CKD

BIOMARKERS CONSORTIUM

PUBLICATIONS

2017

Casey M. Rebholz, PhD, MPH, MS, Lesley A. Inker, MD, MS, Yuan Chen, MS, Menglu Liang, MHS, Meredith C. Foster, ScD, MPH, John H. Eckfeldt, MD, PhD, Paul L. Kimmel, MD, Ramachandran S. Vasan, MD, Harold I. Feldman, MD, MSCE, Mark J. Sarnak, MD, MS, Chi-yuan Hsu, MD, MSc, Andrew S. Levey, MD, and Josef Coresh, MD, PhD, MHS, on behalf of the Chronic Kidney Disease Biomarkers Consortium. **Risk of ESRD and Mortality Associated With Change in Filtration Markers.** Am J Kidney Dis. 2017 October;70(4):551-560. PMID: 28648303

Using change in estimated glomerular filtration rate (eGFR) based on creatinine concentration as a surrogate outcome in clinical trials of chronic kidney disease has been proposed. Risk for end-stage renal disease (ESRD) and all-cause mortality associated with change in concentrations of other filtration markers has not been studied in chronic kidney disease populations. Poisson regression was used to estimate incidence rate ratios and 95% CIs for ESRD and all-cause mortality during long-term follow-up (10-16 years) per 30% decline in mGFR or eGFR for each filtration marker and the average of all 4 markers. 1-year decline in mGFR, eGFRcr, eGFRBTP, and the average of the 4 filtration markers was significantly associated with increased risk for incident ESRD in both studies (all P≤0.02). Compared to mGFR, only decline in eGFRBTPwas statistically significantly more strongly associated with ESRD risk in both studies (both P≤0.03). Decline in eGFRcr, but not mGFR or the other filtration markers, was significantly associated with risk for all-cause mortality in AASK only (incidence rate ratio per 30% decline, 4.17; 95% CI, 1.78-9.74; P<0.001), but this association was not significantly different from decline in mGFR (P=0.2). Declines in mGFR, eGFRcr, eGFRBTP, and the average of 4 filtration markers (creatinine, cystatin C, BTP, and B2M) were consistently associated with progression to ESRD. Read the article > >

Kevin M. Wheelock , Jian Cai, Helen C. Looker, Michael L. Merchant, Robert G. Nelson, Gudeta D. Fufaa, Jennifer E. Weil, Harold I. Feldman, Ramachandran S. Vasan, Paul L. Kimmel, Brad H. Rovin, Michael Mauer, Jon B. Klein, for the CKD Biomarkers Consortium. **Plasma bradykinin and early diabetic nephropathy lesions in type 1 diabetes mellitus**. PLoS One. 2017 Jul 10;12(7):e0180964. PMID: 28700653

To examine the association of bradykinin and related peptides with the development of diabetic nephropathylesions in 243 participants with type 1 diabetes (T1D) from the Renin-Angiotensin System Study who, at baseline, were normoalbuminuric, normotensive and had normal or increased glomerular filtration rate (GFR). Plasma concentrations of bradykinin and related peptides were measured at baseline by quantitative mass spectrometry. All participants were randomly assigned at baseline to receive placebo, enalapril or losartan during the 5 years between kidney biopsies. Kidney morphometric data were available from kidney biopsies at baseline and after 5 years. Relationships of peptides with changes in morphometric variables were assessed using multiple linear regression after adjustment for age, sex, diabetes duration, HbA1c, mean arterial pressure, treatment assignment and, for longitudinal analyses, baseline structure. Baseline median albumin excretion rate of study participants was 5.0 μg/min, and mean GFR was 128 mL/min/1.73 m2. After multivariable adjustment, higher plasma concentration of bradykinin (1-8) was associated with greater glomerular volume (partial r = 0.191, P = 0.019) and total filtration surface area (partial r = 0.211, P = 0.010), and higher bradykinin (1-7) and hyp3-bradykinin (1-7) were associated with lower cortical interstitial fractional volume (partial r = -0.189, P = 0.011; partial r = -0.164, P = 0.027 respectively). In longitudinal analyses, higher bradykinin was associated with preservation of surface density of the peripheral glomerular basement membrane (partial r = 0.162, P = 0.013), and for participants randomized to losartan, higher hyp3-bradykinin (1-8) was associated with more limited increase in cortical interstitial fractional volume (partial r = -0.291, P = 0.033). Higher plasma bradykinin and related peptide concentrations measured before clinical onset of diabeticnephropathy in persons with T1D were associated with preservation of glomerular structures, suggesting that elevations of these kinin concentrations may reflect adaptive responses to early renal structural changes in diabetic nephropathy. Read the article > >

Meyeon Park, Chi-yuan Hsu, Alan S. Go, Harold I. Feldman, Dawei Xie, Xiaoming Zhang, Theodore Mifflin, Sushrut S. Waikar, Venkata S. Sabbisetti, Joseph V. Bonventre, Josef Coresh, Robert G. Nelson, Paul L. Kimmel, John W. Kusek, Mahboob Rahman, Jeffrey R. Schelling, Ramachandran S. Vasan, and Kathleen D. Liu, on behalf of the Chronic Renal Insufficiency Cohort (CRIC) Study Investigators and the CKD Biomarkers Consortium. **Urine Kidney Injury Biomarkers and Risks of Cardiovascular Disease Events and All-Cause Death: The CRIC Study.** Clin J Am Soc Nephrol. 2017 May 8;12(5):761-771. Epub 2017 Mar 2. PMID: 28254771

CKD is an important risk factor for cardiovascular disease (CVD) and death. We investigated whether select urine kidney injury biomarkers were associated with higher risk of heart failure (HF), CVD, and death in persons with CKD enrolled in the Chronic Renal Insufficiency Cohort (CRIC) Study. Urine kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin, liver fatty acid-binding protein, and N-acetyl-β-d-glucosaminidase were measured in urine of a subset of CRIC participants (n=2466). We used Cox proportional hazards regression to examine associations between these biomarkers indexed to urinary creatinine (Cr) and (1) HF, (2) a composite of atherosclerotic CVD events (myocardial infarction, ischemic stroke, or peripheral artery disease), and (3) all-cause death. A t baseline, mean age of study participants was 59.5±10.8 years, 46% were women, and 34% had a self-reported history of any CVD. Median follow-up was 6.5 (interquartile range, 5.6-6.8) years. A total of 333 HF events, 282 atherosclerotic CVD events, and 440 deaths were observed during a median follow-up of 6.5 (interquartile range, 5.6-6.8) years. Those in the highest two quintiles of KIM-1/Cr levels had a higher risk of HF relative to the lowest quintile (quintile 5 versus quintile 1 adjusted hazard ratio [aHR] of 1.73 [95% confidence interval, 1.05 to 2.85]). N-acetyl-β-d-glucosaminidase/Cr was associated with HF in continuous analyses (aHR per log SD higher 1.18 [95% confidence interval, 1.01 to 1.38]). Only KIM-1/Cr was independently associated with atherosclerotic CVD events (aHR per log SD higher 1.21 [95% confidence interval, 1.02 to 1.41]), whereas both KIM-1/Cr (quintile 5 versus quintile 1 aHR of 1.56 [95% confidence interval, 1.06 to 2.31]) and neutrophil gelatinase-associated lipocalin/Cr (quintile 5 versus quintile 1 aHR of 1.82 [95% confidence interval, 1.19 to 2.8]) were associated with all-cause death. Read the article > >

Lesley A. Inker, Josef Coresh, Yingying Sang, Chi-yuan Hsu, Meredith C. Foster, John H. Eckfeldt, Amy B. Karger, Robert G. Nelson, Xun Liu, Mark Sarnak, Lawrence J. Appel, Morgan Grams, Dawei Xie, Paul L. Kimmel, Harold Feldman, Ramachandran S. Vasan, Andrew S. Levey, for the CKD Biomarkers Consortium. **Filtration Markers as Predictors of ESRD and Mortality: Individual Participant Data Meta-Analysis**. Clin J Am Soc Nephrol. 2017 Jan 6;12(1):69-78. Epub 2016 Nov 10.

