Obaid *et. al.*, Babcock Univ. Med. J.2026 9(3):331-337
https://doi.org/10.38029/babcockuniv.med.j..v9i3.1567

BUMJ A Multi-Disciplinary Medical Journal
eISSN: 2756-4657

RESEARCH ARTICLE OPEN ACCESS

Diagnostic value of serum proenkephalin as a biomarker of renal dysfunction in Iraqi patients with chronic kidney disease

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Submitted: 3rd February 2026
Accepted: 4th May 2026
Published: 30th September 2026
ID: Orcid ID

Abstract
Objective: To evaluate serum proenkephalin (PENK) levels in Iraqi patients with chronic kidney disease (CKD) and examine its diagnostic performance and correlation with conventional renal function markers.
Methods: This case-control study included 45 Iraqi patients with CKD stages 3–4 and 45 age- and sex-matched healthy controls. Serum PENK levels were measured using a commercial ELISA kit. Renal function was assessed using serum creatinine, blood urea, and estimated glomerular filtration rate (eGFR) calculated with the CKD-EPI equation.
Results: Serum PENK levels were significantly higher in CKD patients (900.05 ± 212.72 ng/L) than in controls (705.12 ± 135.95 ng/L; $p < 0.001$). PENK positively correlated with creatinine ($r = 0.678$, $p < 0.001$) and urea ($r = 0.579$, $p < 0.001$) and negatively with eGFR ($r = –0.486$, $p < 0.001$). Concentrations rose markedly from stage 3 (717.65 ± 134.74 ng/L) to stage 4 (1124.14 ± 295.63 ng/L; $p < 0.001$). Receiver operating characteristic analysis yielded an area under the curve of 0.723 ($p = 0.001$), with 65% sensitivity and 60% specificity at a cut-off of 728.7 ng/L.
Conclusion: Serum PENK is significantly elevated in Iraqi patients with moderate-to-advanced CKD and correlates with disease severity. However, its modest diagnostic accuracy and inability to distinguish early-stage 3 disease from healthy controls suggest that PENK is best used as an adjunctive marker rather than a standalone screening test.

Keywords: Enkephalins, Renal Insufficiency, Chronic, Kidney, Biomarkers, Iraq

Plain English Summary
Chronic kidney disease (CKD) is a long-term condition where the kidneys gradually lose their ability to filter waste from the blood. Standard blood tests, such as creatinine, often miss early kidney damage because factors like muscle mass and age influence them. Researchers have been searching for more sensitive markers. One promising candidate is proenkephalin (PENK), a small protein that is freely filtered by the kidneys. In this study, we measured PENK levels in 45 Iraqi patients with moderate CKD (stages 3 and 4) and compared them with those of 45 healthy people of similar age and sex. We found that PENK levels were higher in CKD patients and increased as the disease worsened from stage 3 to stage 4. PENK also showed a strong relationship with conventional markers: higher PENK meant higher creatinine and urea, and lower estimated kidney function. However, when we tested PENK as a diagnostic tool, it was only moderately accurate – it correctly identified about two-thirds of CKD cases but also wrongly labelled two-fifths of healthy people as having CKD. Importantly, PENK could not reliably separate people with early-stage 3 CKD from healthy individuals. Therefore, while PENK may be a useful additional test for monitoring disease progression, it is not yet ready to replace standard tests, especially for early detection. Larger studies are needed to confirm its role in clinical practice.

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Introduction

Chronic kidney disease (CKD) is a progressive and often silent condition defined by structural or functional abnormalities of the kidneys that persist for at least three months. Clinically, it is diagnosed when the estimated glomerular filtration rate (eGFR) falls below 60 mL/min/1.73 m² or when markers of kidney damage, such as albuminuria, haematuria, or structural changes, are present (1). The global burden of CKD is staggering: it affects roughly 10% of the world's adult population, contributes to over a million deaths annually, and is projected to become the fifth leading cause of death by 2040 (2, 3, 4).

In Iraq, as in many middle-income countries, the epidemiology of CKD is shaped by a high prevalence of diabetes mellitus, hypertension, and possibly environmental exposures (5). However, specific data on novel biomarkers in this population remain scarce. Early detection of kidney dysfunction is crucial because interventions can slow disease progression, yet conventional markers like serum creatinine and eGFR have important limitations. Creatinine levels are influenced by muscle mass, age, sex, and diet, and they do not rise appreciably until nearly half of kidney function has been lost (6, 7). This diagnostic gap has fuelled the search for more sensitive, real-time biomarkers.

