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Is Renal Function associated with Early Age-Related Macular Degeneration?

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Abstract

Purpose—Age-related macular degeneration (AMD) and chronic kidney disease both involve immune dysregulation and may share underlying pathophysiologic changes to systemic homeostasis. Hence we aim to evaluate associations between impaired kidney function and early AMD, in a search for urinary biomarkers for AMD.

Methods—A population-based, cross-sectional analysis of persons aged 45–84 years was conducted with renal function measured using serum creatinine and cystatin C levels and the estimated glomerular filtration rate (eGFR) calculated. AMD status was ascertained from retinal photographs.

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Competing interests: None exist.

Results—Of 5,874 participants, 221 had early AMD. High serum cystatin C and low eGFR ($< 60\text{ml/min/1.73m}^2$) were not associated with early AMD in our multivariate analyses. Among normotensive persons, however, highest versus other deciles of cystatin C were associated with an increased prevalence of early AMD (odds ratio 1.80, 95% confidence interval 1.00-3.23).

Conclusions—Results could not confirm an association between kidney function and early AMD. The borderline association between cystatin C and early AMD in normotensives require further verification.

Keywords

age-related macular degeneration; kidney; renal function

Age-related macular degeneration (AMD) is a common degenerative retinal disease and is the leading cause of vision loss in the developed world.¹⁻³ Recently, there has been some evidence that persons with chronic kidney disease (CKD) may be more likely to develop AMD,^{4, 5} sparking renewed interest in the potential association between kidney disease and AMD. In the 1980s, reports of an association between a rare kidney disease, type 2 membranoproliferative glomerulonephritis (MPGN-II), and AMD first emerged;^{6, 7} where patients with MPGN-II were observed to develop drusen (yellow deposits in the retina), indistinguishable from that seen in early AMD, and choroidal neovascular disease, characteristic of late or end-stage AMD. Recent studies have shown that the complement factor H gene (CFH) is associated with both diseases.⁸⁻¹² CFH encodes a protein involved in regulating the alternative complement pathway, and dysfunction results in uncontrolled complement activation and inflammation, possibly leading to end organ tissue damage in people with MPGN-II, to both the renal glomerular basement membrane and Bruch's membrane of the retina.⁹ While evidence for the role of rare CFH variants in rare renal disease is strong, a recent study has suggested that more common CFH variants also affects general renal function and increases the risk of AMD.¹³ If similar disease processes are occurring in AMD then one could hypothesize that abnormal complement activation affecting drusen deposition in AMD might be occurring concurrently in the glomerular basement membrane, resulting in abnormal renal function, albeit clinically subtle but potentially important as a biomarker of disease with implications for AMD management.^{10, 14}

To date, a few studies have examined renal function based on creatinine derived equations and AMD,^{4, 5, 15, 16} however only one study has evaluated serum cystatin C and AMD.⁵ These studies however do not specifically select for persons without cardiovascular disease, which is a risk factor for chronic kidney failure¹⁷. Serum cystatin C has also been shown to be a more sensitive measurement of renal function.¹⁸ Hence we aim to evaluate the cross-sectional association between renal function, through the use of serum cystatin C, and early AMD in a large, multi-ethnic population-based study, without clinical cardiovascular disease.

Materials and Methods

Study Population

We used data from the Multi-Ethnic Study of Atherosclerosis (MESA) study of persons aged 45-84 years without clinical cardiovascular disease, to examine the association between impaired kidney function and AMD. The institutional review boards approved the study, which was conducted according to the tenets of declaration of Helsinki. Participants were selected by random sampling of households close to one of the six field centers. Details of the MESA methodology have been reported elsewhere.¹⁹

Assessment of Kidney Function

Kidney function was measured by creatinine and cystatin C from serum samples collected from 6,814 participants at baseline (2000-02).^{20, 21} Cystatin C is a more accurate measure of renal function compared to the estimated glomerular filtration rates (eGFR), especially amongst persons with normal or near normal glomerular filtration rates (GFR).²² It is an alternative marker of renal function less dependent on age, sex, diet, physical activity and lean body mass.^{18, 21} Cystatin C has received considerable attention as an alternative filtration marker with stronger and more linear risk relationships than creatinine.^{18, 23} Cystatin C is typically below 0.95 mg/L in young, healthy adults.²⁴ Kidney function measures were defined as follows: 1) eGFR, derived from serum creatinine-based modified (4 variable) Modification of Diet and Renal Disease formula (MDRD) (see equation below), was dichotomized at eGFR ≥ 60 ml/min/1.73m², consistent with stage 3 CKD;²⁵ 2) Cystatin C was modeled both in quartiles and also dichotomized at the highest decile for a more direct comparison to low eGFR.

