE as a bidirectional secretor of lipids explains both SDD and ordinary drusen.[13] However, the mechanism of this apparent RPE

dysfunction remains poorly understood, with one hypothesis tying it to choroidal pathologic features.[14] The connection between RPD on color fundus photography and a much higher rate of choroidal neovascularization was first observed by Arnold et al.[10] They also histopathologically examined an eye with RPD and found choroidal vascular abnormalities, leading to the theory that poor choroidal perfusion in eyes with RPD causes increased incidence of choroidal neovascularization. Further support for this theory includes the association of SDDs with multilobular geographic atrophy,[15] their positioning at the choroidal watershed zones,[4] and their association with choroidal thinning.[5,16,17] The choroidal vascular system is an end-arterial system consisting of lobules with watershed zones, similar to the kidney.[18] Thus, decreased renal function, which is most commonly caused by perfusion dysfunction, may share a similar systemic pathophysiology with SDD, with both diseases caused by impaired systemic perfusion.

No studies to date have examined the possible link between RPD and renal function. However, a limited number of investigations have examined the link between AMD and renal dysfunction. One population-based study found a 3.2-fold increased risk of AMD if the glomerular filtration rate (GFR) was abnormal (<60 ml/min/1.73 m^2) compared with normal (≥ 60 ml/min/1.73 m^2).[19] The authors attributed this effect to shared risk factors of the 2 diseases, including smoking and hypertension,[8,20,21] atherosclerosis,[22] oxidative stress,[21,23] systemic inflammation,[24,25] common susceptibility genes,[26–32] and microvascular disease.[29] The purpose of this investigation was to describe the relationship between RMD and renal function, as evaluated through GFR, in an AMD population.

Methods

Participants

We obtained institutional review board approval, including a waiver of consent. We collected data in a Health Insurance Portability and Accountability Act–compliant fashion, and all research methods adhered to the tenets of the Declaration of Helsinki. We identified patients from a single large city hospital who were assigned an International Classification of Diseases, Ninth Edition, code associated with AMD (362.50, 362.52, 362.51, and 362.57) between January 2012 and January 2016. The date range chosen corresponds to the length of time for which SD OCT has been available at our institution. We examined the database of our institution's ophthalmic imaging center for those patients diagnosed with AMD to determine whether there was at least 1 high-quality macular SD OCT volume scan. Among patients with imaging, we then selected only those with at least 1 provider note and at least 1 GFR value in the laboratory section of the electronic medical record. We excluded patients with bilateral choroidal neovascularization.

Image Analysis

All SD OCT images were obtained using a single Heidelberg Spectralis HRA+OCT (Heidelberg Engineering, Inc., Vista, CA) with eye-tracking capability. Volume scans consisted of 16 horizontal lines, with an average of 9 B-scans per line, in a $15° \times 20°$ rectangular pattern. In cases where imaging had been performed more than once, we selected the most recent SD OCT image set. Evaluation of SD OCT images for presence or absence of SDDs was performed by 1 trained reader (H.B.L.) who was blinded to the patient's medical record at the time of image reading. A second reader (R.T.S.) was called on for deliberation if SDD presence was questionable. We defined SDD as hyperreflective deposits above the RPE on SD OCT, limited to previously described stages 2 and 3.[3,7] We categorized an eye as RMD positive if we observed 1 SDD or more on at least 1 retinal slice; we categorized a patient as RMD positive if RMD was present in one or both eyes.

Images were analyzed for subfoveal choroidal thickness (CTh; Fig 1). One reader (M.A.) performed measurements using the ruler tool on the Heidelberg Eye Explorer software. We defined CTh as the distance between the hyperreflective line of Bruch's membrane and the hyperreflective line of the inner surface of the sclera. In cases in which the posterior border of the choroid was not identifiable on SD OCT, measurements were omitted.

Chart and Glomerular Filtration Rate Analysis

We extracted patient demographics and medical data from the electronic medical record of eligible patients. Laboratory-determined GFR values were recorded first as dichotomous variables (<60 vs. ≥ 60 ml/min/1.73 m^2). In cases where more than 1 GFR or creatinine value was available, we used the most recent value. Additionally, we used serum creatinine to calculate 2 continuous-variable GFRs to ensure accuracy through the creatinine-based Modification of Diet in Renal Disease (MDRD) Study equation[33] and the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration equation[34]:

MDRD Study:

$$175 \times \text{serum creatinine}^{1.154} \times \text{age}^{0.203} \times (1.212 \text{ if black}) \times (0.742 \text{ if female});$$

CKD-EPI Collaboration:

$$141 \times \min(Scr/\kappa, 1)\alpha \times \max(Scr/\kappa, 1) - 1.209 \times 0.993$$
$$\text{Age} \times 1.018 \text{ (if female)} \times 1.159 \text{ (if black)},$$

where *Scr* is the serum creatinine value (in milligrams per deciliter), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of *Scr*/κ or 1, and max indicates the maximum of *Scr*/κ or 1. For any analysis requiring a dichotomous variable, laboratory-determined GFR values were used, but for more advance statistical analysis requiring continuous variables, Modification of Diet in Renal Disease Study–calculated GFR was used.

Through the chart review feature of our institution's electronic medical record, we obtained patient information from chart sections such as demographics, diagnoses, medical history, provider notes, and laboratory findings. The search feature allowed rapid identification of the most recent values for findings such as body mass index, erythrocyte sedimentation rate, basic metabolic panel/comprehensive metabolic panel, and lipid panel. We determined hypertension, diabetes mellitus, and hyperlipidemia status through review of diagnoses, medications, abnormal vital signs, and laboratory findings. We determined the presence of coronary artery disease based on an abnormal stress test, stent, myocardial infarction, coronary bypass, congestive heart failure, angina (stable, unstable), or pacemaker.

Statistical Methods

We used Microsoft Excel 2010 (Microsoft Corp., Redmond, WA) to manage data and SAS software version 9.3 (SAS Institute, Cary, NC) for statistical analyses. We compared characteristics of participants with and without RMD using the nonparametric