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Proenkephalin: A New Biomarker for Glomerular Filtration Rate and Acute Kidney Injury

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Abstract
Assessment of kidney function is primarily based on urine output and Creatinine (Cr)-based methods to estimate glomerular filtration rate (GFR). The latter is confounded as Cr is not exclusively filtered by the kidney and rises relatively late after the onset of acute kidney injury (AKI). This leads to delays in recognition of reduced kidney function and diagnosis of AKI, particularly in critically ill patients where kidney function can change rapidly. The gold standard methods of GFR determination, such as inulin or iohexol clearance, are labor intensive and unfeasible in acute clinical settings. Proenkephalin A 119–159 (PENK) has been intensively studied as a novel biomarker of kidney function. PENK belongs to the enkephalin peptide family and is freely filtrated in the glomerulus. Plasma PENK concentration appears to correlate strongly with GFR. Moreover, increased plasma PENK concentrations are found to be associated with long-term kidney outcomes and mortality. In this review, we summarize the role of PENK in assessment of kidney function and its capacity to predict various clinical outcomes.

Introduction

Acute kidney injury (AKI) is common and strongly associated with adverse outcomes [1]. Next to a reduction in urine output, AKI is currently defined on the basis of increasing serum Cr concentrations as a surrogate measure for glomerular filtration rate (GFR). However, serum Cr is notoriously unreliable as it is affected by confounding factors such as volume status, muscle mass and metabolism, nutrition, and medication [2]. Furthermore, because of a long half-life of Cr and active secretion in renal tubules, concentrations increase late after reduction of GFR, leading to delays in detection of an acute decrease in renal function. As a result, Cr-based methods of GFR estimations are not validated in non-steady-state settings where kidney function can change rapidly [3]. Due to these limitations, multiple novel biomarkers are being in-

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vestigated to fulfill the unmet medical need for an accurate biomarker for kidney function in non-steady-state situations.

Proenkephalin A 119–159 (PENK) has recently been described as an accurate biomarker of kidney function, as sensitive in detection of AKI, and as being associated with impaired outcomes in various clinical settings, including critical illness, sepsis, heart failure, CKD, and in kidney transplant recipients and donors [4–13]. In this review, we summarize the role of PENK in assessment of kidney function and its association with clinical outcomes.

Enkephalins and the Kidney

Preproenkephalin A is the precursor molecule of the enkephalin family. Cleavage of this pro-peptide yields PENK and several biologically active enkephalins, including met-enkephalin and leu-enkephalin. Enkephalins are endogenous opioids that are widely expressed and act primarily on delta opioid receptors [14]. Intriguingly, the highest density of delta opioid receptors, second to the central nervous system, is found in the kidney [15]. While the exact function of enkephalins on the kidney is not fully known, human and animal studies suggest a possible regulatory role on kidney function such as inducing diuresis and natriuresis through receptor agonism [16] or inhibiting antidiuretic hormone [17]. A compensatory upregulation, decrease in clearance, or both may account for the increase in met-enkephalin levels in patients with renal disease [18]. Biologically active enkephalins are difficult to measure due to their short half-lives and instability after collection [19, 20]. PENK has a long in vivo half-life, is stable after collection, and its levels are not influenced by age or sex [5], making it a suitable surrogate measure of its biologically active counterparts [21]. Furthermore, PENK is not protein bound in plasma and is exclusively filtrated in the glomerulus, making it an promising biomarker for kidney function in critically ill patients [4, 5].

PENK as a Biomarker of GFR

In various patient populations, plasma PENK concentrations strongly correlate with GFR (Table 1). Notably, PENK compared to Cr-based methods, appears to have a stronger correlation with the measured GFR (mGFR) in non-steady-state settings. In a study in septic shock patients, plasma PENK concentrations showed a very strong correlation with measured GFR using the gold standard iohexol plasma clearance ($mGFR_{iohexitol}$) ($R^2 = 0.90$, $p < 0.0001$) [7]. In the same study, there was considerable variability and bias in the Cr-based GFR estimations; the $eGFR_{MDRD}$ overestimated the true GFR with 31 ± 35% (95% limits of agreement: −37 to 100%) and the GFR_{ECC} with 37 ± 49% (95% limits of agreement: −59 to 133%). The true GFR appeared to be more accurately reflected by plasma PENK concentration compared to Cr-based methods. In a large study ($n = 1{,}191$) in potential kidney donors, post-kidney donors, patients with CKD, kidney transplant recipients, and other non-kidney solid organ transplant recipients, PENK correlated with measured GFR using iothalamate clearance ($\beta = -0.77$, $p < 0.0001$) [5]. Receiver operating curve analysis in the same cohort showed an area under the receiver operating curve (AUROC) of 0.86 ($p < 0.001$) for identification of patients with GFR < 60 mL/min/1.73 m^2.