Serum β-trace protein (BTP) and β-2 microglobulin (B2M) are associated with risk of ESRD and death in the general population and in populations at high risk for these outcomes (GP/HR) and those with CKD, but results differ among studies. We performed an individual patient-level meta-analysis including three GP/HR studies (n=17,903 participants) and three CKD studies (n=5415). We compared associations, risk prediction, and improvement in reclassification of eGFR using BTP (eGFRBTP) and B2M (eGFRB2M) alone and the average (eGFRavg) of eGFRBTP, eGFRB2M, creatinine (eGFRcr), and cystatin C (eGFRcys), to eGFRcr, eGFRcys, and their combination (eGFRcr-cys) for ESRD (2075 events) and death (7275 events). Mean (SD) follow up times for ESRD and mortality for GP/HR and CKD studies were 13 (4), 6.2 (3.2), 14 (5), and 7.5 (3.9) years, respectively. Compared with eGFRcr, eGFRBTP and eGFRB2M improved risk associations and modestly improved prediction for ESRD and death even after adjustment for established risk factors. eGFRavg provided the most consistent improvement in associations and prediction across both outcomes and populations. Assessment of heterogeneity did not yield clinically relevant differences. For ESRD, addition of albuminuria substantially attenuated the improvement in risk prediction and risk classification with novel filtration markers. For mortality, addition of albuminuria did not affect the improvement in risk prediction with the use of novel markers, but lessened improvement in risk classification, especially for the CKD cohort. These markers do not provide substantial additional prognostic information to eGFRcr and albuminuria, but may be appropriate in circumstances where eGFRcr is not accurate or albuminuria is not available. Educational efforts to increase measurement of albuminuria in clinical practice may be more cost-effective than measurement of BTP and B2M for improving prognostic information. Read the article > >

2016

Chi-yuan Hsu, Dawei Xie, Sushrut S. Waikar, Joseph V. Bonventre, Xiaoming Zhang, Venkata Sabbisetti, Theodore E. Mifflin, Josef Coresh, Clarissa J. Diamantidis, Jiang He, Claudia M. Lora, Edgar R. Miller, Robert G. Nelson, Akinlolu O. Ojo, Mahboob Rahman, Jeffrey R. Schelling, Francis P. Wilson, Paul L. Kimmel, Harold I. Feldman, Ramachandran S. Vasan, Kathleen D. Liu; and the CRIC Study Investigators; for the CKD Biomarkers Consortium. **Urine biomarkers of tubular injury do not improve on the clinical model predicting chronic kidney disease progression.** Kidney Int. 2017 Jan;91(1):196-203. Epub 2016 Oct 28. PMID: 28029431

Few investigations have evaluated the incremental usefulness of tubular injury biomarkers for improved prediction of chronic kidney disease (CKD) progression. As such, we measured urinary kidney injury molecule-1, neutrophil gelatinase-associated lipocalin, N-acetyl-ß-D-glucosaminidase and liver fatty acid binding protein under highly standardized conditions among 2466 enrollees of the prospective Chronic Renal Insufficiency Cohort Study. During 9433 person-years of follow-up, there were 581 cases of CKD progression defined as incident end-stage renal disease or halving of the estimated glomerular filtration rate. Levels of the urine injury biomarkers, normalized for urine creatinine, were strongly associated with CKD progression in unadjusted Cox proportional hazard models with hazard ratios in the range of 7 to 15 comparing the highest with the lowest quintiles. However, after controlling for the serum creatinine-based estimated glomerular filtration rate and urinary albumin/creatinine ratio, none of the normalized biomarkers was independently associated with CKD progression. None of the biomarkers improved on the high (0.89) C-statistic for the base clinical model. Thus, among patients with CKD, risk prediction with a clinical model that includes the serum creatinine-based estimated glomerular filtration rate and the urinary albumin/creatinine ratio is not improved on with the addition of renal tubular injury biomarkers. Read the article > >

Sushrut S. Waikar, Venkata Sabbisetti, Johan Ärnlöv, Axel C. Carlsson, Josef Coresh, Harold I. Feldman, Meredith C. Foster, Gudeta D. Fufaa, Johanna Helmersson-Karlqvist, Chi-yuan Hsu, Paul L. Kimmel, Anders Larsson, Yumin Liu, Lars Lin, Kathleen D. Liu, Theodore E. Mifflin, Robert G. Nelson, Ulf Risérus, Ramachandran S. Vasan, Dawei Xie6 , Xiaoming Zhang6 and Joseph V. Bonventre1 for the Chronic Kidney Disease Biomarkers Consortium Investigators. **Relationship of proximal tubular injury to chronic kidney disease as assessed by urinary kidney injury molecule-1 in five cohort studies.** Nephrol Dial Transplant. 2016 Sep;31(9):1460-70. Epub 2016 Jun 7. PMID: 27270293

The primary biomarkers used to define CKD are serum creatinine and albuminuria. These biomarkers have directed focus on the filtration and barrier functions of the kidney glomerulus even though albuminuria results from tubule dysfunction as well. Given that proximal tubules make up ~90% of kidney cortical mass, we evaluated whether a sensitive and specific marker of proximal tubule injury, urinary kidney injury molecule-1 (KIM-1), is elevated in individuals with CKD or with risk factors for CKD. We measured urinary KIM-1 in participants of five cohort studies from the USA and Sweden. Participants had a wide range of kidney function and were racially and ethnically diverse. Multivariable linear regression models were used to test the association of urinary KIM-1 with demographic, clinical and laboratory values. In pooled, multivariable-adjusted analyses, log-transformed, creatinine-normalized urinary KIM-1 levels were higher in those with lower eGFR {β = -0.03 per 10 mL/min/1.73 m(2) [95% confidence interval (CI) -0.05 to -0.02]} and greater albuminuria [β = 0.16 per unit of log albumin: creatinine ratio (95% CI 0.15-0.17)]. Urinary KIM-1 levels were higher in current smokers, lower in blacks than nonblacks and lower in users versus nonusers of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Proximal tubule injury appears to be an integral and measurable element of multiple stages of CKD. Read article > >

