• Clinical Research •

Gender as an effect modifier in the relationship between hypertension and reticular pseudodrusen in patients with early or intermediate age-related macular degeneration

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Abstract

● **AIM:** To determine whether the prevalence of treated hypertension is higher among males or females with early/intermediate (e/i) age-related macular degeneration (AMD) with and without bilateral reticular pseudodrusen (RPD).

● **METHODS:** Retrospective review of the records of patients with e/iAMD who were recruited into the University of Colorado AMD registry between July 2014 and November 2019. Images were classified using the Beckman Initiative criteria and presence/absence of RPD. Patients were categorized into three groups: 1) e/iAMD with RPD; 2) e/iAMD without RPD; 3) control patients who did not have AMD. Multinomial logistic regression analysis was used for adjusted analysis with odds ratios (OR) and confidence intervals (CI).

● **RESULTS:** There were 260 patients with e/iAMD of which 101 had bilateral RPD and 159 had no RPD, and 221 controls. Overall, 62% of patients were female and the three groups did not differ by gender. When stratified by gender, the female e/iAMD/RPD group had a higher prevalence of hypertension, 64.1% *vs* 45.2% for controls, OR=2.2 (95%CI: 1.2-4.0). The frequency of hypertension in the e/iAMD/no RPD group was 54.1% and did not significantly differ from the control group. Among males, prevalence rates of treated hypertension did not differ. There is a significant interaction of hypertension and gender for the e/iAMD/RPD group such that women with e/iAMD who had RPD were significantly more likely to have hypertension (*P*=0.042). This relationship was not significant in the e/iAMD/no RPD group (*P*=0.269).

● **CONCLUSION:** Among females treated hypertension is significantly higher among e/iAMD/RPD patients, whereas for males there is no significant association.

● **KEYWORDS:** reticular pseudodrusen; hypertension; gender; intermediate age-related macular degeneration

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INTRODUCTION

Age-related macular degeneration (AMD) is a chronic progressive disease of the macula that represents one of the leading causes of vision loss in patients over the age of 50 across the world[1]. Advanced AMD often results in severe, irreversible central vision loss from geographic atrophy (GA) or choroidal neovascularization (CNV)[2]. The hallmark clinical feature of AMD is the presence of drusen: yellowish, circular lesions in the posterior pole that represent accumulation of extracellular material between retinal pigment epithelium (RPE) and the inner collagenous layer of Bruch's membrane (BM)[2]. Recently, attention has been drawn to the presence of reticular pseudodrusen (RPD) in patients with AMD[3]. RPD were first described by Mimoun *et al*[4] in 1990 as "pseudodrusen visible en lumière bleue" referring to distinct lesions around 100 μm in size that stained on fluorescein angiography (FA) and were better visualized using blue light. In contrast to typical drusen, RPD represent collections of hyperreflective material located above the RPE in the subretinal space[3]. As described elsewhere[3], RPD have distinctive features on multimodal imaging modalities which has allowed for more research into the clinical significance of these lesions.

The clinical importance of RPD is still being explored, with investigators reporting a relationship between RPD and

progression to advanced forms of AMD (GA and CNV)[5]. A relationship between various other non-ocular factors and RPD has also been described including older age, female sex, current smoking, high body mass index (BMI), and less education[5-6]. It has been proposed that the unique appearance of RPD on multimodal imaging could suggest a vascular origin possibly related to choroidal dysregulation[7]. Moreover, several authors have reported that the presence of RPD is associated with systemic hypertension[8]. Indeed, in a study from our group, we found the presence of RPD was significantly associated with hypertension among patients with intermediate AMD (iAMD)[9]. However, other investigators have failed to demonstrate this relationship between RPD and vascular disease[10]. It has been shown that AMD and cardiovascular disease (CVD) share several risk factors, but more research is needed to establish these relationships[11]. One of the risk factors for CVD and cerebrovascular disease is hypertension, a complex, multi-organ disease[12]. Control of hypertension significantly reduces the risk of developing these conditions[13]. It is also accepted that there are gender differences with regard to many of the clinical manifestations and outcomes in patients with CVD[14]. Building on this research, the primary aim of this present study was to investigate the relationship between hypertension and RPD. The secondary objective of this study was to assess these relationships stratified by gender. To address these objectives, we conducted a study in patients with the early or intermediate phenotype AMD.

