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Serum Galectin-3 as a diagnostic and discriminatory biomarker for chronic kidney disease: A case-control study

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ABSTRACT

Background: Diabetic kidney disease (DKD) is the leading cause of end-stage renal disease worldwide. Conventional markers, such as serum creatinine, estimated glomerular filtration rate, and albuminuria, have limited sensitivity for distinguishing among etiologies of advanced chronic kidney disease (CKD) and become abnormal only after substantial nephron loss. Galectin-3 (GAL-3), a beta-galactoside-binding lectin implicated in renal inflammation and fibrosis, has emerged as a candidate biomarker; however, its diagnostic accuracy in distinguishing DKD from non-diabetic CKD in advanced CKD populations remains unclear.

Objective: To quantify serum GAL-3 concentrations in patients with DKD, non-diabetic CKD, and healthy controls, and to evaluate its diagnostic performance in discriminating between these groups in an advanced CKD population.

Materials and methods: A case-control study that enrolled 128 participants: 32 patients with DKD (all with type 2 diabetes mellitus), 32 with non-diabetic CKD (both groups on regular hemodialysis classified as CKD stage 5/ end-stage renal disease [ESRD]), and 64 healthy controls. Serum GAL-3 levels were measured using an enzyme-linked immunosorbent assay (ELISA). Fasting blood glucose, glycated hemoglobin (HbA1c), renal function tests, and serum albumin levels were assessed using an automated analyzer.

Results: Serum GAL-3 concentrations increased progressively from controls (210.04±34.65 ng/mL) to non-diabetic CKD (262.21±3.19 ng/mL) and then to DKD (368.50±67.10 ng/mL, p<0.001). Receiver operating characteristic (ROC) analysis demonstrated very high discrimination in this cohort between DKD and healthy controls area under the curve (AUC=1.00, 95% CI: 0.963-1.000, sensitivity, 100%, specificity, 100%; cutoff, ≥275.77 ng/mL), excellent differentiation of DKD from non-diabetic CKD (AUC=0.987, 95% CI: 0.905-0.999, sensitivity, 84.37%, specificity, 100%), and strong discrimination of all CKD patients from controls (AUC=0.926, 95% CI: 0.866-0.965; sensitivity, 98.44%, specificity, 73.44%). These cutoff values were derived from the same dataset and should be considered exploratory.

Conclusion: Serum GAL-3 demonstrated very high diagnostic accuracy in identifying and stratifying DKD within this cohort of end-stage renal disease patients on hemodialysis. These exploratory findings suggest that GAL-3 may have potential as a discriminatory biomarker in advanced CKD populations; however, prospective validation in larger, independent cohorts including patients with early-stage CKD is warranted before clinical integration can be recommended.

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Introduction

Chronic kidney disease is now recognized as one of the major non-communicable health challenges worldwide, with current estimates suggesting that more than 800-850 million people are living with kidney diseases of various causes.[1] Within this spectrum, diabetes has emerged as the dominant driver of kidney damage: diabetic kidney disease which is also considered the leading cause of CKD and end-stage renal disease in many countries; approximately one-third of individuals with diabetes eventually develop clinically evident DKD, and large clinical cohorts and registry data consistently show that DKD is the most common indication for dialysis or kidney transplantation, despite advances in glycemic and blood pressure control.[2] DKD is a multifaceted condition characterized by interrelated proinflammatory and pro-apoptotic metabolic pathways that contribute to glomerular hypertension, metabolic disturbances, and hemodynamic irregularities.[3] Both type 1 and type 2 diabetes can lead to chronic kidney disease and, ultimately, end-stage renal disease (ESKD); patients with ESKD often suffer from type 2 diabetes, given that type 2 diabetes is more common than type 1.[4] In the present study, all patients in the DKD group had type 2 diabetes mellitus (T2DM), reflecting the predominance of T2DM as the underlying etiology of DKD in our clinical setting. The global prevalence of diabetes will continue to increase over the coming decades, from 415 million people in 2015 to 642 million in 2040.[5]

