Original Paper

Prognostic Value of Urinary Calprotectin, NGAL and KIM-1 in Chronic Kidney Disease

Felix S. Seibert[a,b]   Maximilian Sitz[b]   Jürgen Passfall[c]   Martin Haesner[c]
Peter Laschinski[d]   Martin Buhl[d]   Frederic Bauer[a,b]   Nina Babel[a]
Nikolaos Pagonas[a,b]   Timm H. Westhoff[a,b]

[a]University Hospital Marien Hospital Herne, Medical Department I, Ruhr-University of Bochum, [b]Charité – Campus Benjamin Franklin, Department of Nephrology, Berlin, [c]Nierenzentrum Charlottenburg, Berlin, [d]KfH-Nierenzentrum Teltowkanalstraße, Berlin, Germany

Key Words

Chronic kidney disease • Calprotectin • NGAL • KIM-1

Abstract

Background/Aims: Urinary biomarkers like neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) do not only allow an early diagnosis of acute kidney injury, but also provide prognostic information in this setting. The present prospective study investigates, whether the urinary biomarkers NGAL, KIM-1 and calprotectin have prognostic information in chronic kidney disease (CKD) as well. ***Methods:*** Urinary calprotectin, NGAL and KIM-1 concentrations were assessed in a study population of 143 patients with stable CKD comprising diabetic and hypertensive nephropathy, glomerulonephritis/vasculitis, and autosomal dominant polycystic kidney disease. An eGFR fluctuation > 5ml/min/1.73m^2 in the past 12 months was defined as an exclusion criterion in order to exclude cases with acute on chronic kidney injury. Renal function was monitored for a median follow-up of 37 months. ***Results:*** In the overall study population, all the three biomarkers failed to predict ΔeGFR and ΔACR from baseline to follow-up in linear regression analysis adjusted for age, gender, and baseline eGFR. Contrarily, baseline ACR was significantly associated with ΔeGFR ($p<0.001$). In the subgroup of patients with vasculitis and glomerulonephritis, all the three biomarkers were significantly associated with ΔeGFR, with calprotectin having the highest regression coefficient. ***Conclusion:*** In contrast to the traditional biomarker "albuminuria", neither the inflammatory biomarker calprotectin, nor the tubular biomarkers NGAL and KIM-1, provide robust prognostic information on the loss or renal function in a heterogeneous CKD population. All of them, however, are candidate prognostic biomarkers in primarily inflammatory renal diseases.

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Dr. Felix S. Seibert

University Hospital Marien Hospital Herne, Ruhr-University Bochum, Medical Department I
Hölkeskampring 40, 44625 Herne (Germany)
Tel. + 49 2323 499 5149, Fax + 49 2323 499 3302, E-Mail felix.seibert@elisabethgruppe.de

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Introduction

More than a decade ago the American Society of Nephrology decided to set highest research priority to the discovery of new biomarkers of acute kidney injury (AKI). In the following years, several molecules like neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7) were identified. This allowed to identify patients at risk for AKI and to be able to initiate measures of renoprotection at an early stage of renal damage. Although one biomarker test (TIMP2•IGFBP7) has recently been approved by the Food and Drug Administration (FDA), no biomarker has proceeded to daily clinical practice so far, mainly due to the lack of a specific therapeutic consequence.

In recent years an alternative diagnostic use of two urinary biomarkers was identified: NGAL and calprotectin – a proinflammatory mediator protein of the innate immune system – have been shown to be helpful tools in the differentiation of prerenal and intrinsic AKI [1-5]. Since these two entities require diverging therapeutic measures, this finding appeared promising for daily clinical practice. Beyond the time-point of diagnosis and the differential diagnosis of AKI, biomarkers have proven prognostic value: they predict adverse outcome in both adult and pediatric AKI [6-11]. In pediatric AKI, urinary calprotectin and KIM-1 predict the need for renal replacement therapy. Urinary NGAL concentrations have a good diagnostic performance in predicting mortality in pediatric patients with AKI of heterogeneous aetiology [6]. In adults, it has been demonstrated that urine NGAL predicts severity of acute kidney injury after cardiac surgery and long-term renal outcome after treatment on an intensive-care unit [8, 10].