Casey Rebholz, Morgan Grams, Pamela Lutsey, Andew Hoofnagle, Jeffrey Misialek, Lesley Inker, Andrew Levey, Elizabeth Selvin, Chi-yuan Hsu, Paul Kimmel, Vasan Ramachandran, John Eckfeldt, Joseph Coresh, Chronic Kidney Disease Biomarker Consortium. **Biomarkers of vitamin D status and risk of ESRD.** Am J Kidney Dis 2016 February;67(2):235-242. PMID: 26475393

> Disordered mineral metabolism is characteristic of decreased kidney function. However, the prospective associations between circulating levels of vitamin D binding protein, vitamin D, and end-stage renal disease (ESRD) have not been extensively evaluated in epidemiologic studies. Baseline levels of vitamin D binding protein, 25-hydroxyvitamin D (25[OH]D), and 1,25-dihydroxyvitamin D (1,25[OH]2D) were measured in blood samples collected at study visit 4 (1996-1998) of the ARIC (Atherosclerosis Risk in Communities) Study. ESRD cases (n=184) were identified through hospitalization diagnostic codes from 1996 to 2008 and were frequency matched to controls (n=251) on categories of estimated glomerular filtration rate, albuminuria, diabetes mellitus, sex, and race. Higher vitamin D binding protein levels were associated with elevated risk for incident ESRD (OR, 1.76; 95% CI, 1.22-2.54; P=0.003). Higher free and bioavailable 25(OH)D levels were associated with reduced risk for incident ESRD (ORs of 0.65 [95% CI, 0.46-0.92; P=0.02] and 0.63 [95% CI, 0.43-0.91; P=0.02] for free and bioavailable 25[OH]D, respectively). There was no association between ESRD and overall levels of 25(OH)D (OR, 0.83; 95% CI, 0.58-1.19; P=0.3) or 1,25(OH)2D (OR, 0.73; 95% CI, 0.48-1.13; P=0.2). In the general population, blood levels of vitamin D binding protein were positively associated and blood levels of free and bioavailable 25(OH)D were inversely associated with new-onset ESRD during follow-up. Read the article > >

Khalid Abulaban, Huijuan Song, Xiaoming Zhang, Paul Kimmel, John Kusek , Robert Nelson, Harold Feldman, Vasan Ramachandran, Jun Ying, Michael Mauer, Gary Nelsestuen, Michael Bennett, Hermine Brunner and Brad Rovin. **Predicting decline of kidney function in lupus nephritis using urine biomarkers.** Lupus. 2016 Feb 11. pii: 0961203316631629 [Epub ahead of print]

> To evaluate candidate biomarkers to predict future renal function decline (RFD) in children and adults with lupus nephritis (LN). At the time of enrollment into prospective observational LN cohort studies liver-type fatty acid binding protein (LFABP), albumin, monocyte chemoattractant protein-1 (MCP-1), uromodulin, transferrin, and hepcidin were measured in urine samples of two cohorts of patients with LN, one followed at a pediatric (cohort-1; n = 28) and one at an adult institution (cohort-2; n = 69). The primary outcome was RFD, defined in cohort-1 as a decrease in estimated glomerular filtration rate (eGFR) of ≥20% and in cohort-2 as a sustained increase of ≥25% in serum creatinine concentration (SCr), both from baseline. All patients (n = 97) had normal eGFR or SCr at the time of urine collection at baseline. RFD occurred in 29% (8/28) of patients in cohort-1 during a mean follow-up of 6.1 months, and in 30% (21/69) of those in cohort-2 during a mean follow-up of 60 months. Individually, in cohort-1, levels of MCP-1, transferrin, LFABP, and albumin were higher in the RFD group than those who maintained renal function, with statistical significance for LFABP and albumin. In cohort-2 the RFD group also had higher levels of urine MCP-1 and albumin than others. The combination of LFABP, MCP-1, albumin, and transferrin had good predictive accuracy for RFD in both cohorts (area under the ROC curve = 0.77-0.82). The combinatorial urine biomarker LFABP, MCP-1, albumin, and transferrin shows promise as a predictor of renal functional decline in LN, and warrants further investigation. Read the article > >

Lesley A. Inker, Hocine Tighiouart, Josef Coresh, Meredith C. Foster, Amanda H. Anderson, Gerald J. Beck, Gabriel Contreras, Tom Greene, Amy B. Karger, John W. Kusek, James Lash, Julia Lewis, Jeffrey R. Schelling, Sankar D. Navaneethan, James Sondheimer, Tariq Shafi, Andrew S. Levey. **GFR Estimation Using β-Trace Protein and β2-Microglobulin in CKD.** Am J Kidney Dis. 2016 Jan;67(1):40-8. PMC4485524

β-Trace protein (BTP) and β2-microglobulin (B2M) are novel glomerular filtration markers that have stronger associations with adverse outcomes than creatinine. Comparisons of BTP and B2M to creatinine and cystatin C are limited by the absence of rigorously developed glomerular filtration rate (GFR) estimating equations for the novel markers. For BTP and B2M, coefficients for age, sex, and race were smaller than for creatinine and were similar or smaller than for cystatin C. For B2M, coefficients for sex, age, and race were smaller than for creatinine and were similar (age and race) or smaller (sex) than for cystatin C. The final equations with BTP (BTP, age, and sex) or B2M (B2M alone) were less accurate than either the CKD-EPI (CKD Epidemiology Collaboration) creatinine or cystatin C equations. The combined BTP-B2M equation (BTP and B2M alone) had similar accuracy to the CKD-EPI creatinine or cystatin C equation. The average of the BTP-B2M equation and the CKD-EPI creatinine–cystatin C equation was not more accurate than the CKD-EPI creatinine–cystatin C equation. BTP and B2M are less influenced by age, sex, and race than creatinine and less influenced by race than cystatin C, but provide less accurate GFR estimates than the CKD-EPI creatinine and cystatin C equations. The CKD-EPI BTP and B2M equation provides a methodological advance for their study as filtration markers and in their associations with risk and adverse outcomes, but further study is required before clinical use. Read the article > >

Qin Fu, Eric Grote, Jie Zhu, Christine Jelinek, Anna Köttgen, Josef Coresh , Jennifer E. Van Eyk.   **An Empirical Approach to Signature Peptide Choice for Selected Reaction Monitoring: Quantification ofUromodulin in Urine.** Clin Chem. 2016 Jan;62(1):198-207

Many avenues have been proposed for a seamless transition between biomarker discovery data and selected reaction monitoring(SRM) assays for biomarker validation. Unfortunately, studies with the abundant urinary protein uromodulin have shown that these methods do not converge on a consistent set of surrogate peptides for targeted mass spectrometry. As an alternative, we present an empirical peptide selection work flow for robust protein quantification. We compared the relative SRM signal intensity of 12 uromodulin-derived peptides between tryptic digests of 9 urine samples. Pairwise CVs between the 12 peptides were 0.19-0.99. We used a correlation matrix to identify peptides that reproducibly tracked the amount of uromodulinprotein and selected 4 peptides with robust and highly correlated SRM signals. Absolute quantification was performed with stable isotope-labeled versions of these peptides as internal standards and a standard curve prepared from a tryptic digest of purified uromodulin. Absolute quantification of uromodulin in 40 clinical urine samples yielded interpeptide correlations of ≥0.984 and correlations of ≥0.912 with ELISA data. The SRM assays were linear over >3 orders of magnitude and had typical interdigest CVs of <10%, interinjection CVs of <7%, and intertransition CVs of <7%. Comparing the apparent abundance of a plurality of peptides derived from the same target protein makes it possible to selectsignature peptides that are unaffected by the unpredictable confounding factors inevitably present in biological samples. Read the article > >