SUBJECTS AND METHODS

Ethical Approval The registry is approved by the Colorado Multiple Institutional Review Board and conducted in accordance with the Declaration of Helsinki. Informed written consent is obtained from all study subjects. The registry is composed of patients with AMD as well as patients with recent cataract surgery but no AMD who serve as controls. All patients who receive care at the UC Health Sue Anschutz-Rodgers Eye Center and qualify for the study are invited to be part of the registry. Recruitment into the registry is ongoing.

The University of Colorado AMD Registry This study was conducted using records from an AMD research registry developed by the Department of Ophthalmology at the University of Colorado School of Medicine, described in detail elsewhere[9,15].

Recruitment and Exclusion/Inclusion Criteria Each case and control is consented for the following: 1) review of pertinent medical history, 2) capture and review of the following images: color fundus photo, fundus autofluorescence (FAF), near-infrared fundus reflectance (NIR), and spectral domain optical coherence tomography (SD-OCT). Ocular exclusion criteria for the registry include: panretinal photocoagulation or anti-VEGF injections for diabetic retinopathy, branch and central retinal vein occlusion (with severe macular damage), any active ocular inflammatory disease, or a severe decrease in visual acuity secondary to a preexisting severe retinal disease other than AMD. For this study we restricted our analytic dataset to participants with early AMD or intermediate AMD (e/iAMD) and controls with no AMD[2]. Individuals with unilateral RPD were excluded from the study.

Image Review All images are reviewed by two vitreoretinal specialists. Images are categorized into early, intermediate or advanced AMD using the classification described by Beckman initiative criteria[2]. The presence or absence of RPD is also determined using guidelines established by other authors[3]. Our definition of the presence of RPD is an interlacing network of subretinal drusenoid deposits seen on FAF and/or NIR imaging and confirmed on SD-OCT. Discrepancies following the initial image review are resolved by a third vitreoretinal specialist.

Risk Factors Hypertension was the main exposure for our study. Hypertension was defined as a prior diagnosis of elevated blood pressure for which the patient was taking at least one antihypertensive medication. This was determined after interview with the patient at the time of recruitment into the registry and followed by review of the medical record to confirm the self-reported diagnosis. All cases and controls were classified as either hypertensive or not hypertensive. Other risk factors included in the analysis were: gender, race/ethnicity, family history of AMD, age, BMI, smoking status, type 2 diabetes mellitus, kidney disease, stroke, peripheral vascular disease, atrial fibrillation, and cardiac disease.

Statistical Analysis For the analysis the cohort was divided into 3 groups: 1) eAMD or iAMD without RPD (e/iAMD/no RPD), 2) eAMD or iAMD with bilateral RPD (e/iAMD/RPD), 3) controls with no evidence of AMD.

The relationship between our main exposure and potential risk factors was examined between case groups and controls using the Chi-square or Fisher's exact test for categorical variables and the *t*-test or Wilcoxon rank sum test for differences between continuous variables. Multinomial logistic regression analysis was conducted to determine the odds ratio of hypertension for the two case groups stratified by gender. Variables that were significant in univariate analysis for either of the two AMD case groups compared to controls were included as confounders in the multivariate model. All analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

As shown in Table 1, there were 260 patients with e/iAMD of which 101 had bilateral RPD and 159 had no RPD. The number of control patients without AMD was 221. The e/iAMD/RPD and e/iAMD/no RPD groups were both older than the

Table 1 Characteristics of AMD patients with and without RPD compared to controls