MDRD formula:

$$\text{eGFR} = 186 \times (\text{Cr})^{-1.154} \times \text{age}^{-0.203} (\times 0.742 \text{ if female}) \times (1.212 \text{ if black})$$

where Cr = serum creatinine in mg/dl and age is expressed in years.²⁶

Assessment of AMD

6,176 participants had bilateral retinal photos taken using a 45° digital non-mydratic camera, at the second visit (2002-04). Photos were evaluated independently by two masked graders for signs of early AMD.^{27, 28} Early AMD was defined by either the presence of any soft drusen and pigmentary abnormalities, or reticular drusen in either eye, in the absence of signs of late end-stage AMD.²⁸ As there were very few cases of late AMD (n=27), we decided to evaluate the associations with early AMD only.

Measurement of Other Risk Factors

Serum lipids and inflammatory marker levels were derived from blood samples. Blood pressure, height and weight were measured at baseline (2000-02) according to MESA protocol;²⁷ with vitamin supplementation and alcohol consumption ascertained from

questionnaires. Diabetes status was ascertained from fasting plasma glucose levels where levels ≥ 7.0 mmol/l were confirmatory.²⁹

Statistical Analysis

We examined the association between renal function and early AMD (presence or absence) in logistic regression models adjusting for age, smoking, race and gender as the base model. Additional covariates such as diabetes, hypertension (Joint National Committee criteria, $\geq 140/90$), body mass index (World Health Organization categories³⁰), lipids, vitamin supplementation (yes/no), alcohol consumption (never, former, current) and inflammatory markers (C-reactive protein, interleukin 2, interleukin 6) were retained if they changed the β coefficients by more than 5%. We decided a priori to stratify our analysis by presence or absence of hypertension, as it is associated with both impaired renal function and AMD.^{31, 32}

To detect an odds ratio (OR) of AMD comparing the top to lowest quartile of cystatin C, a sample size of 6000 (1500 in each quartile) will provide 80% power (2 tailed) to detect OR of 1.7; assuming AMD event rate of between 3% and 5% between the lowest and the highest quartile.

Results

The prevalence of early AMD within MESA was 3.6% (221 early AMD). 5,874 retina photographs (95.1%) were gradable for AMD. Using the MDRD formula, it was estimated that 9.6% of the MESA cohort had CKD (eGFR ≤ 60 ml/min/1.73m²). Cystatin C levels (mg/l) ranged from 0.07 to 7.59, with a median value of 0.86 and a value of 1.13 and 1.64 at the 90th and the 99th percentile respectively. Participant demographics and potential risk factors are described in Table 1. Participants in the top cystatin C decile tended to be older, with a higher proportion with hypertension and diabetes. The distributions of sex, smoking habits, race, inflammatory markers, alcohol and supplement intakes, were similar for the two groups.

Table 2 evaluated associations across quartiles of serum cystatin C (lowest quartile as reference) with early AMD; although ORs were in the positive direction in participants without CKD (2nd and 3rd quartiles) and in participants with CKD (4th quartile), results were not statistically significant. No associations were observed between low eGFR, or the top decile of serum cystatin C with AMD (for a more direct comparison to low eGFR). The adjusted OR did not change when we adjusted for body mass index, lipids, vitamin supplementation, alcohol consumption and inflammatory markers (C-reactive protein, interleukin 2, interleukin 6).

In analyses stratifying by hypertensive status (Table 3), amongst normotensives, the top decile of cystatin C, as compared to the bottom nine deciles, was associated with a higher prevalence of early AMD (OR 1.80). No association was observed among persons with hypertension. Low eGFR was not associated with AMD, stratified by hypertension.

Discussion

Based upon evidence suggesting that AMD is a complement mediated disease with similarities to MPGN-II, where immune complexes are deposited in the kidney, and recent studies where CKD was associated with AMD,^{4, 5, 16} suggesting that impaired kidney function may share common pathways with AMD, we decided to evaluate if serum cystatin C, might potentially be a useful biomarker of AMD.