Whereas there is robust data for the prognostic value of urinary biomarkers in AKI, data are rare and very heterogeneous in chronic kidney disease (CKD). Several reasons can be envisioned for this heterogeneity: First, urinary biomarkers detect tubular injury, not tubular atrophy. Thus, acute on chronic kidney injury might have impeded previous evaluations. Second, tubular biomarkers are not able to reflect glomerular and inflammatory aspects of a renal disease. Hence, the present prospective study compares the potency of the traditional glomerular biomarker "albuminuria" to the tubular biomarkers NGAL and KIM-1 and – for the first time – the inflammatory biomarker calprotectin to predict the progression of CKD over a three year follow-up.

Materials and Methods

Study design and protocol

The present work constitutes a prospective multicenter study at two different nephrological offices in Berlin, Germany. This study was approved by the local ethics committee of the Charité – University Hospital Berlin and by the ethics committee of the Ruhr-University of Bochum. All patients provided a written informed consent. 143 patients with stable CKD were enrolled. CKD was defined according to KDIGO criteria [12]. CKD was regarded "stable", if glomerular filtration rate (eGFR, MDRD formula) differed ≤ 5 ml/min per 1.73 m^2 within the past 12 months. We refrained from including subjects with a higher deterioration of eGFR in order to reliably exclude any states of acute on chronic kidney injury. Exclusion criteria were obstructive uropathy, urothelial carcinoma, metastatic cancer and pyuria. Aetiological entities were diabetes, hypertension, combined hypertension and diabetes (no clear attribution to one of these two entities as primary aetiological entity), autosomal-dominant polycystic kidney disease (ADPKD), glomerulonephritis/vasculitis or "others". Glomerulonephritis/vasculitis comprised subjects with lupus nephritis, crescentic glomerulonephritis due to polyangiitis with granulomatosis, membranous glomerulonephritis, IgA-nephropathy and mesangioproliferative glomerulonephritis in Schönlein-Henoch purpura, focal segmental glomerulosclerosis, and glomerulonephritis of unknown origin. Renal outcome was monitored for 20 to 39 months.

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Measurement of urinary NGAL, KIM-1, calprotectin and albumin concentrations

Urine samples (10 ml) were collected and stored frozen (-20°C) until assessment of biomarker concentrations took place. Urinary concentrations of NGAL and KIM-1 were assessed by ELISA (BPD-KIT-036 from BioPorto Diagnostics and ADI-900-226-0001 from Enzo Life Science, respectively). Urine concentrations of calprotectin were quantified using an enzyme-linked immunosorbent assay (ELISA) kit (PhiCal® Calprotectin, catalogue number K 6928, Immundiagnostik AG, Bensheim, Germany) according to the manufacturer's protocol as published previously [1, 2, 13]. Albuminuria was documented as albumin-creatinine ratio (ACR).

Statistical analysis

Data were analysed for Gaussian distribution (D'Agostino Pearson). Due to a non-Gaussian distribution, data was analyzed non-parametrically. Data are presented as median and interquartile range. Bravaris-Pearson correlation was performed to analyse the correlation of individual biomarker concentration with baseline ACR or eGFR. Prospective associations of urinary calprotectin, NGAL, KIM-1 and ACR with ΔeGFR and ΔACR at follow-up were determined by multiple hierarchical linear regression in the presence of age, gender and eGFR at baseline for both the overall study population and the subgroup of subjects with inflammatory renal diseases (glomerulonephritis/vasculitis). $P < 0.05$ was regarded statistically significant. All statistical analyses were performed using Prism 6 (GraphPad Software, La Jolla, CA, USA) and SPSS Statistics 25 (SPSS Inc., Chicago, IL, USA).

