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Proenkephalin A119–159 in Acute kidney injury and sepsis

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Abstract:

Acute kidney injury (AKI) is a frequent and severe complication in critically ill patients, particularly in the context of sepsis, and is associated with increased morbidity, mortality, and healthcare burden. Traditional biomarkers such as serum creatinine and urine output are delayed indicators of renal dysfunction and often fail to detect subclinical injury at an early stage. Proenkephalin A 119–159 (PENK, also known as penKid) is a stable endogenous peptide derived from the enkephalin precursor. It reflects real-time glomerular filtration rate (GFR) and has shown strong potential as an early biomarker for AKI in critically ill and septic patients. Early identification of AKI using PENK may allow timely therapeutic interventions, risk stratification, and improved patient outcomes.

Keywords: Proenkephalin A 119–159; penKid; Acute Kidney Injury; Sepsis; Biomarker; Critical Illness; Renal Dysfunction.

Introduction:

Acute kidney injury (AKI) is a frequent and severe complication among critically ill patients, particularly in those with sepsis, and is associated with significant morbidity and mortality. Despite improvements in supportive care, AKI remains a major cause of adverse outcomes in the intensive care unit (ICU) **(1).**

Traditional diagnostic tools for AKI, including serum creatinine and urine output, have several limitations. They are delayed indicators, often rising only after substantial renal damage has occurred, and are influenced by factors unrelated to kidney function such as muscle mass, hydration status, and medications **(2).**

Proenkephalin A 119–159 (penKid) has emerged as a promising biomarker for early detection of AKI. PENK is a stable endogenous peptide that reflects real-time glomerular filtration rate (GFR) and is less affected by confounding clinical factors. Evidence suggests that it can identify subclinical AKI earlier than creatinine-based measurements **(3).**

Recent clinical studies have demonstrated the utility of PENK in diverse critical care scenarios. Elevated plasma PENK levels have been associated with the early onset of AKI, the need for renal replacement therapy, and higher mortality in septic and post-operative patients **(4).**

Furthermore, meta-analyses and multicenter trials support the predictive accuracy of PENK compared with other novel biomarkers, suggesting its potential role in guiding timely interventions and improving patient outcomes **(5).**

Endorphins, dynorphins, and enkephalins are the endogenous opioid peptides that bind to the μ-, κ-, and δ-opioid receptors (MOR, KOR, and DOR), respectively. The 2 main forms of enkephalin were discovered in 1975: leucine (leu-enkephalin) and methionine (met-enkephalin). The effects of endogenous and exogenous opioids via neural signaling (e.g., antinociception, respiratory depression, physical dependence) are well studied and understood. Intriguingly, the opioid receptors, especially the DORs, are expressed in peripheral organs as

well. All 3 opioid receptors show the highest level of expression in the kidney, implying possible direct effects on kidney function **(6)**.

Table (1): Overview of opioid receptors and their effects upon stimulation.**(6)**

Receptor	Receptor expression density	Effects
δ	KidneyIntestineBrainHeartMuscle	Central Analgesia (chronic pain), convulsions, anxiolysis, antidepressant, physical dependence, neuroprotective in ischemiaPeripheral Diuresis ↑, cardiodepressive, antiarrhythmic in cardiac ischemia, constipation
κ	KidneyIntestineHeartBrainMuscle	Central Analgesia, dysphoria, anticonvulsant, depression, hallucinogenicPeripheral Diuresis ↑, natriuresis ↓, reduced inflammation
μ	KidneyIntestineMuscleBrain	Central Analgesia, euphoria, respiratory depression, physical dependencePeripheral Constipation, diuresis ↓, natriuresis ↓, reduced inflammation

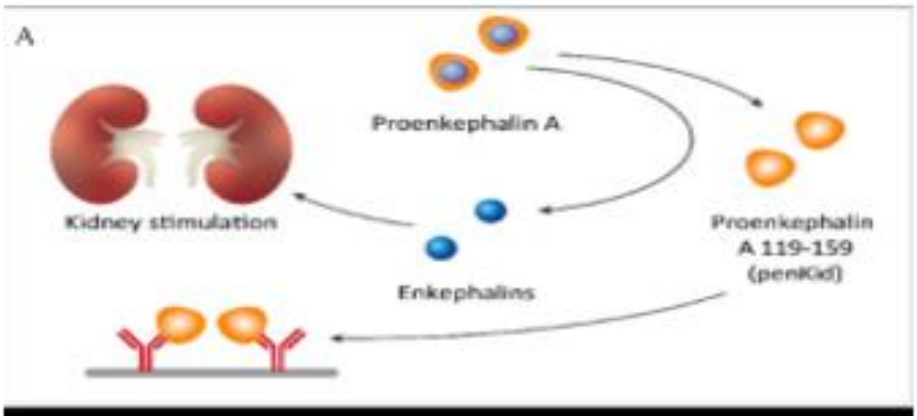
Proenkephalin A 119–159 (PENK) is an endogenous, monomeric peptide cleaved from preproenkephalin A, together with enkephalin peptides **(7)**. PENK is a 41 amino acid-long peptide derived as a by-product fragment from the cleavage of a precursor peptide called preproenkephalin A. Apart from PENK, cleavage of this precursor molecule yields several biologically active enkephalins, with leucine-enkephalin (Leu-Enk) and methionine-enkephalin (Met-Enk) being the two main functionally mature forms **(8)**.