The strong correlations between plasma PENK and mGFR indicate that PENK may be a suitable and accurate marker to estimate true GFR compared to current available methods. Furthermore, elevations in plasma PENK concentration appear to precede the rise in serum Cr concentrations [8, 22], which may make this novel biomarker particularly useful in critically ill patients whose kidney function may be changing rapidly. In combination with novel sensitive tubular injury markers, differentiating between rapid changes in GFR and actual renal damage can be combined. However, the signaling function of enkephalins or (patho)physiological situations that lead to an increased production of enkephalins are possible confounding factors.

PENK as a Biomarker of AKI

Association of PENK with AKI has been demonstrated in multiple cohorts of critically ill patients [4, 6, 9, 10, 23–25]. In a study of 956 patients with sepsis, PENK independently predicted the occurrence of AKI within 48 h and 7 days of admission (adjusted OR = 3.3; CI [2.1–5.1] and adjusted OR = 2.1; CI [1.7–2.8], respectively) [6]. The median PENK levels increased with AKI severity according to the Kidney Disease: Improving Global Outcomes stage and with the renal Sequential Organ Failure Assessment (rSOFA) score. In a subgroup analysis of 299 patients with eGFR > 70 mL/min/1.73 m^2 on admission, PENK levels were still associated with AKI (adjusted OR = 1.9; CI [1.0–3.4], $p = 0.04$). In another cohort of septic patients ($n = 644$), admission plasma PENK levels

Table 1. PENK evaluated as functional biomarker

Study	Population (*n*), renal situation	Compared with damage biomarker		Evaluated as functional biomarker			
		outcome parameter	outcome	outcome parameter	outcome		
Marino et al. [4]	Sepsis (101) Non-steady state	Diagnostic accuracy to detect AKI (RIFLE) compared with NGAL	Comparable accuracy was found	Correlation with Cr clearance	$r^2 = 0.52$, $p < 0.0001$		
			PENK: $\chi2 = 34.9$, $p < 0.001$, AUC = 0.82				
			NGAL: $\chi2 = 31.3$, $p < 0.001$, AUC = 0.80				
Kim et al. [23]	Sepsis (167) Non-steady state	PENK versus NGAL in detecting AKI (diagnosed with KDIGO), compared with eGFRs (MDRD and $CKD\text{-}EPI_{Cr/CystC/Cr\text{-}CystC)}$	AUC: PENK 0.725, NGAL 0.675, not statistically different. Nested logistic regression: PENK superior to NGAL ($p = 0.022$), PENK was not superior over $eGFR_{CysC}$ ($p = 0.473$)				
Matsue et al. [8]	Chronic heart failure Steady state	Association with NGAL and KIM-1	NGAL: $p = 0.563$	Association with RBF and GFR using 131I-hippuran and 123I-iothalamate	Stand β	*t*	*p*
			KIM-1: $p = 0.391$		GFR: −0.71	−9.59	<0.001
					RBF: −0.66	−7.30	<0.001
Gayat et al. [24]	Critically ill patients (200) Non-steady state	Nephrocheck® and PENK	AUROC: Nephrocheck: 0.697 (0.62–0.77)				
		ROC curve for biomarkers for AKI (KDIGO)	PENK: 0.832 (0.77–0.89)				
Caironi et al. [6]	Sepsis (956) Non-steady state			Correlation with Cr	Spearman $r = 0.74$, $p < 0.0001$		
Kieneker et al. [30]	Renal transplant recipients (664) Steady state			Recipients:	Recipients:		
				1. Correlation with $eGFR_{CKD\text{-}EPI}$	1. $r_s = -0.8$, $p < 0.001$		
	Kidney donors (95) Steady state			Donors:	Donors:		
				1. Correlation with $mGFR_{I125\text{-}iothalamate}$	1. mGFR $r_s = -0.74$, $p < 0.001$		
				2. Correlation with $eGFR_{CKD\text{-}EPI}$	2. $eGFR_{CKD\text{-}EPI}$ $r_s = -0.86$, $p < 0.001$		
				3. Correlation with Cr	3. Cr $r_s = 0.6$, $p < 0.001$		
Ng et al. [26]	Acute HF (1,098) Non-steady state			Correlation with eGFR	$r_s = -0.752$; $p < 0.0005$		
Kanagala et al. [27]	HFpEF (522) Steady state			Correlation with eGFR	$r_s = -0.741$; $p < 0.0005$		
Emmens et al. [12]	New onset or worsening HFpEF ($n = 2,189$) Non-steady state			Correlation with eGFR	eGFR $r_s = -0.68$; $p < 0.001$		
				Correlation with Cr	Cr: $r_s = 0.49$ $p < 0.001$		
Beunders et al. [7]	Sepsis (23) Non-steady state			Correlation with $mGFR_{iohexital}$	$GFR_{iohexol}$ $r^2 = 0.90$, $p < 0.0001$		