Results

143 subjects with CKD were enrolled in the prospective study including 29 female and 114 male patients with a median age of 72 (IQR 67-77). Median follow-up was 37 months (IQR 27-38). Diabetes and hypertension were the main aetiologies of CKD in 41 (28.7%) and 42 (29.4%) patients, respectively. In 19 subjects (13.3%) a combination of diabetes and hypertension was regarded as the primary cause of CKD without a preference of one of the two entities. 7 patients (4.9%) suffered from ADPKD and 15 from glomerulonephritis/ vasculitis (10.5%). Nineteen subjects were affiliated to "others" (13.3%). The epidemiological characteristics, the underlying aetiology of CKD, medication, and data on renal function as well biomarker concentrations are presented in Table 1. Assessment of urinary calprotectin, NGAL and KIM-1 was successful in the whole study population.

Table 1. Characteristics of study population. CKD – chronic kidney disease, classification according to KDIGO; eGFR – estimated glomerular filtration rate, calculated according to MDRD formula; CKD stages are expressed corresponding to KDIGO; NGAL - Neutrophil gelatinase-associated lipocalin; KIM-1 – Kidney Injury Molecule-1; ACE-I – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; IQR – interquartile range; BMI – body mass index

Characteristics	Value	Underlying aetiology of CKD		Medication	
Female	29 (20.3%)	Diabetes	41 (28.7%)	ACE-I/ARB	113 (79%)
Male	114 (79.7%)	Hypertension	42 (29.4%)	Diuretics	101 (70.6%)
Age (years)	72 (IQR 67-77)	Comb. diabetes and hypertension	19 (13.3%)	Immunosuppressives	9 (6.3%)
Body mass index (kg/m²)	28.2 (IQR 25.5-32.4)	Autosomal-dominant polycystic kidney disease	7 (4.9%)		
eGFR (ml/min/1.73m²)	39.2 (IQR 39.1-48.9)	Glomerulonephritis/vasculitis	15 (10.5%)		
		Others	19 (13.3%)		
CKD stage	n	Calprotectin (ng/ml)	NGAL (pg/ml)	KIM-1 (pg/ml)	
G1 A1-3	3 (2.1%)	317.5 (10-5957)	22834 (5404-69512)	1442 (1016-5455)	
G2 A1-3	6 (4.2%)	515.3 (17.6-1535)	6682 (4635-63175)	823 (441.5-3637)	
G3a A1-3	39 (27.3%)	95.4 (42.7-324.8)	10915 (4359-18534)	833 (386-1638)	
G3b A1-3	68 (47.6%)	68.3 (21.2-422.8)	11396 (5313-21923)	1011 (413.6-2718)	
G4 A1-3	27 (18.9%)	139.1 (63.7-448.3)	17476 (10571-37811)	1536 (834.4-3277)	
G5 A1-3	0 (0.0%)				
Overall CKD population	143	98.58 (37.8-425.8)	12015 (5658-23448)	1040 (501.9-2672)	

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Urinary calprotectin

Concentrations showed a significant but weak correlation with eGFR at baseline (r=0.259, r^2=0.067, p=0.0018), but not with ACR (r=-0.029, p=0.749; Fig. 1). It was neither able to predict ΔeGFR, nor ΔACR at follow-up (p=0.234 and p=0.875, respectively; Table 2). With regard to calprotectin's proinflammatory function, linear regression analysis was repeated in the subgroup of patients with primarily inflammatory renal disease (glomerulonephritis, vasculitis). In this group, calprotectin had a high predictive value for ΔeGFR (β=2.125, p=0.003), but not for ΔACR (p=0.776).

Urinary NGAL

NGAL was not associated with eGFR (r=-0.153, p=0.067) and did not correlate with ACR (r=0.034, p=0.705; Fig. 1) at baseline. NGAL was not associated with ΔeGFR or ΔACR at follow-up in the overall study population (p=0.907 and p=0.962, respectively; Table 2). In the subgroup analysis for inflammatory entities NGAL showed a significant predictive association for ΔeGFR (β=1.102, p=0.009), but not for ΔACR (p=0.473).