Results from our cross-sectional analysis, however, could not confirm an association between impaired renal function, as measured by cystatin C or creatinine, and the prevalence of early AMD, in this population without clinical cardiovascular disease. In contrast, in the Beaver Dam Eye Study (n=3,779), every log standard deviation (SD) increase in serum cystatin C was associated with incident early AMD [OR 1.16 (1.01-1.35)] and exudative AMD [OR 1.42 (1.03-1.96)]. Our result in per SD increment for cystatin C was OR 1.03 (0.87-1.21), not log-transformed. The Beaver Dam Eye Study also found moderate CKD i.e. eGFR_{MDRD} 45-59 compared to ≥ 60 mL/min/1.73 m² (13% of cohort), but not severe CKD <45 mL/min/1.73 m², associated with early incident AMD, [OR 1.36 (1.00-1.86)].⁵ Another Australian cohort study (n=1,183) found moderate CKD, creatinine-based eGFR_{Cockcroft-Gault} <60 mL/min/1.73 m² (24% of cohort), associated with an increased risk of incident early AMD (OR 3.2, 95% CI 1.8-5.7), adjusting for various risk factors including CFH polymorphism.⁴ Another Korean cross-sectional study similarly found CKD i.e. eGFR_{MDRD} ≥ 60 mL/min/1.73 m² (12% of cohort), associated with early AMD [OR, 1.68 (1.04–2.72)] in a multivariate analysis including adjustment for hypertension.¹⁶ However, a British clinic-based cross-sectional study did not find an association between eGFR_{MDRD} measures and AMD in a multivariate analysis including adjustment for hypertension, this study included only persons older than 75 and approximately 50% of the population had eGFR of <60 (n=2,880).¹⁵ All these studies had a higher prevalence of CKD compared to our study. As hypertension is associated with renal function and AMD,^{31, 32} we stratified by hypertension *a priori*, and found among normotensives, the top decile of cystatin C was associated with an increased prevalence of AMD. This association was not present among persons with hypertension.

Our study is the second to evaluate the association between cystatin C and AMD as a measure of general renal function in a population-based sample. Cystatin C is a non-glycosylated protein of 120 amino acid residues synthesized and secreted at a nearly constant rate by virtually all nucleated cells. Given its 13kDa size, cystatin C is freely filtered by the glomeruli. In contrast to creatinine, cystatin C is not excreted in urine but, rather is metabolized by the proximal tubule, hence an alternative marker of renal function less dependent on age, sex, diet and muscle mass²³ Additionally, serum cystatin C has also been shown to be an inhibitor of cysteine proteinases (cathepsins)³³ which have been hypothesized to be required in the homeostasis of the retinal photoreceptors and the extracellular environment of the Bruch membrane.^{5, 34, 35}

MESA comprises of a large multi-ethnic population, without clinical cardiovascular disease, with standardized protocols to measure CKD risk factors and AMD end points for accurate AMD phenotyping. Despite its strengths, a number of limitations need to be considered in

this cross-sectional analysis. First, there is no gold standard measurement of GFR and in evaluating renal function, both cystatin C and eGFR are indirect estimates of GFR; although cystatin C has been shown to be the better predictor of GFR.^{18, 22, 36, 37} We did not recalculate eGFR based on Cystatin C equations but used only serum cystatin C levels. Second, an association between the top decile of cystatin C and AMD was found only in stratified analysis. Without similar associations with low eGFR stratified by hypertension to support this, this may indicate internal inconsistencies and our findings could be due to chance. Additionally, our finding that the top decile of cystatin C was associated with early AMD only amongst normotensives was unexpected, as hypertension is a risk factor for CKD. This finding requires further verification in other studies. Third, AMD prevalence in the MESA cohort is lower than other epidemiological studies;³⁸ reasons may include a comparatively younger cohort (mean and median age of 62), or misclassification (underestimate of prevalence) attributable to the use of 45° color non-stereoscopic images taken through non-pharmacologically dilated pupils.³⁹ MESA also excluded persons with cardiovascular disease which may have lead to lower prevalence of AMD.⁴⁰ Fourth, in our post-hoc estimate, we had 83% power to detect the difference low vs. high eGFR with (OR 1.885) sample sizes of 5,340 and 515 respectively (0.05 two-sided significance level); and only 51% power to detect the difference between the highest vs. lowest quartile of cystatin (OR 1.5) based on sample sizes of 1,390 and 1,439 in these quartiles. Fifth, other unknown and unmeasured risk factors or residual confounding from imperfect adjustment of risk factors could have confounded results.