AKI, acute kidney injury; NGAL, neutrophil gelatinase-associated lipocalin; PENK, proenkephalin; AUC, area under the curve; (e)GFR, (estimated) glomerular filtration rate; KIM, kidney injury molecule; RBF, renal blood flow; Stand, standardized; AUROC, area under the receiver operating curve; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; KDIGO, Kidney Disease: Improving Global Outcomes; Cr, creatinine.

Table 2. Prediction of outcome [4, 6, 8–13, 23, 26, 29, 31–34]

Study	Population (*n*)	Outcome parameter	Outcome	Comments
Marino et al. [4]	Sepsis (101)	7-day mortality	PENK: $X^2 = 13.4$, $p < 0.001$, AUC = 0.69	PENK outperforms Cr clearance in predicting 7-day mortality
			Cr clearance: $X^2 = 4$	
			$p = 0.045$, AUC = 0.61	
Kim et al. [23]	Sepsis (167)	1. 30-day mortality	1. Optimal cutoff by ROC: HR = 3.9; CI (1.7–8.6)	1. PENK performed similar compared with eGFR calculations based son Cr and cystatin C. PENK performed better than NGAL
			Designated cutoff: HR = 7.9; CI (3.9–16.2)	
		2. Need for RRT	2. ROC: PENK, 0.87; NGAL, 0.74	2. Based on ROC curve analyses, PENK performed slightly better compared with NGAL
Schulz et al. [13]	Population-based cohort (2,568)	1. WRF	1. Greater than annual decline of GFR	1. PENK significantly predicted faster GFR decline and WRF
		2. Incidence of CKD	2. During 16.6-year follow-up: OR = 1.34; 95% CI (1.18–1.94)	2. Independently predicted incidence of CKD
Shah et al. [31]	Cardiac surgery (92)	AKI postoperative	OR = 23.8 ($p = 0.011$; 95% CI [2–270])	PENK significantly predicted AKI, similar to Cr baseline
Ng et al. [26]	Acute heart failure (1,908)	1. 1-year mortality	1. OR: independent predictor; $p < 0.0005$	1, 2. PENK predicted 1-year mortality and/or HF
		2. 1-year death and/or HF	2. HR = 1.27; 95% CI (1.10–1.45)	
		3. WRF	3. OR = 1.58; 95% CI (1.24–2.00); $p < 0.0005$	3. PENK independently predicted WRF
Matsue et al. [8]	Acute heart failure (1,589)	1. WRF	1. Predictor for WRF	1. WRF: No addition to existing renal marker
		2. 180-day mortality	2. Not independent predictor of prognosis in AHF	2. No predictor of prognosis in AHF
Arbit et al. [32]	Chronic heart failure (200)	MACE	Higher incidence of MACE: $p < 0.003$	High PENK predicted MACE
Ng et al. [33]	Acute myocardial infarction (1,141)	1. MACE	1, 2, 3: $p < 0.001$	1, 2, 3: High PENK associated with higher incidence of MACE, hospitalization, and mortality
		2. Hospitalization		
		3. 2-year mortality		
Caironi et al. [6]	Sepsis (956)	1. Incident AKI (KDIGO)	1. OR = 3.3; 95% CI (2.1–5.1); $p < 0.0001$	1. PENK independently predicted AKI
		2. Future RRT	2. $X^2 = 97.2$; $p < 0.0001$; AUC, 0.755; OR: standardized for an increase by one IQR, 4.0 (3.0–5.4)	2. PENK independently predicted future RRT
		3. Improvement in renal function	3. OR of 0.31 (0.18–0.54), $p < 0.0001$	3. Cr alone was significantly weaker in predicting renal improvement
		4. 90-day mortality	4. HR of 1.5 (1.2–1.8) for one IQR increase in PENK, $p < 0.0001$	4. PENK was independent predictor of 90-day mortality
Hollinger et al. [9]	Sepsis (583)	1. MAKE at 7 days (death, RRT, persistent AKI)	1, 2, 3: $p < 0.0001$	PENK predicted MAKE, AKI, WRF, and renal recovery. These results were validated in FROG-ICU cohort ($n = 526$)
		2. Transient AKI (KDIGO)		
		3. WRF		
Rosenqvist et al. [10]	Sepsis on emergency department (588)	1. Incident of AKI	1. $p < 0.001$	1. No longer significant after adjusting for eGFR
		2. Progression of rSOFA score from 0 to ≥1	2. OR = 3.2; CI (1.1–9.1); $p = 0.033$ (adjusted for eGFR)	2. PENK independently predicted progression of rSOFA score
		3. 28-day mortality	3. OR = 1.6; CI (1.1–2.3); $p = 0.02$ (adjusted for eGFR)	3. PENK independently predicted mortality. eGFR was not predictive of mortality