Table 2. Multiple regression for the association of urinary biomarkers with ΔeGFR and ΔACR adjusted for age, gender and baseline eGFR in the overall study population and the subgroup of inflammatory renal diseases (glomerulonephritis/vasculitis) at a follow-up of 3 years

Biomarkers	b	SE b	Coefficient (β)	p
	ΔeGFR			
Calprotectin				
Overall study population	-0.001	-0.001	-0.135	0.234
Glomerulonephritis/vasculitis	0.011	0.002	2.125	0.003
NGAL				
Overall study population	-1.39×10^{-6}	1×10^{-5}	-0.012	0.907
Glomerulonephritis/vasculitis	4.92×10^{-4}	1.36×10^{-4}	1.102	0.009
KIM-1				
Overall study population	2×10^{-4}	3×10^{-4}	0.073	0.454
Glomerulonephritis/vasculitis	0.004	0.001	0.836	0.012
ACR				
Overall study population	0.006	0.002	-0.403	<0.001
Glomerulonephritis/vasculitis	2.86×10^{-4}	0.003	0.022	0.935
	ΔACR			
Calprotectin				
Overall study population	0.014	0.089	0.019	0.875
Glomerulonephritis/vasculitis	1.162	3.373	4.439	0.776
NGAL				
Overall study population	-6.34×10^{-5}	0.001	-0.005	0.962
Glomerulonephritis/vasculitis	-0.023	0.028	-0.915	0.473
KIM-1				
Overall study population	0.004	0.025	0.016	0.876
Glomerulonephritis/vasculitis	-1.192	0.408	-3.825	0.061
ACR				
Overall study population	0.480	0.153	0.320	0.002
Glomerulonephritis/vasculitis	-0.880	0.103	-0.964	0.003

Urinary KIM-1

Urinary concentrations of KIM-1 did neither correlate with ACR (r=0.079, p=0.375) nor with eGFR (r=-0.117, p=0.167; Fig. 1) at baseline. KIM-1 concentrations were not significantly associated with ΔeGFR or ΔACR at follow-up in the overall study population (p=0.454 and p=0.876, respectively; Table 2). In the subgroup of glomerulonephritis/vasculitis KIM-1 showed a significant predictive association for ΔeGFR (β=0.836, p=0.012), but not for ΔACR (p=0.061).