Parameters	Controls	Early and intermediate AMD cases			
		Bilateral RPD		No RPD	
		n (%)	*P*	*n* (%)	*P*
Number of patients	221	101	-	159	-
Gender			0.696		0.914
Male	86 (38.9)	37 (36.6)		61 (38.4)	
Female	135 (61.1)	64 (63.4)		98 (61.6)	
Race/ethnicity			0.162		0.003
White	187 (84.6)	95 (94.1)		153 (96.2)	
African-American	14 (6.3)	3 (3.0)		0	
Hispanic	11 (5.0)	2 (2.0)		2 (1.3)	
Asian	3 (1.4)	1 (1.0)		2 (1.3)	
Other	6 (2.7)	0		2 (1.3)	
Family history of AMD			<0.0001		0.0006
None	168 (76.0)	46 (45.5)		92 (57.9)	
Yes	41 (18.6)	41 (40.6)		47 (29.6)	
Uncertain	12 (5.4)	14 (13.9)		20 (12.6)	
Age, mean (SD)	72.6 (5.8)	77.4 (7.3)	<0.0001	75.4 (7.0)	<0.0001
Body mass index, *n*	216	97		148	
Mean (SD)	27.4 (5.6)	26.7 (4.7)	0.340	26.3 (5.4)	0.069
Smoking			0.080		0.738
Never	119 (53.8)	42 (41.6)		84 (52.8)	
Current	5 (2.3)	5 (5.0)		2 (1.3)	
Former	97 (43.9)	54 (53.5)		73 (45.9)	

AMD: Age-related macular degeneration; RPD: Reticular pseudodrusen.

Table 2 History of comorbidities among AMD patients with and without RPD compared to controls

Parameters	Controls *n* (%)	Early and intermediate AMD cases			
		Bilateral RPD		No RPD	
		n (%)	*P*	*n* (%)	*P*
Type 2 diabetes	28 (12.7)	14 (13.9)	0.768	19 (12.0)	0.833
Hypertension	109 (49.3)	56 (55.4)	0.308	83 (52.2)	0.580
Kidney disease	25 (11.3)	16 (15.8)	0.258	17 (10.7)	0.849
Stroke	3 (1.4)	4 (4.0)	0.133	10 (6.3)	0.009
Peripheral vascular disease	29 (13.1)	13 (12.9)	0.950	24 (15.1)	0.584
Atrial fibrillation	20 (9.0)	10 (9.9)	0.807	18 (11.3)	0.454
Cardiac disease	64 (29.0)	35 (34.6)	0.304	50 (31.4)	0.602

AMD: Age-related macular degeneration; RPD: Reticular pseudodrusen.

controls: 77.4y for e/iAMD/RPD and 75.4y for e/iAMD/no RPD *vs* 72.6y for controls (*P*<0.0001 for both). Overall, 62% of patients were female and the three groups did not differ by gender. Race and a family history of AMD were other factors that were significantly different between the groups.

As displayed in Table 2, hypertension was not significantly different across the three groups. Diabetes, kidney disease, peripheral vascular disease, atrial fibrillation, and cardiac disease were also similar between the three groups. Stroke was the only comorbidity found to be significantly more prevalent in the e/iAMD/no RPD group as compared to the control group, however numbers of patients with a history of stroke were small for all three groups.

We show in Table 3 the results of our analysis stratified by gender. As demonstrated, when stratified by gender, the female e/iAMD/RPD group had a significantly higher prevalence of hypertension, 64.1% *vs* 45.2% for controls (OR=2.2, 95%CI: 1.2-4.0, *P*=0.013). The e/iAMD/no RPD female group also had higher prevalence of hypertension (54.1%), but this difference did not reach statistical significance when compared to controls (OR=1.4, 95%CI: 0.8-2.4, *P*=0.18; Table 3). Among males, prevalence rates of hypertension did not differ for either e/iAMD group compared to controls.

