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Association of Kidney Tubule Biomarkers With Cardiac Structure and Function in the Multiethnic Study of Atherosclerosis

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See page 17 for disclosure information.

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Abstract

Markers of glomerular disease, estimated glomerular filtration rate (eGFR) and albuminuria, are associated with cardiac structural abnormalities and incident cardiovascular disease (CVD). We aimed to determine whether biomarkers of kidney tubule injury, function, and systemic inflammation are associated with cardiac structural abnormalities. Among 393 Multi-Ethnic Study of Atherosclerosis participants without diabetes, CVD, or chronic kidney disease, we assessed the association of 12 biomarkers of kidney tubule injury, function, and systemic inflammation with the left ventricular mass/volume ratio (LVmvr) and left ventricular ejection fraction (LVEF) on cardiac magnetic resonance imaging using linear regression. The average age was 60 ± 10 years; 48% were men; mean eGFR was 96±16 ml/min/1.73 m^2; mean LVmvr was 0.93±0.18 g/ml, and mean LVEF was 62±6%. Each twofold greater concentration of plasma soluble urokinase plasminogen activator receptor was associated with a 0.04 g/ml (95% confidence interval [CI] 0.01 to 0.08 g/ml) higher LVmvr and 2.1% (95% CI 0.6 to 3.5%) lower LVEF, independent of risk factors for CVD, eGFR, and albuminuria. Each twofold greater plasma monocyte chemoattractant protein 1 was associated with higher LVmvr with a similar coefficient to that of plasma soluble urokinase plasminogen activator receptor. Each twofold greater concentration of plasma chitinase-3-like protein 1 and urine alpha-1-microglobulin was associated with a 1.1% (95% CI 0.4 to 1.7%) and 1.2% (95% CI 0.2 to 2.2%) lower LVEF, respectively. In conclusion, abnormal kidney tubule health may lead to cardiac dysfunction above and beyond eGFR and albuminuria.

Introduction

Abnormalities of cardiac structures and function are associated with incident cardiovascular disease (CVD).[1–3] Left ventricular mass/volume ratio (LVmvr) can help assess for abnormal concentric or eccentric cardiac remodeling, and left ventricular ejection fraction (LVEF) is used as a marker of ventricular pump function.[4] In the Multi-Ethnic Study of Atherosclerosis (MESA), higher LVmvr measured with cardiac magnetic resonance imaging (MRI) was associated with incident coronary heart disease events, whereas patients with low-to-normal LVEFs (50% to 55%) had a greater risk for incident heart failure (HF).[1,2,5] Recent HF trials have challenged the definition of a normal LVEF, suggesting pathologic changes might occur at values of LVEFs hitherto considered “normal.”[6,7] Abnormal kidney health is associated with structural heart disease and incident CVD and HF, although the underlying pathophysiologic mechanisms have not been fully elucidated.[3,8–11] These associations have been observed for the traditional measures of glomerular function—serum creatinine, cystatin C, and albuminuria—but these biomarkers primarily reflect kidney health at the glomerulus.[9,12,13] Recent work has identified biomarkers that reflect kidney tubular function and injury and have been associated with incident CVD and HF beyond the traditional risk factors of estimated glomerular filtration rate (eGFR) and albuminuria.[14,15] Whether

abnormalities in biomarkers of tubular health are associated with subtle cardiac structural abnormalities is not known. In this study of participants in MESA without diabetes and known CVD, and with preserved kidney function, we hypothesized that plasma and urine biomarkers of kidney tubular injury, function, and inflammation are associated with LVmvr and LVEF and that such relationships exist beyond known relations of these LV measures with eGFR and albuminuria, reflecting an unrecognized link between nonglomerular aspects of kidney disease and subclinical alterations in cardiac structure.

Methods

MESA is a National Heart, Lung, and Blood Institutes-ponsored cohort study investigating the prevalence, correlates, and risk factors for the development and progression of subclinical and overt CVD. The details of the original study design have been previously reported.[16] Briefly, MESA enrolled 6,814 men and women without clinically recognized CVD, aged 45 to 84 years, from 4 different racial/ethnic groups in 6 different communities in the United States. The institutional review boards at all participating centers approved the study, and all participants gave written informed consent. An ancillary study was initially designed to investigate the associations of kidney tubule biomarkers with chronic kidney disease (CKD) incidence in subjects at low risk and without diabetes.[17] As such, a random sample was selected of 500 subjects who had an eGFR ≥60 ml/min/1.73 m^2, were free of diabetes, and had plasma and urine specimens collected at the baseline study visit (2000 to 2002). Among these, 393 had a cardiac MRI performed at the baseline visit, constituting the analytic sample for this study.