Albuminuria

Baseline ACR showed a highly significant predictive value for ΔeGFR and ΔACR from baseline to follow-up (β=-0.403, p<0.001 and β=0.320, p=0.002, respectively, Table 2). ACR failed to predict ΔeGFR (p=0.935) in the subgroup analysis for inflammatory entities. It showed, however, a high predictive value for ΔACR (β=-0.964, p=0.003).
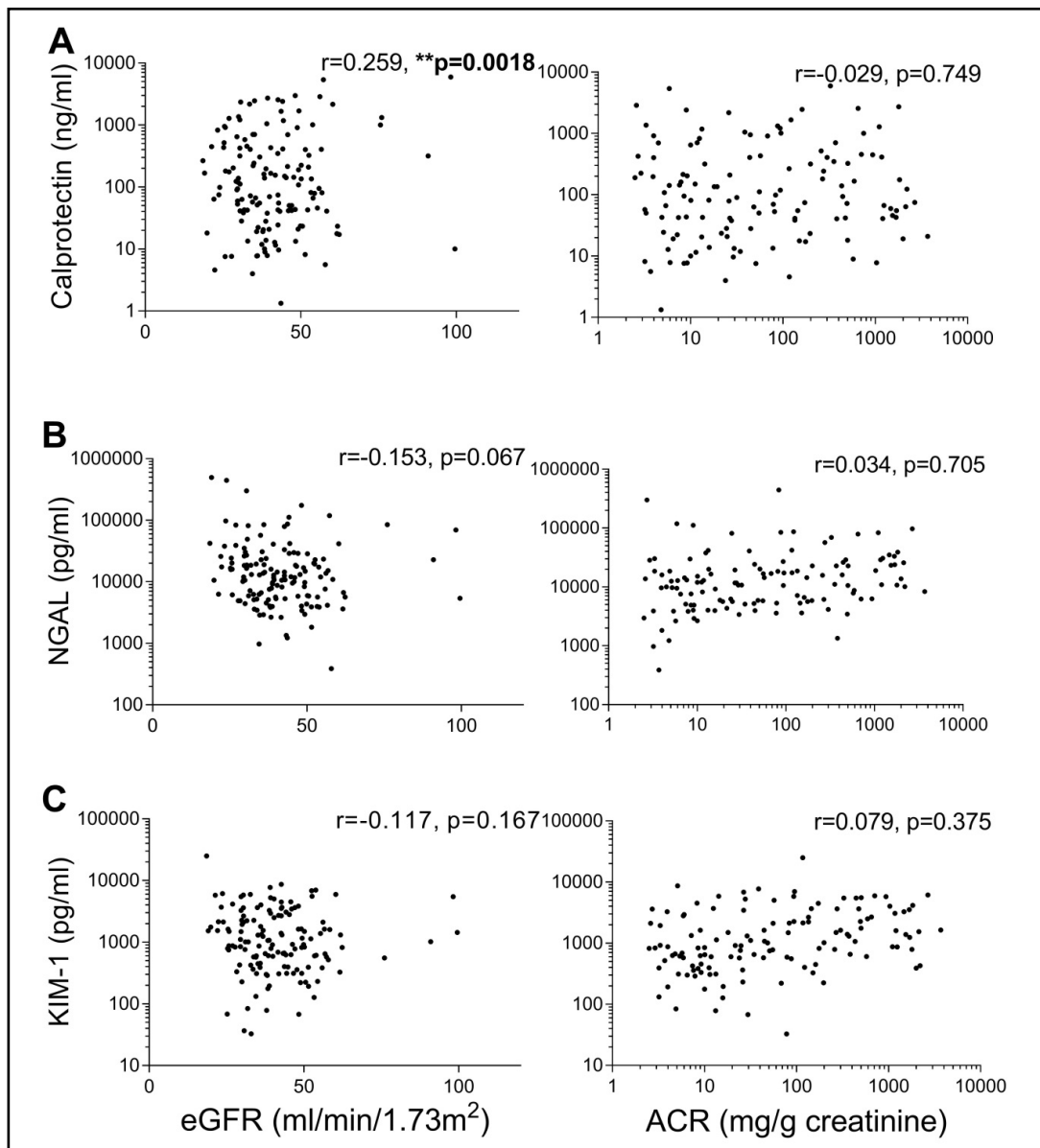
Discussion

Beyond the potential to identify renal damage prior to a rise in serum creatinine, some urinary biomarkers have proven valuable for the prediction of adverse outcome in AKI [1, 2, 13, 14]. The present work reveals, that this prognostic potential does not exist in the same universal way for the heterogeneous population of CKD.

The prognostic use of urinary NGAL and KIM-1 in CKD has been examined before. The findings of these reports, however, are conflicting. On the one hand, a prognostic value was reported in some subgroups of CKD including IgA nephropathy. On the other hand, they failed

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Fig. 1. Correlation analysis for eGFR and ACR at baseline regarding the individual urinary biomarker concentrations of (A) calprotectin, (B) NGAL and (C) KIM-1. NGAL – Neutrophil gelatinase-associated lipocalin; KIM-1 – Kidney Injury Molecule-1; ACR – albumin/creatinine ratio.

to predict the decline of renal function in other populations [15-20]. The reasons for the heterogeneity of these results are incompletely understood and comprise potential states of acute on chronic injury and differences in the underlying aetiologies.

In the present study, urinary calprotectin concentrations were associated with baseline eGFR. However, due to the very weak correlation, we do not see any clinical relevance. None of the three biomarkers provided a predictive value for the deterioration of renal function in this heterogeneous "real life CKD population". Noteworthy, the old traditional glomerular biomarker "albuminuria" outperformed the prognostic performance of the three new biomarkers by far.

