HHS Public Access

Author manuscript

Am J Kidney Dis. Author manuscript; available in PMC 2019 July 17.

Published in final edited form as:

Am J Kidney Dis. 2016 June ; 67(6): 994–996. doi:10.1053/j.ajkd.2015.12.022.

Galectin-3 and soluble ST2 and kidney function decline in older adults: the Cardiovascular Health Study

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Galectin-3 and soluble ST2 (sST2), novel biomarkers of cardiovascular stress, have been found to predict cardiovascular events and death[1, 2]. Relationships with progression of kidney disease are less certain. Galectin-3 is a beta-galactoside-binding lectin expressed by activated macrophages that induces cardiac fibroblasts to deposit type I collagen, which contributes to myocardial fibrosis and adverse remodeling.[3] Soluble ST2 (sST2),a member of the IL-1 receptor family,is thought to neutralize the beneficial effects of IL -33,[4] which has antihypertrophic effects in cardiomyocytes andreduces myocardial fibrosis.

Higher concentrations of galectin-3 and sST2 have recently been linked with the development of CKD in middle-aged adults.[5, 6] It is plausible that elevations in these biomarkers, which may represent subclinical cardiovasuclar disease, would either have direct adverse effects on kidney function or would represent a systemic process that affects both the heart and the kidneys. We hypothesized that elevations in galectin-3 and sST2, possible biomarkers of subclinical heart failure, would be associated with kidney function decline in the Cardiovascular Health Study (CHS), a cohort of older adults.

We included 2,763 adults free of heart failure from CHS who had serum galectin-3 and sST2 measures at baseline and longitudinal measures of creatinine and cystatin C during follow-up (Table S1). Longitudinal changes in glomerular filtration rate (eGFR) were estimated using the combined cystatin C-creatinine equation over 3–7 years.[7] Details of our methods are included in S1. We performed nested logistic and Poisson regression models to examine

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CONTRIBUTIONS

Research idea and study design: NB, RK, JHI, MGS

Data acquisition: SS, CDF, RC

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Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. Dr. Katz takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted, and that any discrepancies from the study as planned (and, if relevant, registered) have been explained

the association of galectin-3 and soluble ST2 in quartiles with odds and incidence rate ratio of rapid kidney function decline (defined as 30% loss in eGFR) and incident eGFR<60 ml/min/1.73 m^2, respectively. We adjusted for demographic characteristics, baseline eGFR and other covariates, including NT-proBNP and troponin T.[8]

Among the 2,763 study participants, mean age was 72±5 years, 63% were female, 16% were black, and baseline eGFR was 74±17 ml/min/1.73m^2. Mean length of follow-up was 6.07±1.54 years. A total of 247 (8.9%) had rapid kidney function decline (mean time of 6.01 ± 1.6 years) and 408 (18.4%) had incident eGFR<60 ml/min/1.73m^2 (mean final eGFR 51±8 ml/min/1.73m^2). Participants with higher levels of galectin-3 and sST2 were more likely to be older, have cardiovascular disease, diabetes and lower eGFR (Tables S2a and S2b). In unadjusted and adjusted models, we found no association between higher galectin-3 with rapid decline in kidney function. In unadjusted models, each standard deviation higher sST2 was associated with 16% higher odds of rapid kidney function decline; however, this association was attenuated with adjustment (Table 1). Similarly, the association of galectin-3 and sST2 with continuous decline in eGFR was not statistically significant (Table S3) Associations of higher galectin-3 and sST2 with development of incident eGFR<60 ml/min/ 1.73m^2were attenuated in multivariable models (Table 2).

Among a community-based, multicenter cohort of older adults free of clinical heart failure, we found that higher serum galectin-3 and sST2 were not associated with 30% decline in eGFR or development of incident eGFR<60 ml/min/1.73m^2 after adjustment for potential confounders and other cardiac biomarkers.

Prior studies have suggested an association of galectin-3 and kidney function. Among patients with varying degrees of kidney disease, higher galectin-3 was associated with adverse clinical outcomes only among those with impaired kidney function.[9] In a model of hyperaldosteronism, increase in galectin-3 expression was associated with renal fibrosis.[10] In a rat model of hypertensive end-organ damage, galectin-3 inhibition attenuated hypertensive nephropathy.[11] Among participants in the Framingham Offspring Study, every log higher galectin-3 was associated with 1.49 greater odds of incident CKD.[6] In our study, we could not confirm these findings in our sample of older adults. Our findings may differ from previous studies due differences in study population – CHS was composed of older adults with a higher burden of morbidity with relatively preserved kidney function.

We also did not find an association with elevated sST2 with kidney function decline. Similarly, among participants in the Framingham Offspring Study, no association was noted with higher sST2 with risk of incident CKD.[5] Other studies have reported that sST2 may significantly discriminate risk for acute kidney injury (C-statistic 0.74)[12] and may also signal early recurrance of idiopathic nephrotic syndrome in kidney transplant recipients.[13] Based on these studies, it is possible that sST2 may be important in other aspects of kidney health.

Our study has several strengths. We studied a large, well-characterized cohort with longitudinal follow-up. We had longitudinal measures of kidney function. Our study has limitations that warrant consideration. Galectin-3 and sST2 were not available in all

participants due to inadequate samples which may have biased our results. Measures of urine albumin were not available at baseline.

