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Elevated Serum Levels of Galectin-3 and Kidney Injury Molecule-1 as Potential Biomarkers for Early Detection and Staging of Chronic Kidney Disease in Iraqi Population

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Abstract

Background: Chronic kidney disease (CKD) is a deadly progressive disorder, particularly when it progresses to end-stage renal disease (ESRD). Conventional diagnostic tools such as serum creatinine and estimated glomerular filtration rate (eGFR) often lack sensitivity for early detection of tubular injury. This study aimed to evaluate the diagnostic potential of Galectin-3 (Gal-3) and Kidney Injury Molecule-1 (KIM-1) in Iraqi patients with CKD.

Methods: This case-control study included 150 participants from Baghdad, Iraq, between August 2022 and May 2023. Participants were categorized into three groups: healthy controls (n=50), mild CKD (n=50), and severe CKD (n=50). Serum levels of Gal-3 and KIM-1 were measured using ELISA kits. Demographic, clinical, and biochemical data were collected, including age, sex, BMI, diabetes status, hypertension, and eGFR. Statistical analyses included ANOVA, Kruskal-Wallis test, and correlation analysis.

Results: Gal-3 levels were significantly higher in CKD patients compared to healthy controls, showing a progressive increase from mild to severe CKD stages ($P < 0.001$). It was also associated with systemic factors such as diabetes mellitus, hypertension, and obesity. In contrast, KIM-1 levels were elevated primarily in patients with advanced CKD or ESRD ($P = 0.036$), but no significant difference was observed between control and mild CKD groups ($P = 0.149$). KIM-1 did not show consistent correlations with traditional markers of renal function, suggesting its specificity for structural tubular damage rather than functional decline.

Conclusions: Our findings suggest that Gal-3 may serve as a broader biomarker reflecting both systemic inflammation and fibrosis, while KIM-1 appears to be more specific to advanced renal injury.

Keywords: Biomarker, Chronic kidney disease, Galectin-3, Kidney Injury Molecule-1, Renal tubular injury, Serum biomarkers.

Introduction

Chronic kidney disease (CKD) is a progressive condition characterized by structural or functional abnormalities of the kidneys that persist for more than three months. It represents a significant global public health burden (1), with increasing prevalence and associated morbidity and mortality due to its progression to end-stage renal disease (ESRD) (2). Early detection and accurate staging of CKD are crucial for timely

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intervention; however, conventional diagnostic tools such as serum creatinine and the estimated glomerular filtration rate (eGFR) often lack sensitivity in identifying early tubular damage or predicting disease progression. This limitation has prompted extensive research into novel biomarkers that can improve the accuracy of diagnosis and provide insight into the underlying pathophysiological mechanisms of CKD (3). Among the emerging candidates, Galectin-3 (Gal-3) and Kidney Injury Molecule-1 (KIM-1) have shown promising potential as indicators of renal injury (4). Galectin-3, a β-galactoside-binding lectin, plays a central role in inflammation, fibrosis, and immune modulation processes closely linked to CKD progression. Its expression has been associated with renal interstitial fibrosis and tubulointerstitial damage, suggesting a potential role not only in diagnosing but also in monitoring CKD progression (5). Similarly, KIM-1, a transmembrane glycoprotein expressed on injured renal tubular epithelial cells, has been demonstrated is elevated following proximal tubule damage and may serve as a specific indicator of renal tubular dysfunction and structural injury (6, 7).

Despite growing evidence supporting their utility, the application of these biomarkers in specific populations remains underexplored. Most studies evaluating Gal-3 and KIM-1 have been conducted in Western or Asian populations, and there are limited data regarding their performance in Middle Eastern or Iraqi patients. Differences in genetic background, environmental factors, comorbidities, and healthcare access may influence biomarker expression and interpretation. Therefore, validation of these markers in diverse ethnic and geographic populations is essential before they can be widely adopted in clinical practice (8).