In summary, results from this large population-based study could not confirm an association between impaired renal function and early AMD. In normotensives, elevated cystatin C was associated with an increased prevalence of early AMD, a finding that should be verified in other studies. A biomarker for AMD risk, if found, would have important implications in directing treatment in this common devastating eye disease.

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Table 1

Demographics of participants in the Multi-Ethnic Study of Atherosclerosis study.

	Cystatin C	
	Top decile n = 711	Bottom nine deciles n = 6,103
Serum creatinine, mean mg/dl (SD)	1.3 (0.6)	0.9 (0.2)
Age, years (SD)	70.0 (9.5)	61.4 (10.0)
Female, n (%)	344 (48.6)	3,245 (53.3)
Race, n (%)		
Caucasian	326 (45.9)	2,298 (37.7)
Chinese-American	58 (8.2)	745 (12.2)
African-American	187 (26.3)	1,708 (28.0)
Hispanic	140 (19.7)	1,352 (22.2)
Cigarette smoking, n (%)		
Never	336 (47.6)	3,090 (50.9)
Former	266 (37.7)	2,198 (36.2)
Current	104 (14.7)	781 (12.9)
Body mass index, n (%)		
Normal	135 (19.0)	1,818 (29.8)
overweight	257 (36.2)	2,407 (39.4)
Obese	319 (44.9)	1878 (30.8)
Hypertension, n (%)	495 (69.6)	2,524 (41.4)
Diabetes, n (%)	141 (19.8)	796 (13.1)
Impaired fasting glucose, n (%)	82 (11.6)	480 (7.9)
Vitamin supplements, n (%)	402 (62.2)	3,364 (60.7)
Alcohol use, n (%)		
Never	162 (23.0)	1,228 (20.3)
Former	228 (32.3)	1,396 (23.0)
Current	315 (44.7)	3,434 (56.7)
Inflammatory markers, mean (SD)		
C-reactive protein, mg/l	4.8 (6.4)	3.7 (5.8)
Interleukin 6, pg/ml	2.2 (1.5)	1.5 (1.2)
Interleukin 2, pg/ml	1.4 (0.7)	0.9 (0.4)

Abbreviations: standard deviation (SD)

Table 2

Association of renal function with early age-related macular degeneration.

Renal Function	# at Risk	# of Early AMD	OR (95% CI) of Early AMD	p value
Cystatin C				
Lowest quartile	1439	30	1.00 [reference]	‡0.422
Second quartile	1558	49	1.23 (0.75-2.00)	
Third quartile	1445	59	1.22 (0.75-1.99)	
Highest quartile	1390	83	1.27 (0.78-2.06)	
eGFR §				
High (>60 ml/min/1.73m ²)	5340	188	1.00 [reference]	0.816
Low (≤ 60 ml/min/1.73m ²)	515	33	1.05 (0.70-1.58)	

Data are odds ratio (OR) and 95% confidence intervals (95%CI), adjusted for age (continuous), smoking (never, former, current), race (white, chinese, black, hispanic) and gender.

† p value for trend

§ estimated glomerular filtration rate (eGFR) categorised into ≤ 60 vs. >60 ml/min/1.73m²

Abbreviations: age-related macular degeneration (AMD), standard deviation (SD)

Table 3

Association of cystatin C, estimated glomerular filtration rate and early age-related macular degeneration, stratified by hypertension status.

* Top Decile Cystatin C	Early AMD OR (95%CI)	p value	p value for interaction
No hypertension , n=3339	1.80 (1.00-3.23)	0.049	0.755
Hypertension , n=2507	0.74 (0.42-1.30)	0.287	
Low §eGFR			
No hypertension , n=3329	0.99 (0.49-1.99)	0.973	0.757
Hypertension , n=2499	1.14 (0.68-1.91)	0.624	

Stratified and presented in odds ratio (OR) and 95% confidence intervals (95%CI)

Adjusted for age (continuous), smoking (never, former, current), race (white, chinese, black, hispanic), diabetes (by fasting criteria, 1997) and gender.

* Top decile cystatin C compared to the bottom nine deciles of cystatin C

§ estimated glomerular filtration rate (eGFR) categorised into ≤ 60 vs. >60 ml/min/1.73m²

Hypertension (by Joint National Committee criteria) $>140/90$

Abbreviations: age-related macular degeneration (AMD)