Proenkephalin (PENK) is a stable endogenous peptide derived from preproenkephalin A. Owing to its low molecular weight (≈4.5 kDa), PENK is freely filtered by the glomerulus, undergoes minimal tubular secretion, and is not significantly bound to plasma proteins (8, 9). Consequently, its circulating levels closely reflect the true glomerular filtration rate, making it an attractive surrogate marker that is less influenced by non-renal factors than creatinine (10). Several international studies have shown that PENK levels rise with declining kidney function, predict adverse renal outcomes, and may outperform creatinine in certain settings (11, 12, 13). Nevertheless, data from Iraqi patients with CKD are lacking, and the diagnostic performance of PENK in this specific demographic has not been adequately evaluated.

Against this background, the present study was designed to measure serum PENK levels in Iraqi patients with stage 3 and 4 CKD, to correlate these levels with conventional renal function parameters, and to assess the diagnostic accuracy of PENK for detecting moderate-to-advanced CKD. We hypothesised that PENK would be significantly elevated in patients and would correlate positively with urea and creatinine and negatively with eGFR.

Materials and Methods

Study design and setting

This was a case-control study conducted at the Department of Chemistry and Biochemistry, College of Medicine, University of Karbala, Iraq, between November 2025 and January 2026. The study protocol was approved by the institutional ethics committee (reference number 26-12, 13 January 2026) and complied with the Declaration of Helsinki. All participants provided written informed consent after receiving a detailed explanation of the study procedures.

Participant recruitment and eligibility

A total of 90 individuals were enrolled. 45 patients with CKD (stages 3 and 4) and 45 age- and sex-matched healthy controls. Patients were recruited from the consultant nephrology clinic at Al Imam Al Sadeq Hospital in Babil. The diagnosis of CKD was made by a consultant nephrologist using the kidney disease: Improving Global Outcomes (KDIGO) criteria, supported by clinical history and laboratory findings. Inclusion criteria for the patient group were: Iraqi nationality, age between 20 and 60 years, and confirmed CKD stage 3 or 4 (eGFR 15–59 mL/min/1.73 m²). Exclusion criteria for all participants were: acute kidney injury, systemic lupus erythematosus, recent kidney surgery, end-stage renal disease requiring dialysis, and any malignancy (renal, pulmonary, or colorectal). Controls were recruited from volunteers accompanying patients and from community members outside the hospital. They had no documented history of acute or chronic kidney disease and had normal baseline renal function (serum creatinine within the normal range and no dipstick abnormalities). However, formal urine albumin testing or imaging was not performed, which is acknowledged as a limitation.

Sample collection and processing

Venous blood (5 mL) was drawn from each participant under aseptic conditions into plain gel serum separator tubes. Blood was allowed to clot at room temperature for 30–60 minutes, then centrifuged at 3000 × g for 20 minutes to separate serum. The serum was aliquoted into three Eppendorf tubes to avoid repeated freeze-thaw cycles and stored at –20°C until analysis. One aliquot was used for PENK quantification by ELISA, another for measurement of creatinine and urea.

Biochemical measurements

Conventional renal function tests

Serum creatinine and blood urea concentrations were measured using an automated biochemical analyser (Abbott ARCHITECT c4000, USA)

following the manufacturer's protocols (Jaffe method for creatinine, enzymatic for urea). Estimated GFR was calculated using the CKD-EPI 2021 equation without race correction (14):

eGFR = 142 × min(Scr/κ, 1)^α × max(Scr/κ, 1)^–1.200 × 0.9938^age × (1.012 if female)

where Scr is serum creatinine in mg/dL, κ is 0.7 (female) or 0.9 (male), and α is –0.241 (female) or –0.302 (male).

Proenkephalin assay

Serum PENK levels were quantified using a commercial sandwich ELISA kit (catalogue No. E2341Hu, BT LAB, China) with a detection range of 10–2000 ng/L, analytical sensitivity of 5.69 ng/L, and intra-- and inter-assay coefficients of variation of <8% and <10%, respectively. All samples were run in duplicate, and the mean value was used for analysis.