2015

Samir V Parikh, Ana Malvar, Huijuan Song, Valeria Alberton, Bruno Lococo, Jay Vance, Jianying Zhang, Lianbo Yu and Brad H Rovin. **Characterising the immune profile of the kidney biopsy at lupus nephritis flare differentiates early treatment responders from non-responders.** Lupus Sci Med. 2015 Nov 18;2(1) PMC4654163

The kidney biopsy is used to diagnose and guide initial therapy in patients with lupus nephritis (LN). Kidney histology does not correlate well with clinical measurements of kidney injury or predict how patients will respond to standard-of-care immunosuppression. We postulated that the gene expression profile of kidney tissue at the time of biopsy may differentiate patients who will from those who will not respond to treatment. The expression of 511 immune-response genes was measured in kidney biopsies from 19 patients with proliferative LN and 4 normal controls. RNA was extracted from formalin-fixed, paraffin-embedded kidney biopsies done at flare. After induction therapy, 5 patients achieved a complete clinical response (CR), 10 had a partial response (PR) and 4 patients were non-responders (NRs). Transcript expression was compared with normal controls and between renal response groups. A principal component analysis showed that intrarenal transcript expression from normal kidney, CR biopsies and NR biopsies segregated from each other. The top genes responsible for CR clustering included several interferon pathway genes (*STAT1*, *IRF1*, *IRF7*,*MX1*, *STAT2*, *JAK2*), while complement genes (*C1R*, *C1QB, C6, C9, C5, MASP2*) were mainly responsible for NR clustering. Overall, 35 genes were uniquely expressed in NR compared with CR. Pathway analysis revealed that interferon signalling and complement activation pathways were upregulated in both groups, while BAFF, APRIL, nuclear factor-κB and interleukin-6 signalling were increased in CR but suppressed in NR. These data suggest that molecular profiling of the kidney biopsy at LN flare may be useful in predicting treatment response to induction therapy.
Read the article > >

Meredith C. Foster, Josef Coresh, Joseph V. Bonventre, Venkata S. Sabbisetti, Sushrut S. Waikar, Theodore E. Mifflin, Robert G. Nelson, Morgan Grams, Harold I. Feldman, Vasan S. Ramachandran, Paul L. Kimmel, Chi-yuan Hsu, Kathleen D. Liu, for the CKD Biomarkers Consortium. **Urinary Biomarkers and Risk of ESRD in the Atherosclerosis Risk in Communities Study.** Clin J Am Soc Nephrol. 2015 Nov 6;10(11):1956-63. PMC4633784

Liver fatty acid binding protein (L-FABP), kidney injury molecule 1 (KIM-1), N-acetyl-β-d-glucosaminidase (NAG), and neutrophil gelatinase-associated lipocalin (NGAL) are urinary markers of tubular injury that may also be markers of chronic kidneydamage. We evaluated the association of these markers with incident ESRD in a community-based sample from the Atherosclerosis Risk inCommunities Study. This was a matched case-control study of 135 patients with ESRD and 186 controls who were matched on sex, race, kidney function, and diabetes status at baseline (Atherosclerosis Risk in Communities Study visit 4, 1996-1998).Urinary KIM-1 indexed to creatinine (Cr), NAG/Cr, NGAL/Cr, and L-FABP/Cr were measured in stored spot urine samples from the baseline examination. Associations of KIM-1/Cr, NAG/Cr, and NGAL/Cr with patients with incident ESRD through 2008 were modeled continuously and categorically (quartiles) using conditional logistic regression. L-FABP/Cr was modeled only categorically because of a large number of measurements below the lower limit of detection for the assay (2.4 ng/ml). Elevated urinary KIM-1/Cr may be associated with a higher risk of incident ESRD, but it does not add to risk prediction after accounting for traditional markers of kidney function in this population.
Read the article > >

Nisha Bansal, Myra A. Carpenter, Daniel E. Weiner, Andrew S. Levey, Marc Pfeffer, John W. Kusek, Jianwen Cai, Lawrence G. Hunsicker, Meyeon Park, Michael Bennett, Kathleen D. Liu and Chi-yuan Hsu. **Urine Injury Biomarkers and Risk of Adverse Outcomes in Recipients of Prevalent Kidney Transplants: The Folic Acid for Vascular Outcome Reduction in Transplantation Trial.** J Am Soc Nephrol. 2015 Nov 4. [Epub ahead of print]

Recipients of kidney transplants (KTR) are at increased risk for cardiovascular events, graft failure, and death. It is unknown whether urine kidney injury biomarkers are associated with poor outcomes among KTRs. We conducted a *post hoc* analysis of the Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT) Trial using a case-cohort study design, selecting participants with adjudicated cardiovascular events, graft failure, or death. Urine neutrophil gelatinase–associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), IL-18, and liver–type fatty acid binding protein (L-FABP) were measured in spot urine samples and standardized to urine creatinine concentration. We adjusted for demographics, cardiovascular risk factors, eGFR, and urine albumin-to-creatinine ratio. Patients had 291 cardiovascular events, 257 graft failure events, and 359 deaths. Each log increase in urine NGAL/creatinine independently associated with a 24% greater risk of cardiovascular events (adjusted hazard ratio [aHR], 1.24; 95% confidence interval [95% CI], 1.06 to 1.45), a 40% greater risk of graft failure (aHR, 1.40; 95% CI, 1.16 to 1.68), and a 44% greater risk of death (aHR, 1.44; 95% CI, 1.26 to 1.65). Urine KIM-1/creatinine and IL-18/creatinine independently associated with greater risk of death (aHR, 1.29; 95% CI, 1.03 to 1.61 and aHR, 1.25; 95% CI, 1.04 to 1.49 per log increase, respectively) but not with risk of cardiovascular events or graft failure. Urine L-FABP did not associate with any study outcomes. In conclusion, among prevalent KTRs, higher urine NGAL, KIM-1, and IL-18 levels independently and differentially associated with greater risk of adverse outcomes.
Read the article > >

Ana Malvar, Paola Pirruccio, Valeria Alberton, Bruno Lococo, Cecilia Recalde, Bernanda Fazini, Haikady Nagaraja, Divya Indrakanti and Brad H. Rovin. **Histologic versus clinical remission in proliferative lupus nephritis. Nephrol Dial Transplant.** 2015 Aug 6. [Epub ahead of print] PMC4402379