This study was designed to evaluate the expression levels of Gal-3 and KIM-1 in relation to established clinical parameters among CKD patients in Baghdad, Iraq. We aimed to assess whether these biomarkers demonstrate significant differences between healthy controls and individuals with mild or severe CKD.

By addressing these objectives, this research contributes to the understanding of novel biomarker roles in CKD within an understudied population. Our findings aim to support the development of more sensitive and stage-specific diagnostic strategies for CKD in Iraqi patients, where epidemiological profiles and risk factor distributions may differ from those reported in global studies.

Materials and Methods

This case-control study was conducted between August 2022 and May 2023 at Al-Kadimiyain Medical City Hospital in Baghdad, Iraq. The study protocol was approved by the Research Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.SPH.REC.1402.042), and written informed consent was obtained from all participants prior to enrollment. All procedures were conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Study Population and Inclusion/Exclusion Criteria

A total of 150 adult participants aged 18–65 years were recruited and categorized into three groups based on clinical diagnosis and laboratory findings:

- Control group (n= 50): Individuals without CKD, selected from hospital visitors or emergency department patients with no history or biochemical evidence of kidney dysfunction (eGFR > 90 mL/min/1.73 m² and albumin-to-creatinine ratio [ACR] < 30 mg/g).
- Mild CKD group (n= 50): Patients diagnosed with early-stage CKD (eGFR > 60 mL/min/1.73 m² and ACR > 30 mg/g), confirmed by medical records and biochemical tests.
- Severe CKD group (n= 50): Patients with end-stage renal disease (ESRD; stages 4–5 CKD) undergoing hemodialysis,

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characterized by eGFR < 15 mL/min/1.73 m² and ACR > 300 mg/g.

All participants underwent physical examination, blood pressure measurement, and routine blood tests, including serum glucose, urea, creatinine, calcium, phosphorus, and iron levels. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation, which incorporates age, sex, and serum creatinine levels.

The inclusion criteria were as follows:

- Age between 18 and 65 years,
- Diagnosis of CKD according to KDIGO 2023 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease,
- Willingness to participate and provide informed consent,
- Residency in Baghdad city.

The exclusion criteria included:

- Presence of overt cardiovascular disease,
- Active viral infections (HBV, HCV, HIV),
- History inconsistent with CKD or presence of acute kidney injury (AKI),
- Patients with malignancies or systemic inflammatory diseases unrelated to CKD,
- Lack of informed consent.

Sample Collection and Biomarker Measurement

Venous blood samples were collected from all participants. Serum was separated via centrifugation and stored at -80 °C until analysis.

For biomarker quantification, serum concentrations of KIM-1 and Gal-3 were measured using commercially available sandwich ELISA kits (Elabscience®, USA), Human KIM-1 ELISA Kit, Catalog number E-EL-H0147 and Human Galectin-3 ELISA Kit: Catalog number E-EL-H0125. All assays were performed according to the manufacturer's instructions.

KIM-1 Levels

KIM-1 levels were also increased in CKD patients, particularly in those with severe disease. A statistically significant difference was found only between the control and severe CKD groups ($P = 0.036$), while no significant difference was observed between the control and mild CKD groups ($P = 0.149$) or between mild and severe CKD groups ($P = 0.668$) (Table 2).

Statistical Analysis

Data were analyzed using SPSS version 26. Continuous variables were expressed as mean ± SD or median (interquartile range) depending on the distribution normality. Categorical variables were presented as frequencies and percentages. Comparisons among the three groups were performed using one-way ANOVA or the Kruskal-Wallis test, followed by appropriate post-hoc tests. Correlation analyses (Pearson or Spearman) were used to assess associations between biomarker levels and clinical parameters such as eGFR, ACR, and biochemical indices. A p-value < 0.05 was considered statistically significant.