The complex interaction of hemodynamic, metabolic, fibrotic, and inflammatory factors, which are often disrupted in diabetes, is believed to be the cause of the development and progression of DKD; dysfunctions in these factors are interconnected and affect the activation of transcription factors, molecular pathways, and gene regulation, leading to structural and functional changes that ultimately result in the clinical manifestations of DKD, characterized by decreased kidney function and elevated albumin levels in the urine[6]. Routine clinical assessment still relies largely on serum creatinine, estimated glomerular filtration rate (eGFR), and albuminuria, which are useful for staging established CKD; however, these markers typically become abnormal only after substantial structural damage and nephron loss have occurred, and both eGFR and albuminuria have limited capacity for discriminating between different etiologies of CKD, particularly in advanced stages where values converge regardless of the underlying cause.[7] This diagnostic limitation is especially problematic in advanced CKD populations, where distinguishing diabetic from non-diabetic etiologies on biochemical grounds alone remains challenging without renal biopsy; these limitations have encouraged an intensive search for novel biomarkers that can capture more specific aspects of kidney injury and enable etiological discrimination, with recent work focusing on markers of tubular damage, fibrosis, inflammation, oxidative stress, and altered signaling pathways.[8]

Galectin-3 (GAL-3) binds to the enzyme beta-galactosidase and is highly expressed in inflammatory and epithelial cells, as well as in kidney and cardiac tissue. It is involved in regulating cell growth during inflammation.[9] GAL-3 has been shown to play a role in the mechanisms underlying chronic kidney disease and acute kidney failure, and its serum levels are negatively correlated with kidney function; high levels of GAL-3 increase the risk of diabetic nephropathy (DN) and predict rapid progression and adverse outcomes in patients with chronic kidney disease prior to dialysis.[10,11] The aim of this study was to quantify and compare serum GAL-3 levels among diabetic and non-diabetic patients with CKD and healthy controls, and to evaluate the diagnostic performance of GAL-3 for discriminating among these groups in an advanced CKD population undergoing hemodialysis.

Materials and methods

This case-control study was conducted in a hospital setting. The study protocol was approved by the Scientific Committee of the College of Medicine, Tikrit University, and the Diyala Health Department. The study included 64 patients of both sexes with chronic kidney disease (32 patients with diabetes and 32 patients without diabetes) who were undergoing regular dialysis sessions and were aged between 20 and 65 years. They were clinically diagnosed with end-stage renal failure by a nephrologist based on their medical history, physical examination, renal function tests, and other relevant laboratory tests. All patients in both the CKD and DKD groups were classified as CKD stage 5 (ESRD; eGFR <15 mL/min/1.73 m^2) and were receiving regular maintenance hemodialysis at the time of enrollment. Patients in the DKD group were exclusively diagnosed with T2DM as the underlying cause of their kidney disease, confirmed by the treating nephrologist based on clinical history, duration of diabetes, presence of diabetic retinopathy, and/or prior documentation of progressive diabetic nephropathy. Patients with type 1 diabetes were not included in this study. The study also included 64 healthy adults of both sexes who had no medical or family history of chronic kidney disease or diabetes as the control group.

Inclusion and exclusion criteria

Patients must have been diagnosed with chronic kidney disease (with or without type 2 diabetes) by a supervising physician and must not have a history of autoimmune diseases (thyroid disease, systemic lupus erythematosus), cancer, liver disease, or heart failure. Patients receiving uric acid-lowering medications (e.g., allopurinol, febuxostat) were not specifically excluded. Pregnant women and individuals with any of the above conditions were excluded from the study.

Data and sample collection

Medical and social history was obtained from each patient using a questionnaire. All patients provided informed consent to participate in the study. Demographic parameters were measured, some of which were obtained from the patients' hospital records, and blood samples were drawn from each participant's vein. A 5 mL sample was collected and distributed into a gel tube and a tube containing an anticoagulant (EDTA). The collected samples in gel tubes were left at room temperature (25 °C) for 30 min to clot, then centrifuged at 4,000 rpm for 10 min to separate the serum. Serum samples obtained from gel tubes were divided into small portions and stored at -80 °C until analysis to prevent thawing and refreezing.