Treatment response in lupus nephritis (LN) is defined clinically, without consideration of renal histology. Few studies have systematically examined histologic responses to induction therapy. In LN patients who underwent protocol kidney biopsies after induction immunosuppression, we describe the renal histology of the second biopsy and correlate histologic activity and damage with short- and long-term kidney outcomes. One-third of patients who achieved a complete clinical response after induction had persistently high histologic activity, and 62% of patients who had complete histologic remission on rebiopsy were still clinically active. Chronic renal damage increased after induction even in complete clinical responders. Chronicity at Biopsy 2 associated with long-term kidney function and development of chronic kidney disease. Early clinical and histologic outcomes are discordant in proliferative LN, and neither correlates with long-term renal outcome. The kidney accrues chronic damage rapidly and despite clinical response in LN. Preservation of kidney function may require therapeutic targeting of both chronic damage and inflammation during LN induction treatment. Read the article > >

Meredith C. Foster, Lesley A. Inker, Chi-yuan Hsu, John H. Eckfeldt, Andrew S. Levey, Meda E. Pavkov, Bryan D. Myers, Peter H. Bennett, Paul L. Kimmel, Ramachandran S. Vasan, Josef Coresh, MD, Robert G. Nelson, on behalf of the CKD Biomarkers Consortium. **Filtration markers as predictors of ESRD and mortality in Southwestern American Indians with type 2 diabetes.** Am J Kidney Dis. 2015 Jul;66(1):75-83. PMC4485524

> A growing number of serum filtration markers are associated with mortality and end-stage renal disease (ESRD) in adults. Whether β-trace protein (BTP) and β2-microglobulin (B2M) are associated with these outcomes in adults with type 2 diabetes is not known. During a median follow-up of 14 years, 69 participants developed ESRD and 95 died. Both novel markers were associated with ESRD in multivariable models. BTP level remained statistically significant after further adjustment for mGFR (1/BTP, 1.53 [95% CI, 1.01-2.30]; 1/B2M, 1.54 [95% CI, 0.98-2.42]). B2M level was associated with mortality in multivariable models and after further adjustment for mGFR (HR, 2.12; 95% CI, 1.38-3.26). The addition of B2M level to established markers increased the C statistic for mortality but only weakly when assessed by either continuous net reclassification improvement or RIDI; none was improved for ESRD by the addition of these markers. In Pima Indians with type 2 diabetes, BTP and, to a lesser extent, B2M levels were associated with ESRD. B2M level was associated with mortality after adjustment for traditional risk factors and established filtration markers. Further studies are warranted to confirm whether inclusion of B2M level in a multimarker approach leads to improved risk prediction for mortality in this population. Read the article > >

Casey M. Rebholz, Morgan E. Grams, Kunihiro Matsushita, Lesley A. Inker, Meredith C. Foster, Andrew S. Levey, Elizabeth Selvin, Josef Coresh. **Change in Multiple Filtration Markers and Subsequent Risk of Cardiovascular Disease and Mortality.** Clin J Am Soc Nephrol. 2015 Jun 5;10(6):941-8. PMC4455217

> Kidney disease progression, assessed by change in eGFR on the basis of creatinine, is an independent riskfactor for cardiovascular disease and death. This study aimed to evaluate whether changes in multiple filtration markers, individually and combined, were associated with cardiovascular disease and death. During a median follow-up of 14 years, there were 1922 cardiovascular events and 2285 deaths from any cause. Decline of >30% in each filtration marker was significantly associated with higher risk of mortality compared with stable kidney function (-9.9% to +9.9% change in thefiltration marker) with hazard ratios (95% confidence intervals) of 1.91 (1.67 to 2.18) for eGFR on the basis of creatinine, 2.29 (1.99 to 2.63) for eGFR on the basis of cystatin C, and 2.48 (2.15 to 2.86) for 1/β2-microglobulin, with similar associations for cardiovascular disease. An average decline of >30% across the three markers was strongly associated with higher risk of all-cause mortality (hazard ratio, 2.82; 95% confidence interval, 2.42 to 3.29). Kidney disease progression was assessed using >30% decline in eGFR on the basis of creatinine, eGFR on the basis of cystatin C, and 1/β2-microglobulin and average decline of >30% across the three filtration markers is strongly associated with risk of cardiovascular disease and death. Read the article > >

Chi-yuan Hsu, Shawn Ballard, Daniel Batlle, Joseph V. Bonventre, Erwin P. Böttinger, Harold I. Feldman, Jon B. Klein, Josef Coresh, John H. Eckfeldt, Lesley A. Inker, Paul L. Kimmel, John W. Kusek, Kathleen D. Liu, Michael Mauer, Theodore E. Mifflin, Mark E. Molitch, Gary L. Nelsestuen, Casey M. Rebholz, Brad H. Rovin, Venkata S. Sabbisetti, Jennifer E. Van Eyk , Ramachandran S. Vasan, Sushrut S. Waikar, Krista M. Whitehead, Robert G. Nelson for the CKD Biomarkers Consortium. **Cross-Disciplinary Biomarkers Research: Lessons Learned by the CKD Biomarkers Consortium.** CJASN ePress. 2015 May 7;10(5):894-902. PMC4422251

> Significant advances are needed to improve the diagnosis, prognosis, and management of persons withCKD. Discovery of new biomarkers and improvements in currently available biomarkers for CKD hold great promise to achieve these necessary advances. Interest in identification and evaluation of biomarkers forCKD has increased substantially over the past decade. In 2009, the National Institute of Diabetes and Digestive and Kidney Diseases established the CKD Biomarkers Consortium(http://www.ckdbiomarkersconsortium.org/), a multidisciplinary, collaborative study group located at over a dozen academic medical centers. The main objective of the consortium was to evaluate new biomarkers for purposes related to CKD in established prospective cohorts, including those enriched for CKD. During the first 5 years of the consortium, many insights into collaborative biomarker research were gained that may be useful to other investigators involved in biomarkers research. These lessons learned are outlined in this Special Feature and include a wide range of issues related to biospecimen collection, storage, and retrieval, and the internal and external quality assessment of laboratories that performed the assays. The authors propose that investigations involving biomarker discovery and validation are greatly enhanced by establishing and following explicit quality control metrics, including the use of blind replicate and proficiency samples, by carefully considering the conditions under which specimens are collected, handled, and stored, and by conducting pilot and feasibility studies when there are concerns about the condition of the specimens or the accuracy or reproducibility of the assays. Read the article > >

Gudeta D. Fufaa, E. Jennifer Weil, Robert G. Nelson, Robert L. Hanson, William C. Knowler, Brad H. Rovin, Haifeng Wu, Jon B. Klein, Theodore E. Mifflin, Harold I. Feldman, Vasan S. Ramachandran, Paul L. Kimmel, John W. Kusek and Michael Mauer for the CKD Biomarkers Consortium and the RASS Investigators. **Urinary monocyte chemoattractant protein-1 and hepcidin and early diabetic nephropathy lesions in type 1 diabetes mellitus.** Nephrol Dial Transplant. 2015 Feb 3. PMC4402379