Concentrations of 12 biomarkers reflecting kidney tubule injury, function, repair, defense, inflammation, and fibrosis were measured in plasma or urine. Markers of kidney tubule injury include plasma Kidney Injury Marker-1 (pKIM-1) and urine KIM-1 (uKIM-1). Markers of kidney tubule repair and defense include urine epidermal growth factor (uEGF) and urine uromodulin (uUMOD). Markers of repair and inflammation include plasma chitinase-3-like protein 1 (pYKL-40) and urine YKL-40 (uYKL-40). Markers of inflammation and fibrosis include plasma tumor necrosis factor receptor-1 (pTNFR-1), plasma tumor necrosis factor receptor-2 (pTNFR-2), plasma monocyte chemoattractant protein 1 (pMCP-1), urine MCP-1 (uMCP-1), and plasma soluble urokinase plasminogen activator receptor (psu-PAR). Urine alpha-1 microglobulin (uα1m) reflects proximal tubule reabsorptive function. Plasma biomarker concentrations were measured using samples stored at −80°C after a single freeze-thaw using a multiplex assay on the Meso Scale Discovery platform (Meso Scale Discovery, Gaithersburg, Maryland). The urine biomarker concentrations were measured using samples stored at −80°C after a single freeze-thaw using a Luminex multiplex assay (Luminex Corporation, Austin, Texas). Urine α1m concentration was measured using a Siemens nephelometer. Each biomarker was assayed in duplicate except for uα1m, and results were averaged to improve precision. Overall, the coefficient of variation was <6% for all biomarkers. All biomarker assays were performed blinded to clinical outcomes and cardiac imaging findings and performed at the Brigham and Women's Hospital Renal Division Biomarker Facility, according to protocols delineated.[18]

Cardiac MRI was performed at each study site, with 1.5-T magnets for the determination of LV mass and volumes. Image analysis was performed at a core laboratory, with the methods for obtaining measurements previously described.[1,19] Measures of LV mass, volume, and LVEF were based on steady-state free precession pulse sequence measurements without adjustment for age, gender, or body mass index, as described.[1,20] LVmvr was calculated as LV mass divided by LV end-diastolic volume.[21] LVEF was calculated by summation of slices using Simpson's rule (summation of all slice volumes calculated as the area of a slice multiplied by the sum of slice thickness).

Descriptive statistics for the cohort and biomarkers are presented as means and standard deviations (SD) for normally distributed variables, medians and interquartile ranges (IQR) for non-normally distributed variables, and counts and percentages for categorical variables. Spearman pairwise correlations were examined between biomarkers, urine albumin/urine creatinine ratio (ACR), eGFR (calculated using the CKD-EPI serum creatinine-Cystatin C estimate without race), LVmvr, and LVEF.[22] Urine biomarkers were indexed to urine creatinine for Spearman correlations to adjust for urine concentration at the time of collection.

Because 14 participants were missing cystatin C, 1 participant was missing urine albumin and urine creatinine, and 1 participant was missing cystatin C, urine albumin, and urine creatinine, we performed multiple imputations by chained equations with a total of 5 imputations using all the variables from the multivariable-adjusted model 2 below. Estimates were combined using Rubin's rule to account for variability in the imputation procedure.[23] Next, the associations of individual biomarkers with LVmvr and LVEF were assessed in nested multivariable linear regression models. Biomarkers were right-skewed, and $\log_2$ transformed biomarkers were used such that the results can be interpreted in terms of the changes in LVmvr or percentage changes in LVEF associated with a twofold higher biomarker level. Urine biomarkers were entered into models without indexing for urine creatinine, but 1/urine creatinine was adjusted for in the models. Model 1 adjusted for age, gender, race, the highest level of education attained, the study site, blood pressure medication use, systolic blood pressure, total cholesterol, lipid-lowering medication use, body mass index, and 1/urine creatinine (urine biomarkers only). Model 2 adjusted for variables in model 1 and eGFR and urine albumin (urine biomarkers only) or ACR (plasma biomarkers only). Biomarkers with significant associations were then examined by quartiles to assess the functional form of associations. In addition, 49% of participants had uα1m below the level of detection, and these values were imputed at a level of detection of 5.62 mg/L; thus, we examined α1m as tertiles of detectable values compared with those below the level of detection for both LVmvr and LVEF.

All analyses were performed using R version 4.0.3 (https://www.R-project.org/). A 2-sided p value of <0.05 was considered significant for all analyses.