The results of the multinomial logistic regression analysis with the interaction term of gender and hypertension are shown in Table 4. In this analysis we adjusted for age, white race, family history of AMD, and BMI as confounders and examined the interaction of hypertension and gender. We found a significant interaction of hypertension and gender for the e/iAMD/RPD group compared to controls (*P*=0.042) such that women with

Table 3 Prevalence of hypertension stratified by gender

Parameters	Controls *n* (%)	Early and intermediate AMD cases			
		Bilateral RPD		No RPD	
		n (%)	Odds ratio (95%CI), *P*	*n* (%)	Odds ratio (95%CI), *P*
Males, patients	86	37	-	61	-
Hypertension	48 (55.8)	15 (40.5)	0.5 (0.2-1.2), 0.120	30 (49.2)	0.8 (0.4-1.5), 0.427
Females, patients	135	64	-	98	-
Hypertension	61 (45.2)	41 (64.1)	2.2 (1.2-4.0), 0.013	53 (54.1)	1.4 (0.8-2.4), 0.180

AMD: Age-related macular degeneration; RPD: Reticular pseudodrusen.

Table 4 Multinomial Logistic regression of hypertension as a risk factor for AMD groups versus controls

Parameters	e/iAMD cases with RPD *vs* controls, *P*	e/iAMD cases with no RPD *vs* controls, *P*
Gender	0.511	0.506
Hypertension	0.069	0.439
Interaction of gender and hypertension	0.042	0.269

Adjusted for age, white race, family history of AMD and BMI.

e/iAMD who had RPD were significantly more likely to have hypertension. This relationship was not significant when compared to the e/iAMD/no RPD group (*P*=0.269).

DISCUSSION

In this study, among all patients with eAMD and iAMD, hypertension did not differ significantly in the study participants with and without RPD compared with control patients with no evidence of AMD. However, an important novel finding of our study was that when we stratified by gender, women with RPD and e/iAMD showed a significantly higher prevalence of hypertension when compared to controls. Females with e/iAMD but no RPD showed a higher prevalence of hypertension, but this relationship did not reach statistical significance. There were no significant differences in hypertension across the three groups among males. To our knowledge, the interaction of RPD, female gender, and hypertension has not been previously reported.

It is also well-recognized that CVD is the leading cause of death in women across the world with hypertension representing the most common modifiable risk factor[16]. Furthermore, hypertension is more common in women compared to men in elderly populations[13]. Several researchers have also shown that RPD is more common in females than males[6,8]. In fact, Klein *et al*[17] reported a 2.5-fold increase in the prevalence of RPD in women when compared to men. We did not find a difference in the present study.

The association between hypertension/vascular disease and RPD remains unclear. While several authors have reported a link between RPD and systemic hypertension[8], including a study from our group[9], McCarter *et al*[10] found no evidence to suggest a link between coronary heart disease and RPD. Conflicting results between studies could be explained by underlying study characteristics and differences in study methodologies, including not stratifying by gender, insufficient sample size, and the approach to imaging and classification of AMD phenotype. In our study we have demonstrated a significant link between RPD and treated hypertension among women. This finding adds further support to a possible vascular etiology for RPD which could be linked to choroidal dysfunction. Indeed, several authors have suggested that choroidal dysregulation specifically choroidal thinning could be responsible for RPD lesions[18]. Furthermore, Saito *et al*[19] reported an interesting case of preeclampsia in a 36-year-old pregnant woman with similar reticular appearing retinal lesions possibly due to vasospasm of the choroidal arteries.

There are several strengths to this study. The main strength is the precise classification of images based on multimodal imaging producing very accurate AMD phenotypes. We also stratified by gender in our analysis, to acknowledge the importance of gender-sensitive study approaches. We recognize some weaknesses including a relatively small sample size and a retrospective study design. The diagnosis of treated hypertension was self-reported but was confirmed by a careful review of the medical record for all study participants. The small sample size may have impacted our ability to determine significance in the role of RPD for men. However, notwithstanding some weaknesses, the results are novel. We suggest it will be important to validate the findings of our study with a larger sample size.

In conclusion, this study found that women with RPD and e/iAMD showed a significantly higher prevalence of hypertension when compared to control patients without AMD. We suggest that RPD may be a marker of underlying vascular risk in women with the early or intermediate forms of AMD.

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