> Urinary monocyte chemoattractant protein-1 (MCP-1) and hepcidin are potential biomarkers of renal inflammation. We examined their association with development of diabetic nephropathy (DN) lesions in normotensive normoalbuminuric subjects with type 1 diabetes (T1D) from the Renin-Angiotensin System Study. Biomarker concentrations were measured in baseline urine samples from 224 subjects who underwent kidney biopsies at baseline and after 5 years. Fifty-eight urine samples below the limit of quantitation (LOQ, 28.8 pg/mL) of the MCP-1 assay were assigned concentrations of LOQ/√2 for analysis. Relationships between ln(MCP-1/Cr) or ln(hepcidin/Cr) and morphometric variables were assessed by sex using multiple linear regression after adjustment for age, T1D duration, HbA1c, mean arterial pressure, albumin excretion rate (AER) and glomerular filtration rate (GFR). In models that examined changes in morphometric variables, the baseline morphometric value was also included. Baseline mean age was 24.6 years, mean duration of T1D 11.2 years, median AER 6.4 µg/min and mean iohexol GFR 129 mL/min/1.73 m2. No associations were found between hepcidin/Cr and morphometric variables. Higher MCP-1/Cr was associated with higher interstitial fractional volume at baseline and after 5 years in women (baseline partial r = 0.244, P = 0.024; 5-year partial r = 0.299, P = 0.005), but not in men (baseline partial r = -0.049, P = 0.678; 5-year partial r = 0.026, P = 0.830). MCP-1 was not associated with glomerular lesions in either sex. Elevated urinary MCP-1 concentration measured before clinical findings of DN in women with T1D was associated with changes inkidney interstitial volume, suggesting that inflammatory processes may be involved in the pathogenesis of early interstitial changes in DN. Read the article > >

Kathleen D. Liu, MD, PhD, Wei Yang, PhD, Alan S. Go, MD, Amanda H. Anderson, PhD, Harold I. Feldman, MD, MSCE, Michael J. Fischer, MD, MSPH, Jiang He, MD, PhD, Radhakrishna R. Kallem, MD, MPH, John W. Kusek, PhD, Stephen R. Master, MD, PhD, Edgar R. Miller III, MD, Sylvia E. Rosas, MD, Susan Steigerwalt, MD, Kaixiang Tao, PhD, Matthew R. Weir, MD, Chi-yuan Hsu, MD, MScemail on behalf of the CRIC Study Investigators. **Urine Neutrophil Gelatinase-Associated Lipocalin and Risk of Cardiovascular Disease and Death in CKD: Results From the Chronic Renal Insufficiency Cohort (CRIC) Study.** Am J Kidney Dis. 2015 Feb;65(2):267-74. PMC4353671

Chronic kidney disease is common and is associated with increased cardiovascular disease risk. Currently, markers of renal tubular injury are not used routinely to describe kidney health and little is known about the risk of cardiovascular events and death associated with these biomarkers independent of glomerular filtration-based markers (such as serum creatinine or albuminuria). 3,386 participants with estimated glomerular filtration rate of 20 to 70mL/min/1.73m^2 enrolled from June 2003 through August 2008. Adjudicated heart failure event, ischemic atherosclerotic event (myocardial infarction, ischemic stroke, or peripheral artery disease), and death through March 2011. Urine NGAL measured at baseline with a 2-step assay using chemiluminescent microparticle immunoassay technology on an ARCHITECT i2000SR (Abbott Laboratories). There were 428 heart failure events (during 16,383 person-years of follow-up), 361 ischemic atherosclerotic events (during 16,584 person-years of follow-up), and 522 deaths (during 18,214 person-years of follow-up). In Cox regression models adjusted for estimated glomerular filtration rate, albuminuria, demographics, traditional cardiovascular disease risk factors, and cardiac medications, higher urine NGAL levels remained associated independently with ischemic atherosclerotic events (adjusted HR for the highest [>49.5ng/mL] vs lowest [≤6.9ng/mL] quintile, 1.83 [95% CI, 1.20-2.81]; HR per 0.1-unit increase in log urine NGAL, 1.012 [95% CI, 1.001-1.023]), but not heart failure events or deaths. Among patients with chronic kidney disease, urine levels of NGAL, a marker of renal tubular injury, were associated independently with future ischemic atherosclerotic events, but not with heart failure events or deaths.
Read the article > >

Casey M. Rebholz, Morgan E. Grams, Josef Coresh, Elizabeth Selvin, Lesley A. Inker, Andrew S. Levey, Paul L. Kimmel, Ramachandran S. Vasan, John H. Eckfeldt, Harold I. Feldman, Chi-yuan Hsu, Pamela L. Lutsey, for the Chronic Kidney Disease Biomarkers Consortium. **Serum Fibroblast Growth Factor-23 Is Associated with Incident Kidney Disease.** J Am Soc Nephrol. 2015 Jan;26(1):192-200. PMC4279743

Fibroblast growth factor-23 is a bone-derived hormone that increases urinary phosphate excretion and inhibits hydroxylation of 25-hydroxyvitamin D. Recent studies suggest that fibroblast growth factor-23 may be an early biomarker of CKD progression. However, its role in kidney function decline in the general population is unknown. We assessed the relationship between baseline (1990-1992) serum levels of intact fibroblast growth factor-23 and incident ESRD in 13,448 Atherosclerosis Risk in communities study participants (56.1% women, 74.7% white) followed until December 31, 2010. At baseline, the mean age of participants was 56.9 years and the mean eGFR was 97 ml/min per 1.73 m^2. During a median follow-up of 19 years, 267 participants (2.0%) developed ESRD. After adjustment for demographic characteristics, baseline eGFR, traditional CKD risk factors, and markers of mineral metabolism, the highest fibroblast growth factor-23 quintile (>54.6 pg/ml) compared with the lowest quintile (<32.0 pg/ml) was associated withrisk of developing ESRD (hazard ratio, 2.10; 95% confidence interval, 1.31 to 3.36; trend P<0.001). In a large, community-based study comprising a broad range of kidney function, higher baseline fibroblast growth factor-23 levels were associated with increased risk of incident ESRD independent of the baseline level of kidney function and a number of other risk factors. Read the article > >

Gudeta D. Fufaa, E. Jennifer Weil, Robert G. Nelson, Robert L. Hanson, Joseph V. Bonventre, Venkata Sabbisetti, Sushrut S. Waikar, Theodore E. Mifflin, Xiaoming Zhang, Dawei Xie, Chi-yuan Hsu, Harold I. Feldman, Josef Coresh, Ramachandran S. Vasan, Paul L. Kimmel, Kathleen D. Liu, for the Chronic Kidney Disease Biomarkers Consortium Investigators. **Association of urinary KIM-1, L-FABP, NAG and NGAL with incident end-stage renal disease and mortality in American Indians with type 2 diabetes mellitus**. Diabetologia. 2015 Jan; 58 (1): 188-98. PMC4258130

> Kidney injury molecule 1 (KIM-1), liver fatty acid-binding protein (L-FABP), N-acetyl-β-D-glucosaminidase (NAG) and neutrophil gelatinase-associated lipocalin (NGAL) are urinary biomarkers of renal tubular injury. We examined their association with incident end-stage renaldisease (ESRD) and all-cause mortality in American Indians with type 2 diabetes. Biomarker concentrations were measured in baseline urine samples in 260 Pima Indians who were followed for a median of 14 years. HRs were reported per SD of creatinine (Cr)-normalised log-transformed KIM-1, NAG and NGAL, and for three categories of L-FABP. In Pima Indians with type 2 diabetes, urinary concentrations of NGAL and L-FABP are associated with important health outcomes, but they are unlikely to add to risk prediction with standard markers in a clinically meaningful way given the small increase in the c-statistic.
> Read the article > >