Results

The average age was 60 ± 10 years; 48% were men; 47% were White; 21% were Black; 20% were Hispanic/Latino; and 12% were Chinese (Table 1). As specified by the sample

design, kidney function was preserved with an average eGFR of 96 ± 16 ml/min/1.73 m^2, and none had an eGFR <60 ml/min/1.73 m^2, diabetes, or clinically apparent CVD. Average systolic blood pressure was 122 ± 21 mm Hg, and diastolic blood pressure was 71 ± 11 mm Hg. Approximately 1/3 of patients (34%) had hypertension, and 29% were receiving antihypertensive therapy. The average low-density lipoprotein was 116 ± 32 mg/dL with 13% of participants using lipid-lowering therapies. The average LVmvr was 0.93 ± 0.18 g/ml, and LVEF was 62 ± 6%.

Most biomarkers were correlated with LVmvr (Table 2); uMCP-1, pMCP-1, pTNFR-1, pTNFR-2, psuPAR, pYKL-40, pKIM-1, and ACR were positively correlated with LVmvr, whereas uEGF, uUMOD and eGFR were negatively correlated with LVmvr. ACR had the highest correlation ($r = 0.25$) with LVmvr. Only pKIM-1 was positively correlated with LVEF, whereas all other biomarkers were not correlated (Table 2).

Greater pMCP-1 was significantly associated with LVmvr in the first model, with 0.03 g/ml higher LVmvr (95% confidence interval [CI] 0.00 to 0.06 g/ml) per twofold higher pMCP-1 (Table 3). The association remained statistically significant with a similar coefficient after adjusting for eGFR and ACR. psuPAR was also associated with LVmvr after adjusting for eGFR and ACR, with a similar coefficient to that of pMCP-1. When categorized by quartiles, LVmvr increased incrementally across quartiles of both pMCP-1 and psuPAR (Figure 1). Evaluation of uα1m by values below the detectable range and tertiles of measured values above this threshold did not show a statistically significant association with LVmvr (Figure 1).

Urine α1m, pYKL-40, and psuPAR had significant inverse associations with LVEF in models adjusting for clinical variables, eGFR, and albuminuria (Table 3). Per twofold greater uα1m, pYKL-40, and psuPAR, the decrements in LVEF were 1.2% (95% CI 0.2 to 2.2%), 1.1% (95% CI 0.4 to 1.7%), and 2.1% (95% CI 0.6 to 3.5%), respectively. Ascending quartiles of pYKL-40 and psuPAR showed an incrementally lower LVEF, whereas only subjects in the highest tertile for uα1m appeared to have lower LVEF (Figure 2).

Discussion

In this cross-sectional study in 393 participants living in the community, free of diabetes or CVD and with eGFR >60 ml/min/1.73 m^2, we observed that greater plasma MCP-1 and plasma suPAR concentrations were associated with higher LVmvr, whereas greater urine α1m, plasma YKL-40, and plasma suPAR concentrations were all associated with lower LVEF. These associations persisted despite adjustment for traditional CVD risk factors, eGFR and albuminuria. These findings suggest that the relationship of kidney disease with cardiac structure and function may be incompletely captured by traditional kidney function markers because these biomarkers of inflammation and proximal tubule function were associated with LV structure and function even when eGFR and ACR were accounted for. Potential explanations for these associations include that kidney tubular disease is causally related to CVD through other factors such as anemia or inflammation, or that there are common risk factors promoting both CVD and tubular disease, or that cardiac abnormalities promote kidney tubular disease. Of these, we hypothesize that factors leading

to kidney tubule dysfunction and inflammation also promote LV dysfunction beyond the known contribution of the glomerular health of the kidney.

Inflammation and immune-mediated damage contribute to the pathophysiology of cardiorenal disease.[24] In agreement and supporting this, we observed higher levels of 3 plasma biomarkers reflecting inflammation—suPAR, MCP-1, and YKL-40—were associated with abnormalities in cardiovascular structures and function. Previous studies have shown higher levels of these biomarkers were associated with incident kidney disease and CVD.[25–37] We have also shown that higher psuPAR and pYKL-40 are associated with incident CKD in MESA and now extend the associations of biomarkers of inflammation and kidney tubule function to measurements of LV structure and function.[17] Although it has been shown that higher urine levels of suPAR and YKL-40 are associated with kidney tubule dysfunction and injury, the associations we found are from plasma measurements. Therefore, whether these blood-based biomarkers reflect subclinical kidney disease, subclinical cardiac disease, or a systemic inflammatory process linked to both cannot be determined for our study. However, the previously indicated associations of these biomarkers with kidney tubule function, injury, and inflammation support considering kidney tubule health, in addition to glomerular health, in the pathophysiology of cardiorenal disease. Furthermore, these findings stress the importance of the role of inflammation and the immune response in the systemic pathophysiology of cardiorenal disease.