In conclusion, our study found that there was no association between elevated galectin-3 and sST2 with subsequent decline of kidney function among older adults. Further studies are needed to understand biological pathways that link heart disease with kidney disease in high-risk patient populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKOWLEDGEMENTS

This research was supported by: grants from the National Institute for Diabetes Digestive and Kidney Diseases K23DK088865 (Bansal), an American Heart Association Established Investigator Award EIA18560026 (Ix), and investigator-initiated grants from Critical Diagnostics (DeFilippi and Seliger) and BG Medicine (DeFilippi and Seliger).

The Cardiovascular Health Study was supported by contracts HHSN268201200036C, HHSN268200800007C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086, and grant U01HL080295 from the National Heart, Lung, and Blood Institute (NHLBI), with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided by R01AG023629 from the National Institute on Aging (NIA). A full list of principal CHS investigators and institutions can be found at CHS-NHLBI.org

The funders of the study did not have any role in study design, collection, analysis, interpretation of data, writing and report and the decision to submit the report for publication.

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Table 1.

Association of baseline Galectin-3 and ST-2 with 30% decline of kidney function among participants in the Cardiovascular Health Study (N=2,763)

Biomarker	#w/ 30% decline	Unadjusted	Model 1	Model 2
Galectin-3		**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Continuous (per SD = 6)	247	1.09 (0.97, 1.22)	0.92 (0.79, 1.08)	0.90 (0.77, 1.06)
Quartiles				
<12.77	62	1.00 (ref)	1.00 (ref)	1.00 (ref)
12.77 – 15.63	61	1.03 (0.71, 1.51)	0.92 (0.63, 1.37)	0.93 (0.63, 1.38)
15.64 – 19.18	62	1.10 (0.76, 1.61)	0.86 (0.57, 1.27)	0.84 (0.56, 1.26)
>19.18	62	1.19 (0.81, 1.75)	0.65 (0.41, 1.01)	0.62 (0.39, 1.00)
ST-2				
Continuous (per SD = 10)	247	1.16 (1.04, 1.30)*	1.07 (0.94, 1.22)	1.03 (0.90, 1.18)
Quartiles				
<18.84	56	1.00 (ref)	1.00 (ref)	1.00 (ref)
18.84 – 23.62	56	1.04 (0.70, 1.54)	0.91 (0.61, 1.36)	0.90 (0.60, 1.34)
23.63 – 29.72	66	1.31 (0.89, 1.91)	1.04 (0.70, 1.55)	0.98 (0.66, 1.47)
> 29.72	69	1.60 (1.09, 2.34)	1.18 (0.78, 1.78)	1.07 (0.70, 1.62)

Model 1: adjusted for age, gender, race, baseline estimated glomerular filtration rate (eGFR), body mass index (BMI), systolic blood pressure, hypertension medications, diabetes, smoking, LDL cholesterol, HDL cholesterol and prevalent cardiovascular disease (defined as coronary heart disease or stroke)

Model 2: Model 1 + NTproBNP and troponin T

* $p<0.05$

Table 2.

Association of baseline Galectin-3 and ST-2 with incidenteGFR<60 ml/min/1.73m^2, excluding participants with eGFR≥60 ml/min/1.73m^{2}at baseline (N=2,215)

Biomarker	#w/ incident eGFR<60 ml/min/1.73m^2	Unadjusted	Model 1	Model 2
Galectin-3		**IRR (95% CI)**	**IRR (95% CI)**	**IRR (95% CI)**
Continuous (per SD = 6)	408	1.11 (1.04, 1.19) *	0.99 (0.90, 1.09)	0.99 (0.90, 1.08)
Quartiles				
<12.77	105	1.00 (ref)	1.00 (ref)	1.00 (ref)
12.77 – 15.63	116	1.23 (0.96, 1.54)	0.99 (0.79, 1.25)	1.00 (0.79, 1.26)
15.64 – 19.18	105	1.28 (1.00, 1.64) *	0.92 (0.73, 1.16)	0.92 (0.73, 1.16)
>19.18	82	1.55 (1.20, 2.02) *	0.93 (0.72, 1.20)	0.93 (0.72, 1.20)
ST-2				
Continuous (per SD = 10)	408	1.11 (1.04, 1.19) *	1.02 (0.92, 1.12)	1.01 (0.91, 1.11)
Quartiles				
<18.84	97	1.00 (ref)	1.00 (ref)	1.00 (ref)
18.84 – 23.62	119	1.35 (1.06, 1.73) *	1.09 (0.87, 1.37)	1.08 (0.86, 1.36)
23.63 – 29.72	103	1.38 (1.07, 1.78) *	1.05 (0.83, 1.32)	1.03 (0.81, 1.30)
> 29.72	89	1.42 (1.10, 1.85) *	1.02 (0.78, 1.33)	1.00 (0.76, 1.30)

Model 1: adjusted for age, gender, race, baseline estimated glomerular filtration rate (eGFR), body mass index (BMI), systolic blood pressure, hypertension medications, diabetes mellitussmoking, LDL cholesterol, HDL cholesterol and prevalent cardiovascular disease (defined as coronary heart disease and stroke)

Model 2: Model 1 + adjusted for NTproBNP and troponin

* p<0.05