2014

Casey M. Rebholz, PhD, MS, MPH, Morgan E. Grams, MD, PhD, MHS, Kunihiro Matsushita,MD, PhD, Elizabeth Selvin, PhD, MPH, Josef Coresh, MD, PhD, MHS **Change in Novel Filtration Markers and Risk of ESRD.** Am J Kidney Dis. 2014 Dec 23. PMC4478244

> Chronic kidney disease progression is a risk factor for end-stage renal disease (ESRD). A 57% decline in creatinine-based estimated glomerular filtration rate (eGFR$_{cr}$) is an established surrogate outcome for ESRD in clinical trials, and a 30% decrease recently has been proposed as a surrogate end point. However, it is unclear whether change in novel filtration marker levels provides additional information for ESRDrisk to change in eGFR$_{cr}$. During a median follow-up of 13 years, there were 142 incident ESRD cases. In adjusted analysis, declines > 30% in eGFR$_{cr}$, eGFR$_{cys}$, and 1/B2M were associated significantly with ESRD compared with stable concentrations of filtration markers (HRs of 19.96 [95% CI, 11.73-33.96], 16.67 [95% CI, 10.27-27.06], and 22.53 [95% CI, 13.20-38.43], respectively). Using the average of declines in the 3 markers, >30% decline conferred higher ESRD risk than that for eGFR$_{cr}$ alone (HR, 31.97 [95% CI, 19.40-52.70; P=0.03] vs eGFR$_{cr}$). A >30% decline in kidney function assessed using novel filtration markers is associated strongly with ESRD, suggesting the potential utility of measuring change in cystatin C and B2M levels in settings in which improved outcome ascertainment is needed, such as clinical trials.
> Read the article > >

Venkata S. Sabbisetti, Sushrut S. Waikar, Daniel J. Antoine, Adam Smiles, Chang Wang, Abinaya Ravisankar, Kazumi Ito, Sahil Sharma, Swetha Ramadesikan, Michelle Lee, Rebeccah Briskin, Philip L. De Jager, Thanh Thu Ngo, Mark Radlinski, James W. Dear , Kevin B. Park, Rebecca Betensky, Andrzej S. Krolewski and Joseph V. Bonventre. **Blood Kidney Injury Molecule-1 Is a Biomarker of Acute and Chronic Kidney Injury and Predicts Progression to ESRD in Type I Diabetes.** J Am Soc Nephrol. 2014 Oct;25(10):2177-86. PMC4178434

> Currently, no blood biomarker that specifically indicates injury to the proximal tubule of the kidney has been identified. Kidney injury molecule-1 (KIM-1) is highly upregulated in proximal tubular cells following kidney injury. The ectodomain of KIM-1 is shed into the lumen, and serves as a urinary biomarker of kidney injury. We report that shed KIM-1 also serves as a blood biomarker of kidney injury. Sensitive assays to measure plasma and serum KIM-1 in mice, rats, and humans were developed and validated in the current study. Plasma KIM-1 levels increased with increasing periods of ischemia (10, 20, or 30 minutes) in mice, as early as 3 hours after reperfusion; after unilateral ureteral obstruction (day 7) in mice; and after gentamicin treatment (50 or 200 mg/kg for 10 days) in rats. In humans, plasma KIM-1 levels were higher in patients with AKI than in healthy controls or post-cardiac surgery patients without AKI (area under the curve, 0.96). In patients undergoing cardiopulmonary bypass, plasma KIM-1 levels increased within 2 days after surgery only in patients who developed AKI (P<0.01). Blood KIM-1 levels were also elevated in patients with CKD of varous etiologies. In a cohort of patients with type 1 diabetes and proteinuria, serum KIM-1 level at baseline strongly predicted rate of eGFR loss and risk of ESRD during 5-15 years of follow-up, after adjustment for baseline urinary albumin-to-creatinine ratio, eGFR, and Hb1Ac. These results identify KIM-1 as a blood biomarker that specifically reflects acute and chronic kidney injury. Read the article > >

Wenrui Hao, Brad H. Rovin, and Avner Friedmanc. **Mathematical model of renal interstitial fibrosis.** Proc Natl Acad Sci U S A. 2014 Sep 30;111(39):14193-8. PMC4191765

> Lupus nephritis (LN) is an autoimmune disease that occurs when autoantibodies complex with self-antigen and form immune complexes that accumulate in the glomeruli. These immune complexes initiate an inflammatory response resulting in glomerular injury. LN often concomitantly affects the tubulointerstitial compartment of the kidney, leading first to interstitial inflammation and subsequently to interstitial fibrosis and atrophy of the renal tubules if not appropriately treated. Presently the only way to assess interstitial inflammation and fibrosis is through kidney biopsy, which is invasive and cannot be repeated frequently. Hence, monitoring of disease progression and response to therapy is suboptimal. In this paper we describe a mathematical model of the progress from tubulointerstitial inflammation to fibrosis. We demonstrate how the model can be used to monitor treatments for interstitial fibrosis in LN with drugs currently being developed or used for nonrenal fibrosis. Read the article > >

Michael Mauer, Maria Luiza Caramori, Paola Fioretto and Behzad Najafian. **Glomerular structural-functional relationship models of diabetic nephropathy are robust in type 1 diabetic patients.** Nephrol Dial Transplant. 2014 Sep 1. [Epub ahead of print] PMC4438739

Studies of structural-functional relationships have improved understanding of the natural history of diabetic nephropathy (DN). However, in order to consider structural end points for clinical trials, the robustness of the resultant models needs to be verified. This study examined whether structural-functional relationship models derived from a large cohort of type 1 diabetic (T1D) patients with a wide range of renal function are robust. The predictability of models derived from multiple regression analysis and piecewise linear regression analysis was also compared. T1D patients (n = 161) with research renal biopsies were divided into two equal groups matched for albumin excretion rate (AER). Models to explain AER and glomerular filtration rate (GFR) by classical DN lesions in one group (T1D-model, or T1D-M) were applied to the other group (T1D-test, or T1D-T) and regression analyses were performed. T1D-M-derived models explained 70 and 63% of AER variance and 32 and 21% of GFR variance in T1D-M and T1D-T, respectively, supporting the substantial robustness of the models. Piecewise linear regression analyses substantially improved predictability of the models with 83% of AER variance and 66% of GFR variance explained by classical DN glomerular lesions alone. These studies demonstrate that DN structural-functional relationship models are robust, and if appropriate models are used, glomerular lesions alone explain a major proportion of AER and GFR variance in T1D patients. Read the article > >

2013

Meredith C. Foster, Lesley A. Inker, Andrew S. Levey, Elizabeth Selvin, John Eckfeldt, Stephen P. Juraschek, and Josef Coresh, on behalf of the CKD Biomarkers Consortium. **Novel Filtration Markers as Predictors of All-cause and Cardiovascular Mortality in US Adults.** Am J Kidney Dis. 2013 Jul;62(1):42-51. PMC4076821

