Plasma galectin-3 levels are associated with the risk of incident chronic kidney disease

Casey M. Rebholz[1,2], Elizabeth Selvin[1,2,3], Menglu Liang[1], Christie M. Ballantyne[4], Ron C. Hoogeveen[4], David Aguilar[4], John W. McEvoy[5], Morgan E. Grams[2,6] and Josef Coresh[1,2,3]

[1]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA; [2]Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins University, Baltimore, Maryland, USA; [3]Division of General Internal Medicine, Department of Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland, USA; [4]Section of Cardiovascular Research, Department of Medicine, Baylor College of Medicine, Houston, Texas, USA; [5]Division of Cardiology, Department of Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland, USA; and [6]Division of Nephrology, Department of Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland, USA

Galectin-3 has been proposed as a novel biomarker of heart failure and cardiac fibrosis, and may also be associated with fibrosis of other organs such as the kidney. To determine this, we prospectively analyzed data from 9,148 Atherosclerosis Risk in Communities (ARIC) Study participants with measured plasma galectin-3 levels (baseline, visit 4, 1996-98) and without prevalent chronic kidney disease (CKD) or heart failure. We identified 1,983 incident CKD cases through December 31, 2013 over a median follow-up of 16 years. At baseline, galectin-3 was cross-sectionally associated with estimated glomerular filtration rate and urine albumin-to-creatinine ratio; both significant. The results were adjusted for age, sex, race-center, education, physical activity, smoking status, body mass index, systolic blood pressure, anti-hypertensive medication use, history of cardiovascular disease, diabetes, fasting blood glucose, and rs4644 (a single nucleotide polymorphism of galactin-3). There was a significant, graded, and positive association between galectin-3 and incident CKD (quartile 4 vs. 1 hazard ratio: 2.22 [95% confidence interval: 1.89, 2.60]). The association was attenuated but remained significant after adjustment for estimated glomerular filtration rate, urine albumin-to-creatinine ratio, troponin T, and N-terminal pro-brain natriuretic peptide (quartile 4 vs. 1 hazard ratio: 1.75 [95% confidence interval: 1.49, 2.06]), and was stronger among those with hypertension at baseline (significant interaction). Thus, in this community-based population, higher plasma galectin-3 levels were associated with an elevated risk of developing incident CKD, particularly among those with hypertension.

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Correspondence: *Casey M. Rebholz, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Welch Center for Prevention, Epidemiology, and Clinical Research, 2024 East Monument Street, Suite 2–600, Baltimore, Maryland 21287, USA. E-mail: crebhol1@jhu.edu*

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Galectin-3 is a 35-kDa, soluble, β-galactoside-binding lectin composed of 250 amino acids that has multiple biological functions.[1,2] A total of 15 galectins have been identified and are classified into 3 forms: dimeric, tandem, and chimeric.[3] When concentrations of galectin-3 are high, this chimeric-type of galectin is found as a multimeric complex allowing for adhesion between cells and the extracellular matrix to facilitate fibrogenesis.[2] Recently, galectin-3 has been proposed as a novel biomarker of heart failure due to its involvement in myocardial fibrosis in addition to inflammation, immunity, and adhesion.[4–6] Beyond myocardial fibrosis, elevated galectin-3 levels may be associated with the development of fibrosis of other organ tissues, such as the kidney, and may increase the risk of developing chronic kidney disease (CKD) through its other mechanisms of action.[7–9]

Two epidemiologic studies have been conducted in general population samples (Framingham Heart Study and Cardiovascular Health Study) yielding conflicting results about the role of galectin-3 in CKD.[10,11] These prior studies included approximately 3000 participants each and consisted primarily of white individuals. They were able to prospectively identify several hundred incident CKD cases over 3 to 10 years of follow-up. Given the promising yet inconsistent findings, further research is warranted to better understand the association between galectin-3 and CKD and to provide more broadly generalizable results.

The objective of the present study was to investigate the prospective association between plasma levels of galectin-3 and risk of incident CKD in a community-based population consisting of African American and white adults.

RESULTS

Baseline characteristics

Those with higher plasma levels of galectin-3 were more likely to be older, female, African American, and to have completed less education ($P < 0.001$ for all comparisons; Table 1). Higher levels of galectin-3 were also associated with worse health

Table 1 | Baseline characteristics[a] of study participants according to quartile of plasma level of galectin-3