Only 1 of the 6 urine-based biomarkers of kidney tubule health, α1m, was associated with measurements of LV structure and function. The physiology of urine α1m for kidney tubule function is distinct from the other biomarkers and gives insight into potential pathophysiologic mechanisms by which kidney tubule health contributes to cardiovascular dysfunction. With normal proximal tubule function, α1m is filtered at the glomerulus and nearly completely reabsorbed in the proximal tubule, resulting in little to no measurable α1m in the urine; thus, elevated levels in the urine indicate proximal tubule dysfunction.[38] This likely explains why nearly 50% of participants selected for the absence of CKD, diabetes, and CVD did not have detectable α1m in this study, and why our data suggest only the highest tertile of α1m appeared to be associated with lower LVEF.

Potential mechanisms by which proximal tubule dysfunction associates with lower LVEF include abnormalities in maintaining normal electrolyte, acid-base, or fluid balance. Tubular function is critical to the regulation of salt and water excretion, and tubular injury and dysfunction can lead to volume expansion, hypertension, and increased ventricular end-diastolic pressure, all potentially contributing to cardiac structural abnormalities. Changes in proximal tubule function may also have broader impacts on kidney physiology. For example, sodium-glucose cotransport-2 inhibitors block the absorption of sodium and glucose in the proximal tubule and protect the cardiorenal axis, which is thought to result from protective changes in tubuloglomerular feedback.[39] Subclinical proximal tubule dysfunction may alter pathways such as tubuloglomerular feedback, resulting in neurohormonal activation (i.e., renin-angiotensin-aldosterone system and sympathetic nervous system), and subsequently promote cardiac dysfunction. Tubular injury and a reduction in nephron mass may also activate the renin-angiotensin-aldosterone system, leading to an increased risk of hypertension and LVmvr. Because the association of higher urine α1m with lower LVEF

was independent of eGFR, albuminuria, and other risk factors, it highlights the potential role of kidney tubule health in promoting cardiac structural changes. The fact that previous studies have linked higher urine α1m with the risk of incident HF further supports this hypothesis.

Strengths of our study include the availability of both plasma and urine biomarkers of kidney tubule health and cardiac MRIs in healthy participants living in the community and the availability of multiple potential confounding variables. This study also has important limitations. The sample size limits our ability to look at outcomes such as incident CVD or death, but LVmvr and LVEF have previously been strongly associated with incident coronary heart disease and HF in MESA.[1,2] Our findings are observational and cross-sectional in design, so temporal directions of associations between biomarkers and structural cardiac abnormalities cannot be proven. There could be selection bias in those willing to participate in MESA and obtain a cardiac MRI. The associations between biomarkers and cardiac measurements were numerically small; however, participants were selected for preserved eGFR and an absence of CVD and diabetes, so the findings reflect those in a healthy population. In addition, the cardiac measurements evaluated tend to become abnormal during later stages of CVD, and associations may have been stronger if we had earlier measurements of cardiac disease, such as strain, available to evaluate. Thus, whether results generalize to populations at greater risk is uncertain. It is also uncertain whether cardiac MRI measures not evaluated in this study may have provided insight into earlier cardiac structural changes. Many biomarkers were evaluated, so there is a chance of Type 1 error. There is also a potential for residual confounding. However, the consistency of the findings of psuPAR, pMCP-1, and pYKL-40, which are all related to inflammation and immune response, support a systemic pathophysiologic process contributing to cardiorenal disease, and previous studies linking several of these biomarkers with incident HF and CVD support our findings.[30,32,33,40] The finding of urine α1m suggests that certain proximal tubule functions may contribute to the risk of structural heart disease.

In a multiethnic population of community-living subjects selected for preserved eGFR and absence of CVD and diabetes, certain abnormalities of kidney tubule injury, function, and inflammation are associated with measurements of LV structure and function. Further evaluation of kidney tubule health in subclinical and clinical CVD is needed because likely both kidney tubular and glomerular health can provide insights into novel pathways contributing to cardiorenal disease.

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Disclosures

Dr. Gutierrez receives grant funding and honoraria from Amgen and Akebia. He receives honoraria from AstraZeneca, Reata, and Ardelyx and serves on a Data Monitoring Committee for QED Therapeutics.

Dr. Bonventre is cofounder and holds equity in Goldfinch Bio and Autonomous Medical Devices, is coinventor on KIM-1 patents assigned to Mass General Brigham, and has received consulting income and/or equity from Cadent, Renalytix, Sarepta, and Seagen and laboratory support from Kantum Pharma. He has equity in Pacific Biosciences, DxNow, and MediBeacon. Dr. Bonventre's interests were reviewed and are managed by BWH and MGB in accordance with their conflict-of-interest policies.