Statistical analysis

Data were analysed using SPSS version 26.0. The Shapiro-Wilk test was used to assess the normality of continuous variables. Normally distributed data are presented as mean ± standard deviation (SD); categorical data as frequencies and percentages. Between-group comparisons were performed using independent t-tests (continuous) or chi-square tests (categorical). For correlation analysis, Pearson's correlation was used for normally distributed variables; Spearman's rank correlation was applied when normality was violated. To ensure consistency, we report Spearman correlations throughout because not all variables (e.g., eGFR, PENK) were perfectly normal. Logistic regression was performed to estimate the association between PENK and CKD status. Because PENK values were on a scale of hundreds, we rescaled the variable by dividing by 100 (i.e., per 100 ng/L increase) to make the odds ratio more interpretable. Owing to the case-control design and the fact that all controls had zero prevalence of diabetes and hypertension, a fully adjusted multivariable model was not feasible (perfect separation). Therefore, we present unadjusted logistic regression results with the caveat that confounding by these strong risk factors cannot be ruled out.

Receiver operating characteristic (ROC) curve analysis was used to assess the diagnostic accuracy of PENK for discriminating CKD from control; the area under the curve (AUC), sensitivity, specificity, and optimal cut-off (maximising Youden's index) were calculated. Statistical significance was set at two-tailed $p < 0.05$.

Results

Participant characteristics (Table 1)

The study groups were well matched for age, sex, and body mass index (BMI). The mean age was 53.3 ± 9.6 years in the CKD group and 50.1 ± 11.0 years in controls ($p = 0.149$). Males comprised 60.0% of the CKD group and 44.4% of controls ($p = 0.140$). As expected, patients with CKD had significantly higher blood urea (114.96 ± 37.72 vs. 34.53 ± 5.76 mg/dL, $p < 0.001$), higher serum creatinine (5.96 ± 1.78 vs. 0.75 ± 0.08 mg/dL, $p < 0.001$), and lower eGFR (29.58 ± 9.35 vs. 113.72 ± 10.34 mL/min/1.73 m², $p < 0.001$). The prevalence of diabetes, hypertension, and family history of CKD was substantially higher in the patient group, consistent with their disease status.

Table 1: Demographic and clinical characteristics of the study groups

Characteristic	Control (n=45)	CKD patients (n=45)	p-value
Sex, n (%)			0.14
Male	20 (44.4)	27 (60.0)	
Female	25 (55.6)	18 (40.0)	
Age (years), mean ± SD	50.11±11.04	53.29±9.64	0.149
BMI (kg/m²), mean ± SD	24.09±2.95	24.43±3.72	0.625
Family history of CKD, n (%)			<0.001
No	45 (100.0)	28 (62.2)	
Yes	0	17 (37.8)	
Diabetes mellitus, n (%)			<0.001
No	45 (100.0)	19 (42.2)	
Yes	0	26 (57.8)	
Hypertension, n (%)			<0.001
No	45 (100.0)	20 (44.4)	
Yes	0	25 (55.6)	
Blood urea (mg/dL), mean ± SD	34.53±5.76	114.96±37.72	<0.001
Serum creatinine (mg/dL), mean ± SD	0.75±0.08	5.96±1.78	<0.001
eGFR (mL/min/1.73 m²), mean ± SD	113.72±10.34	29.58±9.35	<0.001
PENK (ng/L), mean ± SD	705.12±135.95	900.05±212.72	<0.001

p-values from an independent t-test (continuous) or chi-square test (categorical)

Proenkephalin levels by CKD stage
The CKD group included 22 patients with stage 3 (eGFR 30–59) and 23 with stage 4 (eGFR 15–29). Serum PENK levels were markedly higher in stage 4 (1124.14 ± 295.63 ng/L) compared to stage 3 (717.65 ± 134.74 ng/L), and this difference was highly significant ($p < 0.001$). Notably, PENK levels in stage 3 patients were very close to those in healthy controls (717.65 vs. 705.12 ng/L, $p = 0.72$), indicating that PENK did not discriminate early stage 3 disease from health. Table 2 presents these data.