NGAL is expressed at very low concentrations in different cell types. It is highly upregulated on mRNA and protein level in the distal tubule following ischemic or toxic kidney injury [21]. Accordingly, KIM-1 is expressed at low levels in the normal kidney as

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well as in other organs, but its expression is dramatically up-regulated in the proximal tubules after ischemia/reperfusion injury [22]. Thus, both of them are markers of kidney injury located at the tubules. The present work and the above mentioned studies, however, aimed to characterize their potency in chronic kidney disease. Hence, it is mandatory to try to exclude acute on chronic kidney injury. In contrast to previous studies, the present study therefore precluded subjects with an eGFR loss > 5ml in the 12 months prior to inclusion in the study. Acute tubular injury in preexisting CKD is one of the potential explanations for the conflicting data of previous data on this issue. The role of NGAL and KIM-1 in kidney disease is reminiscent to the diagnostic information of transaminases in liver disease: An acute injury of the hepatocytes is associated with an increase of serum transaminases, e. g. in hepatitis or shock. Liver cirrhosis, in contrast, is characterized by fibrosis and not by acute epithelial cell degradation. It therefore does not mandatorily lead to increased serum concentrations of transaminases. In analogy, NGAL and KIM-1 are sensitive biomarkers for acute tubular injury, but not for tubular atrophy.

To extend the focus of urinary biomarkers beyond the tubules, the present study investigated the prognostic potential of calprotectin as an inflammatory biomarker for the first time. In analogy to the tubular biomarkers, however, calprotectin failed to provide prognostic information in the overall CKD population as well. Noteworthy, the study population constituted a mixture of inflammatory and non-inflammatory kidney diseases. Immunohistochemistry findings revealed that the predominant source of urinary calprotectin is not the epithelial tubular cell but inflammatory cells in the interstitium [1, 3]. Hence, the extent of tubulointerstitial inflammation did not predict the progression of CKD in the overall population. Thus, the most likely explanation for the lack of prognostic information of the investigated biomarkers may be found in the nature of the underlying renal diseases: Diabetic and hypertensive nephropathy are primarily glomerular diseases. As long as there is a low degree of accompanying tubulointerstitial damage or inflammation, these biomarkers are unable to reflect the prognosis of the disease.

In accordance with this assumption, calprotectin predicted the loss of eGFR over three years in the subgroup of patients with glomerulonephritis or vasculitis. As a mediator protein of the innate immune system its prognostic value is obviously limited to inflammatory diseases. Although presenting a lower statistical power than calprotectin, the tubular biomarkers NGAL and KIM-1 revealed a predictive value in this subgroup as well. In this context, NGAL and KIM-1 concentrations most likely reflect the tubular damage associated with the collateral tubulointerstitial inflammation in glomerulonephritis/vasculitis. In accordance with this finding, KIM-1 has proven valuable for the prediction of adverse outcome in IgA nephropathy as an example for inflammatory renal diseases before [17].

The present trial design differed from previous ones on the prognostic value of biomarkers in CKD in several aspects. First, the study provides information on both a heterogeneous "real life" CKD population and a subgroup of inflammatory renal diseases. Second, states of acute on chronic disease were excluded. Third, it tested the prognostic value of an inflammatory biomarker in addition to tubular biomarkers. The study is limited by the sample size of subjects with inflammatory kidney diseases. Future studies addressing this specific CKD population should be welcomed.

Conclusion

Neither the tubular biomarkers NGAL and KIM-1, nor the inflammatory biomarker calprotectin were able to predict renal function in a heterogeneous CKD population over a three-year period. The prognostic potency seems to be restricted to inflammatory diseases like glomerulonephritis and vasculitis. Albumin, as the traditional glomerular biomarker, exceeds the prognostic performance of these new kids on the block by far and remains the gold standard of prognostic urinary biomarkers in CKD.

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Disclosure Statement

Patent for "Assay method for intrinsic acute kidney injury" is granted.

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