Dr. Kimmel is a coeditor with Mark Rosenberg of Chronic Renal Disease Academic Press and a coeditor with Daniel Cukor and Scott D. Cohen of Psychosocial Aspects of Chronic Kidney Disease Academic Press.

Dr. Shlipak is on advisory boards and receives honoraria from Bayer, Boehringer-Ingelheim, Astra-Zeneca. He receives grant support from Bayer.

Dr. Ix has grant support from Baxter International. He is on advisory boards for Akebia, AstraZeneka, Ardelyx, Alpha Young, and Bayer. He serves on a Data and Safety Monitoring Board from Sanifit International. The remaining authors have no conflicts of interest to declare.

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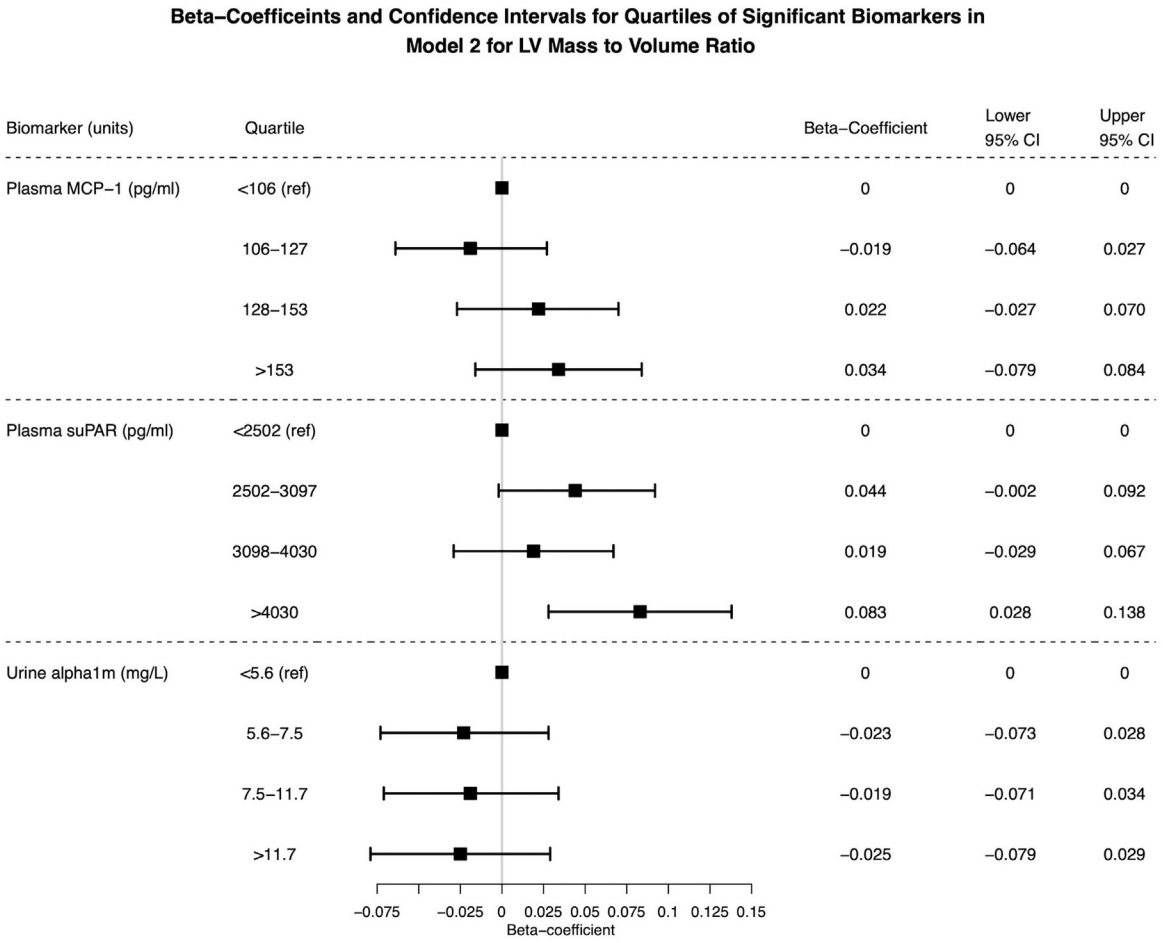

Figure 1.