Table 2: Serum proenkephalin concentrations according to CKD stage

CKD stage	n	PENK (ng/L), mean ± SD	p-value (stage 3 vs. 4)
Stage 3	22	717.65 ± 134.74	<0.001
Stage 4	23	1124.14 ± 295.63	

Correlations with conventional renal markers
Spearman correlation analysis (Table 3) revealed that serum PENK was positively correlated with blood urea ($r = 0.579$, $p < 0.001$) and serum creatinine ($r = 0.678$, $p < 0.001$). A significant negative correlation was observed with eGFR ($r = –0.486$, $p < 0.001$). These relationships are in the expected direction and support the notion that PENK accumulation parallels declining kidney function.

Table 3: Correlation of serum proenkephalin with renal function parameters

Parameter	Spearman's r	p-value
Blood urea	0.579	<0.001
Serum creatinine	0.678	<0.001
eGFR	–0.486	<0.001

Logistic regression and diagnostic accuracy
In univariate logistic regression with PENK rescaled per 100 ng/L increase, each 100 ng/L rise in PENK was associated with an approximately 40% increase in the odds of having CKD (odds ratio = 1.40; 95% confidence interval: 1.13–1.73; $p = 0.002$). The raw OR of 1.004 per ng/L (as originally reported) is equivalent but less clinically intuitive. Because all controls had zero prevalence of diabetes and hypertension, adjustment for these confounders was not statistically feasible (perfect separation leads to unstable estimates). Therefore, the observed association should be interpreted as unadjusted.
ROC curve analysis (Figure 1) gave an AUC of 0.723 (95% CI: 0.617–0.829; $p = 0.001$). The optimal cut-off for distinguishing CKD from controls was 728.7 ng/L, yielding a sensitivity of 65.0% and a specificity of 60.0%. While statistically significant, these metrics indicate only moderate diagnostic performance – far from the high accuracy needed for a stand-alone screening test.

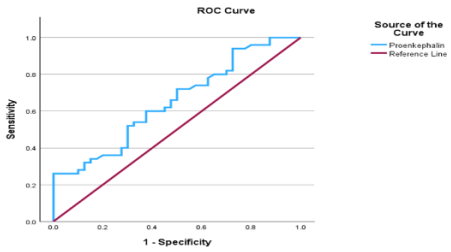

Figure 1: Receiver operating characteristic (ROC) curve of proenkephalin for CKD diagnosis. The area under the curve is 0.723 ($p = 0.001$)

Discussion

Chronic kidney disease remains a major public health challenge, and the search for biomarkers that overcome the inherent limitations of creatinine and eGFR continues intensively. Proenkephalin has emerged as a candidate because of its favourable pharmacokinetics: low molecular weight, free glomerular filtration, minimal tubular handling, and stability in circulation (8, 9). In the present study of Iraqi patients with moderate-to-advanced CKD, we found that serum PENK levels were significantly higher than in healthy controls, increased from stage 3 to stage 4, and correlated with conventional markers in the expected directions. Nevertheless, the diagnostic accuracy was only modest (AUC 0.723), and PENK failed to distinguish stage 3 CKD from healthy individuals. These findings qualify but do not fully support the early promise of PENK.

Comparison with existing literature
Our results align with several international studies showing that PENK levels rise as kidney

function declines. For instance, Khorashadi and colleagues demonstrated that plasma PENK correlated strongly with measured GFR (R^2 = 0.90) using iohexol clearance, suggesting that PENK could serve as a reliable filtration marker (10). Similarly, Beunders et al. reported that a PENK-based equation for estimating GFR performed comparably to creatinine-based equations, with an AUC of 0.86 for identifying GFR <60 mL/min/1.73 m² (15). However, our AUC of 0.723 is lower than those reported in many larger cohorts. Possible reasons include the relatively small sample size, the specific characteristics of the Iraqi population (genetic background, environmental exposures, high burden of diabetes and hypertension), and the fact that we used a commercial ELISA rather than a more standardised assay.

Importantly, the inability of PENK to separate stage 3 CKD from healthy controls in our study is a concern. Stage 3 CKD represents a clinically significant reduction in eGFR (30–59 mL/min/1.73 m²), but the mean PENK level in our stage 3 patients (717.65 ng/L) was almost identical to that in controls (705.12 ng/L). This raises the possibility that PENK may only become markedly elevated when eGFR falls below approximately 30 mL/min/1.73 m² (stage 4). If confirmed in larger studies, PENK would be of limited value for early detection but could still serve as a marker of progression from moderate to severe disease.