Table 2 (continued)

Study	Population (*n*)	Outcome parameter	Outcome	Comments
Kieneker et al. [30]	Renal transplant recipients (664)	1. Graft failure	1. HR = 2.36; 95% CI (1.37–4.06) (adjusted for eGFR)	1. PENK independently predicted graft failure
		2. All-cause mortality	2. HR = 1.34; 95% CI (0.90–2.09)	2. After adjusting for eGFR PENK did not independently predict mortality
Ng et al. [26]	Acute heart failure (1,908)	1. WRF	1, 2: $p < 0.0005$	PENK levels were prognostic of WRF and in-hospital mortality as well as mortality during 1-year follow-up
		2. Mortality at 1 year		
		3. Mortality and/or HF rehospitalization at 1 year	3. $p < 0.001$	
Kanagala et al. [27]	HFpEF (522)	All-cause mortality and/or HF rehospitalization at 2 years	HR = 1.45; 95% CI (1.13–2.33), $p = 0.009$	PENK independently predicted mortality and/or HF rehospitalization at 2 years
Molvin et al. [11]	Acute heart failure (530)	1. WRF	1. OR = 1.74; $p = 0.004$	PENK was an independent predictor of in-hospital mortality and WRF in AHF patients
		2. In-hospital mortality	2. OR = 2.24; $p < 0.001$	
Emmens et al. [12]	New or worsening heart failure (2,180)	1. WRF (>25% decrease in eGFR from baseline)	1. OR = 1.29; $p = 0.038$	Higher PENK levels were independently associated with WRF and mortality. The results were validated in large HF cohort (1,703)
		2. All-cause mortality	2. HR = 1.23; $p = 0.004$	
Depret et al. [34]	Critically ill burn patients (113)	1. AKI	1. AKI versus no AKI 86.4 pmol/L (IQR 56.5–153.4) versus 52.5 pmol/L (IQR 35.5–71.2); $p < 0.001$	1. PENK on admission was significantly higher in patients with AKI versus those without
		2. 90-day mortality	2. Survivors versus nonsurvivors 86.9 pmol/L (IQR 53.3–166.1) versus 52.9 pmol/L (IQR 37.1–70.7); $p = 0.0001$	2. PENK had strong association with 90-day mortality PENK provided added value on top of serum Cr and SOFA score to predict 90-day mortality
Legrand et al. [29]	Following ICU discharge	1-year mortality	AUROC 0.67 (0.63–0.70), $p < 0.0001$	Higher PENK levels at ICU discharge were associated with higher mortality at 1 year

PENK, proenkephalin; AUC, area under the curve; RRT, renal replacement therapy; NGAL, neutrophil gelatinase-associated lipocalin; WRF, worsening of renal function; (e)GFR, (estimated) glomerular filtration rate; OR, odds ratio; MACE, major adverse cardiac event; IQR, interquartile range; HR, hazard ratio; RRT, renal replacement therapy; MAKE, major adverse kidney event; HFpEF, Heart failure with preserved ejection fraction; AKI, acute kidney injury; ICU, intensive care unit; AUROC, area under the receiver operating curve; rSOFA, renal Sequential Organ Failure Assessment; KDIGO, Kidney Disease: Improving Global Outcomes; Cr, creatinine.

predicted AKI within 48 h and 7 days [10]. Additionally, PENK levels significantly predicted progression of rSOFA scores from 0 to ≤1 to higher rSOFA scores.