Change in left ventricular mass to volume ratio (g/ml) by quartiles of plasma monocyte chemoattractant protein 1 (pMCP-1), plasma soluble urokinase plasminogen activator receptor (psuPAR), and urine alpha-1-microglobulin (uα1m) in the last multivariable model. Left ventricular mass/volume ratio rises incrementally with higher quartiles for pMCP-1 and psuPAR, but no change is seen with increasing quartiles of uα1m.

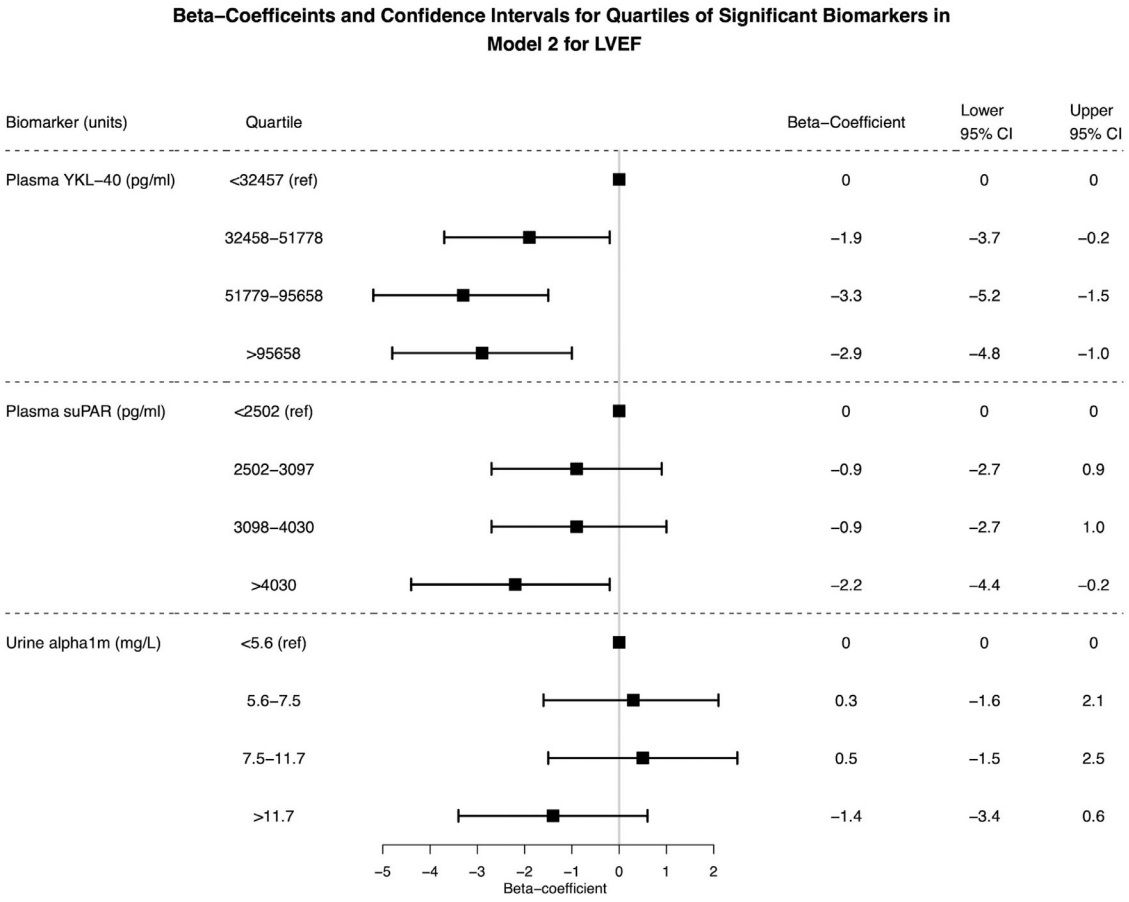

Figure 2.

Change in left ventricular ejection fraction (percentage) by quartiles of plasma chitinase-3-like protein 1 (pYKL-40), plasma soluble urokinase plasminogen activator receptor (psuPAR), and urine alpha-1-microglobulin (uα1m) in the last multivariable model. LVEF decreased incrementally with higher quartiles for pYKL-40 and psuPAR, whereas only the highest quartile of uα1m appeared to have a lower ejection fraction.