PENK possesses several characteristics for an ideal GFR biomarker: it is endogenous, freely filtered by glomeruli due to its small molecular size (4.5 kDa), has no known tubular handling or extra-renal clearance, is not bound to plasma proteins and is stably produced in various disease states, independent of inflammation and other non-renal factors **(6)**.

Proenkephalin (PENK) is a stable, non-protein-binding, low-interfering, small endogenous opioid peptide with a long half-life, produced by nephron structures in response to damage. It is harmful to renal function, and has also been reported to have a strong negative correlation with estimated glomerular filtration rate (eGFR) **(9)**.

Proenkephalin A 119-159

In healthy states (Figure 1A), kidney function is stimulated by the hormone enkephalin and endogenous opioid peptide. When kidney function is low (Figure 1B), enkephalin levels rise to stimulate the kidneys. By indirectly measuring enkephalin production, high penKid levels indicate impaired kidney function **(3)**.



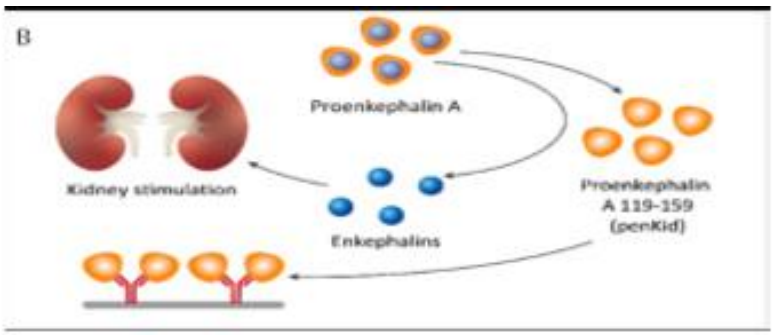


Figure (1): Proenkephalin A production in healthy (A) and ill (B) patients **(10)**

This peptide is derived from the cleavage of proenkephalin A 1-243, but it is unstable and difficult to measure. During this process, another peptide, proenkephalin A 119-159 (penKid), is produced in equimolar concentrations and can be used as a surrogate marker because of its stability (Figure 2) **(10)**.

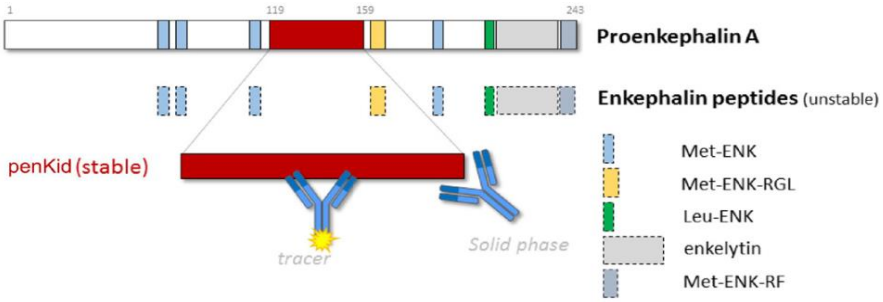


Figure (2): Cleavage of proenkephalin 1-243 results in the release of enkephalin and penkid, among other peptides. PenKid is detected through monoclonal antibodies directed against its middle portion (tracer antibody) and C-terminus (capture antibody on solid phase) **(11)**

PENK as a Biomarker of GFR

Plasma PENK concentrations strongly correlate with GFR. 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 ($R^2 = 0.90$, $p < 0.0001$). 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 **(12)**.

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 ($\beta = -0.77$, $p < 0.0001$). 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 **(11)**.

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, which may make this novel biomarker particularly useful in critically ill patients whose kidney function may be changing rapidly **(13)**.

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 **(14)**.

Sepsis and Septic Shock

Recently, new biomarkers have been investigated in this setting, such as bio-adrenomedullin, which can be useful to identify patients at high risk of progression and could be a target for new drugs **(15)**.

In septic patients, monitoring renal function is crucial for several reasons. First, kidney function is predictive of mortality and is one of the items in the Sequential Organ Failure Assessment (SOFA) Score, which is used to evaluate the severity of organ failure and predict mortality. Second, antibiotic therapy can be nephrotoxic; therefore, physicians need to tailor it to each patient. Finally, AKI requiring renal replacement therapy (RRT) is one of the most common complications of sepsis and septic shock **(16)**.

In an analysis involving 956 septic patients, it was observed that penKid exhibited independent predictive abilities for the development of AKI within 48 h and 7 days of hospital admission. The adjusted odd ratios were 3.3 (CI: 2.1-5.1) and 2.1 (CI: 1.7-2.8), respectively. Furthermore, the median levels of penKid demonstrated a correlation with the severity of AKI based on the KDIGO stage and renal SOFA score **(17)**.

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