When compared to other biomarkers of kidney injury, PENK performed similar or better in detecting AKI. The diagnostic accuracy of PENK was similar to neutrophil gelatinase-associated lipocalin (NGAL) ($n = 101$, $X^2 = 34.9$, $p < 0.001$, AUC = 0.82 and $X^2 = 31.3$, $p < 0.001$, AUC = 0.80, respectively) [4]. Notably, while PENK remained low in patients without or at risk of AKI, NGAL was elevated in patients without AKI, suggesting an impact of systemic inflammation on NGAL levels. Using nested logistic regression analysis, PENK outperformed NGAL for detection of AKI ($p = 0.02$). In a head-to-head comparison of PENK and the cycle cell arrest marker TIMP-2*IGFBP-7, a biomarker of kidney stress, PENK was superior in detecting renal failure in a cohort of 200 critically ill patients (area under the receiver operating curve 0.91 [0.71–0.84] versus 0.67 [0.59–0.74], respectively, $p < 0.001$) [24].

The association between PENK and development of AKI is possibly related to the strong correlation with the true GFR; an accurate reflection of the current GFR may provide a good signal for risk of future deterioration or improvement. It is also possible that the opioid receptors of the kidney and the signaling function of enkephalins account for the strong association with AKI. Finally, a combination of the 2 mentioned hypotheses may explain

the association of PENK with AKI: a decreased filtration of PENK and simultaneously an increased production of PENK during a period of AKI. Studies on the endogenous clearance studies should investigate these hypotheses.

Association of PENK with Clinical Outcome

PENK has been studied as a prognostic marker of various clinical outcomes (Table 2). The kidney in sepsis and septic shock study (n = 583) evaluated the association of PENK with the composite outcome of the incidence of major adverse kidney event (MAKE) and worsening renal function (WRF) which was defined as an increase in serum Cr level by ≥1.5-fold or ≥0.3 mg/dL (26.5 μmol/L), or need for renal replacement therapy (RRT), or death within 48 h of admission [9]. Admission PENK plasma concentrations were independently associated with MAKE and WRF (OR = 3.3 [1.8–6.0], $p < 0.0001$ and OR = 3.4 [1.9–6.2], $p < 0.0001$, respectively). Notably, when restricting the analysis to patients with low serum Cr on admission and patients without CKD, PENK was superior to serum Cr in predicting MAKE and WRF. In another large cohort of septic patients (n = 956), elevated plasma PENK concentrations predicted future need for RRT and 90-day mortality (OR_{RRT} = 4.0, CI [3.0–5.4] and $HR_{mortality}$ = 1.5, CI [1.2–1.8]) independently of potential confounding factors [6]. Similar results were found in burn patients [25] and patients with acute heart failure (n = 530 [11] and n = 2,180, respectively [12]). Other studies in heart failure patients have reported similar findings with regard to the association of PENK with these clinical outcomes [8, 26, 27] which might partly be driven by enkephalin gene expression in cardiac muscle cells [28].

In a study of patients discharged alive from an intensive care unit (n = 1,207), higher PENK levels at discharge were independently associated with higher mortality at 1 year (OR = 2.2 [1.44–3.38]) [29]. Notably, in patients without severe renal dysfunction at discharge (based on serum Cr), elevated PENK plasma concentrations were strongly associated with 1-year mortality. In a study of renal transplant recipients (n = 664) with a stable kidney function who were followed over a 3-year period, plasma PENK concentrations were associated with the risk of graft failure (defined as return to RRT or retransplantation) ($HR_{GraftFailure}$ = 4.80, CI [3.55–6.48]) [30]. PENK was also shown to predict future changes in kidney function in 2,568 individuals without CKD at baseline (eGFR > 60 mL/min/1.73 m^2) who were followed up for average of 16 years [13]. In this study, individuals with higher baseline PENK levels had greater yearly decline in mean eGFR and at higher risk for developing CKD (OR = 1.51; CI [1.18–1.94]). Again, the accurate reflection of the GFR of PENK or a signaling function of enkephalins may enable the association with future renal disease or clinical outcome. Clearly, implementation of a new biomarker is always troublesome, and the reasons for this are similar for the different biomarkers: the availability, the price (compared to Cr), and limited data available on the effect of PENK-based management on clinical outcome. Finally, despite early implementation of preventive and therapeutic strategies in patients at risk has been shown to improve outcome (i.e., Kidney Disease: Improving Global Outcomes bundles), the importance of early recognition of AKI might still be underappreciated by many clinicians and institutions.

Conclusion

In summary, in the search to find an accurate method to assess actual GFR in critically ill patients with a non-steady-state kidney function, the available evidence suggests that PENK is a more accurate and precise surrogate marker to estimate GFR or to detect AKI compared to Cr-based methods. Furthermore, PENK is associated with precise prediction of future deterioration of kidney function and impaired outcome in various patient populations.

Conflict of Interest Statement

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Author Contributions

All authors confirmed that they contributed to the intellectual content of this review. M.K. drafted the manuscript. R.B., P.P., and M.L. revised the manuscript.

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