Table 1

Baseline characteristics of 393 patients with both kidney tubule biomarkers and cardiac MRI measurements in the MESA cohort

Age, years (SD)	60 (10)
Men, n (%)	188 (48%)
Race/Ethnicity, n (%)	
White	184 (47%)
Chinese	49 (12%)
Black	82 (21%)
Hispanic/Latino	78 (20%)
Education, n (%)	
<High School	51 (13%)
High school, no college	162 (41%)
College or higher	180 (46%)
BMI, kg/m^2 (SD)	27.4 (4.7)
Systolic blood pressure, mmHg (SD)	122 (21)
Diastolic blood pressure, mmHg (SD)	71 (11)
LDL, mg/dL (SD)	116 (32)
Total cholesterol, mg/dL (SD)	192 (36)
Creatinine, mg/dL (SD)	0.82 (0.16)
Cystatin C, mg/dL (SD)	0.86 (0.16)
eGFR (crCysC), ml/min/1.73m^2 (SD)	96 (16)
Hypertension, n (%)	135 (34%)
Antihypertensive use, n (%)	114 (29%)
Anti-hyperlipidemia use, n (%)	51 (13%)
LV mass-to-volume ratio, g/ml (SD)	0.93 (0.18)
LVEF, percentage (SD)	62 (6)
uKIM-1/uCr, pg/mg [IQR]	18.8 [12.2, 26.3]
uMCP-1/uCr, pg/mg [IQR]	1.64 [1.25, 2.32]
uEGF/uCr, pg/mg [IQR]	77.8 [56.1, 104.0]
uYKL-40/uCr, pg/mg [IQR]	3.89 (1.79,7.79)
uα1m/uCr, mg/mg [IQR]	0.077 [0.048, 0.118]
uUMOD/uCr, pg/mg [IQR]	262429 [138486, 442285]
ACR, (ug/mg) [IQR]	4.83 [3.10,9.20]
pTNFR-1, pg/ml [IQR]	827.7 [649.9, 1073.4]
pTNFR-2, pg/ml [IQR]	18231 [15402, 22264]
psuPAR, pg/ml [IQR]	3041 [2473, 3905]
pYKL-40, pg/ml [IQR]	52072 [31769, 95842]
pKIM-1, pg/ml [IQR]	201.2 [134.8, 316.0]
pMCP-1, pg/ml [IQR]	125.5 [104.9, 151.0]

ACR = urine albumin to urine creatinine ratio; BMI = body mass index; eGFR = estimated glomerular filtration rate; IQR = interquartile range; LDL = low-density lipoprotein; LVEF = left ventricular ejection fraction; pKIM-1 = plasma kidney injury molecule 1; pMCP-1 = plasma monocyte chemoattractant protein 1; psuPAR = plasma soluble urokinase plasminogen activator receptor; pTNFR-1 = plasma tumor necrosis factor

receptor-1; pTNFR-2 = plasma tumor necrosis factor receptor-2; pYKL-40 = plasma chitinase-3-like protein 1; SD = standard deviation; uα1m = urine alpha-1-microglobulin; uCr = urine creatinine; uEGF = urine epidermal growth factor; uKIM-1 = urine kidney injury molecule 1; uMCP-1 = urine monocyte chemoattractant protein 1; uUMOD = urine uromodulin; uYKL-40 = urine chitinase-3-like protein 1.

Table 2

Spearman correlation for kidney tubule biomarkers, eGFR, and ACR with LV mass/volume ratio and LVEF in the MESA cohort

Biomarker	LV Mass to Volume Ratio		LVEF	
	R	p- Value	R	p Value
uKIM-1 *	0.06	0.27	0.05	0.32
uMCP-1 *	0.15	<0.01	0.01	0.77
uEGF *	−0.18	<0.01	0.06	0.21
uYKL-40 *	0.01	0.82	0.09	0.07
uα1m *	0.00	0.93	−0.06	0.28
uUMOD *	−0.13	<0.01	0.01	0.89
pTNFR-1	0.16	<0.01	−0.00	0.98
pTNFR-2	0.12	0.02	−0.02	0.76
psuPAR	0.15	<0.01	−0.02	0.65
pYKL-40	0.18	<0.01	−0.09	0.09
pKIM-1	0.16	<0.01	0.10	0.05
pMCP-1	0.20	<0.01	−0.01	0.79
eGFR	−0.18	<0.01	−0.05	0.26
ACR	0.25	<0.01	0.06	0.26

ACR = urine albumin to urine creatinine ratio; eGFR = estimated glomerular filtration rate; LV = left ventricle; LVEF = left ventricular ejection fraction; pKIM-1 = plasma kidney injury molecule 1; pMCP-1 = plasma monocyte chemoattractant protein 1; psuPAR = plasma soluble urokinase plasminogen activator receptor; pTNFR-1 = plasma tumor necrosis factor receptor-1; pTNFR-2 = plasma tumor necrosis factor receptor-2; pYKL-40 = plasma chitinase-3-like protein 1; uEGF = urine epidermal growth factor; uKIM-1 = urine kidney injury molecule 1; uMCP-1 = urine monocyte chemoattractant protein 1; uUMOD = urine uromodulin; uYKL-40 = urine chitinase-3-like protein 1; uα1m = urine alpha-1-microglobulin.