Results

Patient Characteristics

The study involved 150 participants divided into three groups: 50 healthy controls, 50 patients with mild CKD, and 50 patients with severe CKD. The mean age of participants with CKD was 51.1 years (SD: 17.4), with a higher prevalence in men (52%). This distribution is consistent with national and international reports indicating a higher incidence of CKD in males.

Galectin-3 Levels

Serum levels of Gal-3 were significantly elevated in CKD patients compared to healthy controls, with a progressive increase observed from mild to severe stages of the disease ($P < 0.001$) (Table 2).

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Table1. Demographic and Clinical Characteristics of Study Participants.

Variable	Control group (n=50)	Mild CKD group (n=50)	Severe CKD group (n=50)
Age (years), Mean ± SD	43.2 ± 12.8	54.4 ± 12.6	55.5 ± 11.9
Sex, n (%)			
- Male	23 (46%)	27 (54%)	28 (56%)
- Female	27 (54%)	23 (46%)	22 (44%)
Marital Status, n (%)			
- Married	27 (54%)	47 (94%)	52 (100%)
- Not married	23 (46%)	3 (6%)	0 (0%)
Education, n (%)			
- Primary school	6 (11.3%)	6 (11.3%)	5 (11.3%)
- Middle school	21 (41.3%)	20 (41.3%)	21 (41.3%)
- Bachelor's degree	22 (44.7%)	23 (44.7%)	22 (44.7%)
- Master's degree	1 (2.7%)	1 (2.7%)	1 (2.7%)
Smoking Status, n (%)			
- Smoker	0 (0%)	0 (0%)	44 (88%)
- Non-smoker	50 (100%)	50 (100%)	6 (12%)
Comorbidities, n (%)			
- Hypertension	0 (0%)	14 (28%)	28 (56%)
- Diabetes mellitus	0 (0%)	8 (16%)	18 (36%)
BMI (kg/m²), n (%)			
- Underweight (<18.5)	0 (0%)	0 (0%)	3 (6%)
- Normal weight (18.5–24.9)	34 (68%)	29 (58%)	0 (0%)
- Overweight/Obese (≥25)	16 (32%)	18 (36%)	47 (94%)
CKD Stage, n (%)			
- Stage 1	—	16 (32%)	—
- Stage 2	—	34 (68%)	—
- Stage 4	—	—	8 (16%)
- Stage 5 / ESRD	—	—	43 (86%)
- Dialysis patients	—	—	43 (86%)

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Table 2. Mean serum concentrations of Gal-3 and KIM-1 in study groups.

Variable	Control group (n=50)	Mild CKD group (n=50)	Severe CKD group (n=50)	*p* value
Gal-3 (ng/mL)	4.2157 ± 1.68	4.0945 ± 1.53	4.5726 ± 1.53	<0.001
KIM-1 (pg/mL)	0.4477 ± 0.43	0.8771 ± 1.99	1.0594 ± 2.02	0.036

Discussion

The present study demonstrates that serum levels of Gal-3 are significantly elevated in Iraqi patients with CKD, showing a progressive increase from mild to severe stages. This aligns with a growing body of evidence indicating the role of Gal-3 as a key mediator of inflammation and fibrosis, which are two major pathological mechanisms underlying CKD progression. Notably, our findings also reveal a strong association between Gal-3 levels and metabolic comorbidities such as diabetes, hypertension, and obesity, which are highly prevalent among our cohort. These observations suggest that Gal-3 may serve not only as a marker of renal injury but also as an indicator of systemic metabolic stress contributing to CKD pathogenesis.

In contrast, KIM-1 was primarily elevated in patients with advanced CKD or ESRD, with no significant differences observed between healthy controls and individuals with mild CKD. This pattern supports previous reports suggesting that KIM-1 reflects established tubular damage rather than early functional decline. While KIM-1 has been proposed as a promising biomarker for acute kidney injury (AKI), its limited sensitivity in early CKD stages highlights the need to evaluate its utility within different clinical contexts and patient populations (9, 10).