New filtration markers, including β-trace protein (BTP) and $β_2$-microglobulin (B2M), may, similar to cystatin C, enable a stronger prediction of mortality compared to serum creatinine-based estimated glomerular filtration rate (eGFRcr). We sought to evaluate these mortality associations in a representative sample of US adults. 6,445 adults 20 years or older from the Third National Health and Nutrition Examination Survey (1988-1994) with mortality linkage through December 31, 2006. Serum cystatin C, BTP, and B2M levels and eGFRcr categorized into quintiles, with the highest quintile (lowest for eGFRcr) split into tertiles (subquintiles Q5a-Q5c). All-cause, cardiovascular disease, and coronary heart disease mortality. During follow-up, 2,392 deaths (cardiovascular, 1,079; coronary heart disease, 605) occurred. Levels of all 4 filtration markers were associated with mortality risk after adjusting for demographics (P trend<0.02). Adjusted for mortality risk factors, compared to the middle quintile, the highest subquintiles for cystatin C (Q5c: HR, 1.94; 95% CI, 1.43-2.62), BTP (Q5c: HR, 2.14; 95% CI, 1.56-2.94), and B2M (Q5c: HR, 2.58; 95% CI, 1.96-3.41) were associated with increased all-cause mortality risk, whereas the association was weaker for eGFRcr (Q5c: HR, 1.31; 95% CI, 0.84-2.04). Associations persisted for the novel markers and not for eGFRcr at eGFRcr ≥60 mL/min/1.73 m². Trends were similar for cardiovascular disease and coronary heart disease mortality. The strong association of cystatin C level with mortality compared with serum creatinine estimates is shared by BTP and B2M. This supports the utility of alternative filtration markers beyond creatinine when improved risk prediction related to decreased GFR is needed. Read the article > >

Kathleen D Liu, Wei Yang, Amanda H Anderson, Harold I Feldman, Sevag Demirjian, Takayuki Hamano, Jiang He, James Lash, Eva Lustigova, Sylvia E Rosas, Michael S Simonson, Kaixiang Tao, and Chi-yuan Hsu, on behalf of the Chronic Renal Insufficiency Cohort (CRIC) study investigators. **Urine neutrophil gelatinase-associated lipocalin levels do not improve risk prediction of progressive chronic kidney disease.** Kidney Int. 2013 May;83(5):909-14. PMC3642209

Novel biomarkers may improve our ability to predict which patients with chronic kidney disease (CKD) are at higher risk for progressive loss of renal function. Here, we assessed the performance of urine neutrophil gelatinase-associated lipocalin (NGAL) for outcome prediction in a diverse cohort of 3386 patients with CKD in the Chronic Renal Insufficiency Cohort study. In this cohort, the baseline mean estimated glomerular filtration rate (eGFR) was 42.4 ml/min per 1.73 m(2), the median 24-h urine protein was 0.2 g/day, and the median urine NGAL concentration was 17.2 ng/ml. Over an average follow-up of 3.2 years, there were 689 cases in which the eGFR was decreased by half or incident end-stage renal disease developed. Even after accounting for eGFR, proteinuria, and other known CKD progression risk factors, urine NGAL remained a significant independent risk factor (Cox model hazard ratio 1.70 highest to lowest quartile). The association between baseline urine NGAL levels and risk of CKD progression was strongest in the first 2 years of biomarker measurement. Within this time frame, adding urine NGAL to a model that included eGFR, proteinuria, and other CKD progression risk factors led to net reclassification improvement of 24.7%, but the C-statistic remained nearly identical. Thus, while urineNGAL was an independent risk factor of progression among patients with established CKD of diverse etiology, it did not substantially improve prediction of outcome events.
Read the article > >

Samir V. Parikh, Haikady N. Nagaraja, Lee Hebert, Brad H. Rovin. **Renal Flare as a Predictor of Incident and Progressive CKD in Patients with Lupus Nephritis.** Clin J Am Soc Nephrol. 2014 Feb;9(2):279-84. PMC3913239

Renal flares are common in lupus nephritis. The impact of flares on the development of CKD in lupus nephritis was examined. A retrospective analysis of prospectively collected data from the Ohio Systemic Lupus Erythematosus (SLE) Study was conducted to determine if renal flares predispose to new CKD or progression of preexisting CKD. Patients in the Ohio SLE Study were followed from 2001 to 2009, with a median follow-up of 6 years. For this analysis, patients with biopsy-proven lupus nephritis and at least 3 years of follow-up were included (n=56). Frequency and duration of renal flares were compared between patients who never developed CKD (n=29) and patients who developed new CKD (n=12) and between patients with preexisting but stable CKD (n=7) and patients who progressed (n=8). Groups were also combined into good (no CKD and stable CKD) or poor (new CKD and progressive CKD) for analysis. The new CKD group had more renal flares per year compared with the no CKD group (median=0.56 flares/yr [range=0-2] versus median=0 flares/yr [range=0-1.4]; P<0.001). Additionally, the poor outcome group had more renal flares per year compared with the good outcome group (median=0.50 flares/yr [range=0-2] versus median=0 flares/yr [range=0-1.4]; P<0.001). New or progressive CKD was not preferentially associated with nephritic compared with proteinuric renal flares. Logistic regression showed that spending more than 30% of time in renal flare (odds ratio, 20; 95% confidence interval, 4.6 to 91.3; P<0.001) and age>35 years (odds ratio, 69; 95% confidence interval, 6.3 to 753.6; P<0.001) were independent predictors of the combined end point of developing new or progressive CKD. All four subjects over 35 years of age that spent over 30% of time in renal flare had a poor outcome. In patients with lupus nephritis, the relative duration of renal flare is an independent predictor of incident and progressive CKD.
Read the article > >

Michael L Merchant, Monika A Niewczas, Linda H Ficociello, Janice A Lukenbill, Daniel W Wilkey, Ming Li, Syed J Khundmiri, James H Warram, Andrzej S Krolewski and Jon B Klein. **Plasma kininogen and kininogen fragments are biomarkers of progressive renal decline in type 1 diabetes.** Kidney Int. 2013 Jun;83(6):1177-84. PMC4241022

The ability of microalbuminuria to predict early progressive renal function decline in type 1 diabetic patients has been questioned. To resolve this, we determined the plasma proteome differences between microalbuminuric patients with type 1 diabetes and stable renal function (controls) and patients at risk for early progressive renal function decline (cases) and asked whether these differences have value as surrogate biomarkers. Mass spectrometry was used to analyze small (<3 kDa) plasma peptides isolated from well-matched case and control plasma obtained at the beginning of an 8-12 year follow-up period. A Spearman analysis of plasma peptide abundance and the rate of renal function decline during follow-up identified seven masses with a significant negative correlation with early progressive renal function decline. Tandem mass spectrometry identified three fragments of high-molecular-weight kininogen. Increased plasma high-molecular-weight kininogen in the cases was confirmed by immunoblot. One peptide, des-Arg9-BK(1-8), induced Erk1/2 phosphorylation when added apically to two proximal tubular cell lines grown on permeable inserts. Thus, we have identified plasma protein fragments, some of which have biological activity with moderate to strong correlation, with early progressive renalfunction decline in microalbuminuric patients with type 1 diabetes. Other peptides are candidates for validation as candidate biomarkers of diabetes-associated renal dysfunction. Read the article > >