* Urine biomarkers are indexed to urine creatinine.

Table 3

Association of kidney tubule biomarkers with LV mass/volume ratio and LV ejection fraction in multivariable linear regression models in the MESA cohort

LV Mass to Volume Ratio		
Biomarker	**Model 1 (g/ml, 95% CI)**	**Model 2 (g/ml, 95% CI)**
uKIM-1	0.01 (−0.01 to 0.03)	0.00 (−0.02 to 0.02)
uMCP-1	0.02 (0.00 to 0.04)	0.01 (−0.01 to 0.04)
uEGF	−0.01 (−0.04 to 0.02)	−0.01 (−0.04 to 0.02)
uYKL-40	0.01 (−0.01 to 0.02)	0.00 (−0.01 to 0.02)
uα1m	0.01 (−0.02 to 0.03)	0.00 (−0.03 to 0.03)
uUMOD	−0.01 (−0.03 to 0.01)	−0.01 (−0.03 to 0.01)
pTNFR-1	0.01 (−0.02 to 0.04)	0.02 (−0.02 to 0.06)
pTNFR-2	0.01 (−0.03 to 0.05)	0.02 (−0.03 to 0.06)
psuPAR	0.03 (0.00 to 0.07)	**0.04 (0.01 to 0.08)**
pYKL-40	0.00 (−0.02 to 0.02)	0.00 (−0.01 to 0.02)
pKIM-1	0.01 (−0.01 to 0.03)	0.01 (−0.01 to 0.03)
pMCP-1	**0.03 (0.00 to 0.06)**	**0.04 (0.00 to 0.07)**
LVEF		
Biomarker	**Model 1 (%, 95% CI)**	**Model 2 (%, 95% CI)**
uKIM-1	−0.0 (−0.8 to 0.7)	0.0 (−0.8 to 0.8)
uMCP-1	0.4 (−0.5 to 1.3)	0.5 (−0.4 to 1.4)
uEGF	0.5 (−0.6 to 1.6)	0.6 (−0.6 to 1.8)
uYKL-40	−0.1 (−0.6 to 0.4)	−0.1 (−0.5 to 0.4)
uα1m	**−1.2 (−2.1 to −0.2)**	**−1.2 (−2.2 to −0.2)**
uUMOD	−0.2 (−0.9 to 0.4)	−0.2 (−0.9 to 0.5)
pTNFR-1	−0.7 (−1.9 to 0.5)	−1.2 (−2.6 to 0.3)
pTNFR-2	−0.9 (−2.4 to 0.5)	−1.3 (−2.8 to 0.3)
psuPAR	**−1.7 (−3.0 to −0.3)**	**−2.1 (−3.5 to −0.6)**
pYKL-40	**−1.0 (−1.7 to −0.3)**	**−1.1 (−1.7 to −0.4)**
pKIM-1	0.3 (−0.4 to 1.0)	0.3 (−0.4 to 1.1)
pMCP-1	−0.5 (−1.7 to 0.6)	−0.6 (−1.8 to 0.6)

*Bolded values have p-value <0.05.

Model 1: age, gender, race, education, site, blood pressure medications, systolic blood pressure, total cholesterol, lipid-lowering medication, BMI (for urine biomarkers, 1/urine creatinine)

Model 2: age, gender, race, education, site, blood pressure medications, systolic blood pressure, total cholesterol, lipid-lowering medication, BMI, eGFR, and ACR (for urine biomarkers, urine albumin and 1/urine creatinine used)

ACR = urine albumin to urine creatinine ratio; CI = confidence interval; eGFR = estimated glomerular filtration rate; LV = left ventricle; LVEF = left ventricular ejection fraction; pKIM-1 = plasma kidney injury molecule 1; pMCP-1 = plasma monocyte chemoattractant protein 1; pYKL-40 = plasma chitinase-3-like protein 1; psuPAR = plasma soluble urokinase plasminogen activator receptor, pTNFR-1 – plasma tumor necrosis factor receptor-1, pTNFR-2 – plasma tumor necrosis factor receptor-2; uα1m = urine alpha-1-microglobulin; uEGF = urine epidermal growth factor; uKIM-1 = urine kidney injury molecule 1; uMCP-1 = urine monocyte chemoattractant protein 1; uUMOD = urine uromodulin; uYKL-40 = urine chitinase-3-like protein 1.