Clinical implications

Given the modest sensitivity (65%) and specificity (60%), PENK in its current form is not suitable as a standalone screening test for CKD. However, it may have adjunctive value. For patients with established CKD (especially stage 4), rising PENK levels could signal worsening kidney function, potentially adding confidence to eGFR trends. Moreover, because PENK is less influenced by muscle mass and nutritional status than creatinine, it might be particularly helpful in elderly or malnourished patients where creatinine-based eGFR is unreliable (6, 7). The logistic regression results (OR 1.40 per 100 ng/L increase) indicate a meaningful association, but this does not translate into high diagnostic accuracy.

Study limitations and future directions

Several limitations must be acknowledged. First, the sample size is small (n=45 per group), and no a priori power calculation was performed; this limits the precision of our estimates and the generalisability of findings. Second, the case-control design with perfect separation on key confounders (zero diabetes/hypertension in controls) precluded adjusted multivariable analysis, so we cannot rule out confounding by these strong risk factors. Third, the control group lacked a comprehensive kidney assessment (no urine albumin-to-creatinine ratio, no renal imaging), meaning some controls may have had undiagnosed early kidney damage – this would have biased PENK levels upward, potentially underestimating the true difference. Fourth, we studied only stages 3 and 4; results cannot be extrapolated to early CKD (stages 1–2) or end-stage disease. Fifth, the study period was short (three months), and we have no follow-up data to assess whether PENK predicts disease progression.

Future research should address these gaps. Large, multicentre prospective cohorts are needed to establish reference ranges for PENK in different ethnic groups, including Iraqi and other Middle Eastern populations. Longitudinal studies should examine whether baseline PENK predicts decline in eGFR, need for dialysis, or mortality – the true tests of a prognostic biomarker. Additionally, head-to-head comparisons of PENK with emerging markers such as cystatin C, NGAL, and KIM-1 would help position PENK in the biomarker panel. Finally, cost-effectiveness analyses are necessary before advocating widespread clinical adoption, especially in resource-limited settings where many patients with CKD are managed.

Conclusion

Serum proenkephalin levels are significantly elevated in Iraqi patients with stage 4 CKD and correlate moderately with conventional markers of kidney function. However, PENK does not distinguish early-stage 3 CKD from healthy individuals and shows only modest diagnostic accuracy (AUC 0.723). Therefore, while PENK may serve as an adjunctive biomarker for monitoring disease progression in moderate-to-advanced CKD, it is not a replacement for established tests and should not be used as a standalone screening tool. Larger, well-controlled studies are urgently needed to clarify its clinical role, particularly in diverse and under-represented populations like Iraq.

List of Abbreviations

AUC: Area under the curve
BMI: Body mass index
CI: Confidence interval
CKD: Chronic kidney disease
CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration
eGFR: Estimated glomerular filtration rate
ELISA: Enzyme-linked immunosorbent assay
KDIGO: Kidney Disease: Improving Global Outcomes
OR: Odds ratio

PENK: Proenkephalin
ROC: Receiver operating characteristic
SD: Standard deviation

Declarations

Ethics Approval and Consent to Participate

This study was approved by the Scientific Research Ethics Committee of the College of Medicine, University of Karbala, Iraq (reference number 26-12, dated 13 January 2026). All procedures were performed in accordance with the ethical standards of the Declaration of Helsinki (1964 and subsequent amendments). Written informed consent was obtained from every participant after a full explanation of the study's purpose and procedures.

Consent for Publication

All authors gave explicit consent for the publication of this work under the Creative Commons Attribution Non-Commercial 4.0 International license.

Data Availability

The datasets generated and analysed during the current study are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare that they have no competing interests, financial or otherwise.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Author Contributions

OHS worked on the conceptualisation, data curation, formal analysis, funding acquisition, resources, software, and writing of the original draft, review & editing.
YAG and AAJ worked on the conceptualisation, investigation, methodology, project administration, supervision, visualisation, and writing of the original draft, review & editing.

Acknowledgements

The authors extend their sincere gratitude to the staff of the Babylon Nephrologist Centre, Iraq, for their invaluable assistance during sample collection. We also thank all the volunteers and patients who participated in this study; without their generosity, this work would not have been possible.

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