Characteristic	Quartile of plasma level of galectin-3 (range, ng/ml)				P[a]
	Quartile 1 (4.4–12.0)	Quartile 2 (12.1–14.1)	Quartile 3 (14.2–16.7)	Quartile 4 (16.8–91.6)	
n (%)	2367 (25.9%)	2182 (23.9%)	2303 (25.2%)	2296 (25.1%)	—
Galectin-3, ng/ml	10.3 (1.3)	13.1 (0.6)	15.4 (0.7)	20.2 (4.7)	<0.001
Age, yr	61.7 (5.4)	62.3 (5.6)	63.1 (5.6)	64.2 (5.6)	<0.001
Female	39.5% (936)	51.3% (1119)	62.4% (1437)	72.6% (1668)	<0.001
African American	15.3% (363)	18.4% (402)	20.7% (477)	25.6% (588)	<0.001
Education					
Less than high school	14.0% (331)	17.1% (374)	18.0% (414)	23.3% (535)	<0.001
High school	41.9% (991)	42.3% (923)	42.4% (976)	42.6% (977)	
College or above	44.1% (1045)	40.6% (885)	39.6% (913)	34.1% (784)	
Smoking status					
Current	14.2% (335)	15.4% (337)	13.3% (307)	14.5% (332)	<0.001
Former	47.9% (1133)	43.9% (958)	44.0% (1013)	39.5% (908)	
Never	38.0% (899)	40.7% (887)	42.7% (983)	46.0% (1056)	
Physical activity[b]	2.5 (2.0, 3.3)	2.5 (2.0, 3.3)	2.5 (2.0, 3.0)	2.3 (1.8, 3.0)	<0.001
Body mass index	28.0 (4.7)	28.2 (5.2)	28.9 (5.5)	30.0 (6.5)	<0.001
Systolic blood pressure, mm Hg	125.3 (17.5)	126.5 (18.6)	127.6 (18.8)	129.5 (19.8)	<0.001
Antihypertensive medication use	42.9% (1015)	47.3% (1031)	51.2% (1178)	65.6% (1506)	<0.001
History of CVD	8.0% (190)	8.6% (188)	10.3% (237)	11.9% (273)	<0.001
Diabetes status	17.9% (423)	16.7% (364)	19.5% (449)	23.9% (549)	<0.001
Fasting blood glucose, mg/dl	109.1 (33.1)	108.4 (32.9)	110.7 (39.2)	111.8 (39.2)	0.85
Troponin T,[b] ng/l	5.0 (1.5, 7.0)	5.0 (1.5, 8.0)	4.0 (1.5, 8.0)	5.0 (1.5, 9.0)	<0.001
NT-proBNP,[b] pg/ml	55.2 (26.9, 108.6)	64.6 (30.4, 124.0)	66.9 (34.3, 128.6)	89.4 (44.8, 170.9)	<0.001
eGFR-Cr,[b] ml/min/1.73 m^2	92.0 (81.9, 98.0)	90.8 (80.3, 97.3)	88.8 (77.0, 95.6)	83.3 (68.4, 93.2)	<0.001
eGFR-Cys,[b] ml/min/1.73 m^2	92.7 (81.0, 102.1)	88.8 (77.4, 98.8)	84.3 (73.5, 95.9)	73.6 (62.0, 87.3)	<0.001
UACR, mg/g					<0.001
<30	95.1% (2251)	94.4% (2060)	93.1% (2143)	87.3% (2005)	
30–300	4.6% (109)	4.7% (103)	5.9% (137)	9.1% (210)	
>300	0.3% (7)	0.9% (19)	1.0% (23)	3.5% (81)	
rs4644					0.39
AA	40.1% (949)	12.3% (269)	5.2% (120)	2.1% (49)	
AC	50.1% (1187)	59.9% (1306)	46.5% (1071)	30.2% (694)	
CC	9.8% (231)	27.8% (607)	48.3% (1112)	67.6% (1553)	

CVD, cardiovascular disease; eGFR-Cr, estimated glomerular filtration rate based on creatinine; eGFR-Cys, estimated glomerular filtration rate based on cystatin C; NT-proBNP, N-terminal pro-brain natriuretic peptide; UACR, urine albumin-to-creatinine ratio
Values are % (n) for categorical variables; mean (SD) for continuous variables unless otherwise stated.
[a]Cochran-Armitage trend tests for categorical variables and linear regression for continuous variables were used to test for trend in baseline characteristics across quartiles of plasma level of galectin-3.
[b]Median (25th percentile, 75th percentile).

status, including higher body mass index and blood levels of N-terminal pro B-type natriuretic peptide (NT-proBNP), and a greater burden of risk factors, including elevated blood pressure and diabetes ($P < 0.001$ for all comparisons).

Cross-sectional analysis of kidney measures and galectin-3

The median (25th, 75th percentiles) plasma level of galectin-3 was 14.2 (12.0, 16.8) ng/ml. The distribution of plasma galectin-3 levels was right-skewed with values ranging from 4.4 up to 91.6 ng/ml (Supplementary Figure S1). In this community-based population, participants had well-preserved kidney function at baseline with median (25th, 75th percentiles) estimated glomerular filtration rate (eGFR) of 89.4 (77.2, 96.2) ml/min/1.73 m^2 and 7.5% of participants had moderately or severely increased albuminuria at baseline (urine albumin-to-creatine ratio [UACR] >30 mg/g).

At baseline, galectin-3 was inversely associated with eGFR ($r = -0.23$, $P < 0.001$; Supplementary Figure S2) and directly associated with UACR ($r = 0.08$, $P < 0.001$; Supplementary Figure S3). The correlation between galectin-3 and kidney measures was stronger among those with impaired kidney filtration (eGFR <60 ml/min/1.73 m^2: $r = -0.42$, $P < 0.001$ vs. eGFR ≥60 ml/min/1.73 m^2: $r = -0.16$, $P < 0.001$; 95% confidence interval [CI] for the correlation difference: −0.33 to −0.18) and kidney damage (UACR >300 mg/g: $r = 0.24$, $P = 0.005$ vs. UACR ≤300 mg/g: $r = 0.06$, $P < 0.001$; 95% CI for the correlation difference: −0.34 to −0.01).

Prospective analysis of galectin-3 and incident CKD

Over a median follow-up of 16 years, a total of 1983 participants (22%) developed incident CKD. After adjusting for age, sex, race-center, education level, physical activity, smoking status, body mass index, systolic blood pressure, antihypertensive medication use, history of cardiovascular disease, diabetes status, fasting blood glucose, and rs4644, there was a significant, graded, and positive association between plasma levels of galectin-3 and incident CKD (Model 1, hazard ratio [HR] for quartile 2 vs. 1: 1.25, 95% CI 1.09–1.44; HR for quartile 3 vs. 1: 1.53, 95% CI 1.32–1.77; HR for quartile 4 vs. 1: 2.22, 95% CI 1.89–2.60; $P < 0.001$; Table 2).