Our observation that Gal-3 levels correlate with traditional markers of renal dysfunction, such as creatinine and urea reinforce findings reported by Rebholz et al., who demonstrated that elevated plasma Gal-3 is associated with an increased risk of incident CKD. Moreover, experimental studies have shown that Gal-3 promotes renal fibrosis through activation of the TGF-β signaling pathway, supporting its role in structural tissue remodeling and interstitial scarring. In line with these findings, we propose that Gal-3 may be particularly useful in identifying patients at higher risk of CKD progression due to both metabolic and inflammatory drivers (11).

On the other hand, KIM-1 expression appears to be more specific to irreversible tubular injury. As noted by Jana et al., KIM-1 is upregulated on the surface of injured proximal tubule epithelial cells and is shed into the urine following acute insults. However, our data suggest that, in the context of chronic disease, KIM-1 may not rise until substantial structural damage has occurred. This distinction underscores the complementary nature of these two biomarkers: Gal-3 as an early indicator of systemic and renal inflammation, and KIM-1 as a late-stage marker of tubular injury (12, 13).

An important aspect of our findings is the high prevalence of metabolic syndrome among CKD patients in Iraq. Our data show that Gal-3 levels are closely linked to BMI, diabetes, and hypertension, reinforcing the hypothesis that this lectin serves as a bridge between metabolic dysregulation and organ-specific pathology (14). This is consistent with global studies that have identified Gal-3 as a downstream effector of adipose tissue inflammation and insulin resistance **.**Emerging evidence from clinical trials, such as EMPA-REG OUTCOME and CREDENCE, has shown that SGLT2 inhibitors significantly slow CKD progression through mechanisms beyond their glucose-lowering effects (15, 16).

These drugs activate AMP-activated protein kinase (AMPK), a central regulator of cellular energy metabolism, which in turn suppresses inflammation and fibrotic pathways, including those involving Gal-3

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(17). Experimental models have further demonstrated that SGLT2 inhibition reduces Gal-3 expression via modulation of NF-κB and TGF-β signaling, offering a potential molecular explanation for the renoprotective effects of these agents (18).

Given that AMPK activity is often impaired in metabolic syndrome, which is common in our population, our findings raise the possibility that targeting the AMPK-SGLT2-Gal-3 axis could offer novel therapeutic strategies for delaying CKD progression in metabolically complex patients (19). Future studies should explore whether Gal-3 can serve as a surrogate marker for assessing the efficacy of anti-inflammatory or antifibrotic therapies in this context (20).

This study provides one of the first reports evaluating Gal-3 and KIM-1 in an Iraqi CKD population, a group that has been largely underrepresented in biomarker research. By comparing biomarker levels across different stages of CKD and correlating them with clinical parameters, we offer insights into their potential use in the diagnosis and staging within this specific demographic.

However, several limitations must be acknowledged. First, the cross-sectional design limits our ability to establish causal relationships or assess predictive value over time. Second, the relatively small sample size restricts the generalizability of our findings. Finally, while we measured serum levels of Gal-3 and KIM-1, future studies should also consider measuring urinary concentrations to better understand their excretion patterns and diagnostic performance.

In conclusion, our findings support the use of Gal- 3 as a broader indicator of systemic inflammation and fibrosis, while KIM-1 appears more specific to advanced tubular injury. These biomarkers may play complementary roles in CKD diagnosis and monitoring within the Iraqi population, particularly in patients with metabolic comorbidities. Further longitudinal investigations are warranted to assess their dynamic changes over time and to evaluate whether targeting related the molecular pathways can improve outcomes in high-risk patients.

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Conflict of Interest

The authors declare that they have no competing interests related to this manuscript.

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Authors' Contribution

H.C., A.HA., and Z.M. contributed to material preparation, data collection, and analysis. Z.M., N.D. and N.AM. drafted the initial manuscript. All authors contributed to the study conception and design, critically revised the manuscript for important intellectual content, and approved the final version for publication.

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