Laboratory analysis

Several tests were performed, including measurements of blood urea, creatinine, serum albumin, fasting blood glucose, and glycated hemoglobin (HbA1c), using a German-made Roche Diagnostic Cobas C311 analyzer. GAL-3 levels (Cat. No. E1951Hu) were measured using ELISA kits with automated readings. All reagents were prepared and processed according to the manufacturer's instructions to ensure test accuracy. The ELISA kit used for GAL-3 measurement had a reported intra-assay coefficient of variation (CV) of <8% and an inter-assay CV of <10%, as specified by the manufacturer. The detection range was 15.6-1,000 ng/mL. Sample storage at -20 °C was performed in accordance with the manufacturer's recommendations; however, we acknowledge that storage at -80 °C may provide superior long-term protein stability, which represents a potential limitation of the present study.

Statistical analysis

The data in this study were analyzed using SPSS version 25.0 for primary statistical analyses. Statistical data, including range, mean, and standard deviation, were measured to describe the variables. The normality of continuous variables was assessed using the Shapiro-Wilk test prior to parametric analyses. Groups were compared using one-way analysis of variance (ANOVA), followed by Tukey's multiple comparisons test, the chi-squared test (for categorical data), and diagnostic performance was evaluated using receiver operating characteristic (ROC) curve analysis, with calculation of the area under the curve (AUC), 95% confidence intervals (CI), sensitivity, specificity, and optimal cutoff values. Effect sizes were calculated using eta-squared (η^2) for ANOVA comparisons. Correlation between variables was calculated using Pearson's correlation coefficient. Results were considered statistically significant at $p<0.05$ for all analyses. All ROC-derived cutoff values were determined from the study dataset and are considered exploratory; external validation in independent cohorts is required to confirm their clinical applicability.

Results

The demographic and baseline clinical characteristics of the study participants are presented in Table 1. All patients in both the CKD and DKD groups were classified as CKD stage 5 (ESRD) and were receiving maintenance hemodialysis. All patients in the DKD group had type 2 diabetes mellitus as the underlying etiology. No significant differences were observed in the distribution of sex, mean age, or body mass index (BMI) among the CKD, DKD, and control groups. However, significant variations were noted in key biochemical markers. Patients in the DKD group exhibited significantly higher fasting blood glucose (156.34±30.47 mg/dL) and glycated hemoglobin (HbA1c; 7.14±0.64%) levels than those in both the CKD and control groups ($p<0.001$). Furthermore, both the CKD and DKD groups demonstrated markedly elevated serum urea (89.28±25.57 and 95.95±30.78 mg/dL, respectively) and creatinine (6.202.26± and 6.33±1.47 mg/dL, respectively) levels compared with the control group ($p<0.001$ for both). The p-values presented in Table 1 were calculated using one-way ANOVA for continuous variables and the Chi-square test for categorical variables. Post hoc pairwise comparisons were performed using Tukey's multiple comparisons test.

Table 1. Baseline demographic and anthropometric characteristics of study participants.

Parameter	Mean±SD		DKD (N=32)	*p* value
	CKD (N=32)	Control (N=64)		
CKD stage	Stage 5 (ESRD)	N/A	Stage 5 (ESRD)	N/A
Diabetes type	None	None	Type 2	N/A
Age (years)	41.06±10.57	42.05±11.76	44.03±9.47	0.538
Gender (Male/Female)	16 (50.0%)/ 16 (50.0%)	33 (51.6%)/ 31 (48.4%)	15 (46.9%)/ 17 (53.1%)	0.911
BMI (kg/m^2)	27.05±4.09	27.08±3.95	28.09±7.57	0.618
FBG (mg/dL)	89.99±10.35*	94.23±13.12*	156.34±30.47**	<0.001
HbA1c (%)	5.31±0.54*	5.35±0.46*	7.14±0.64**	<0.001

Table 1. Baseline demographic and anthropometric characteristics of study participants (continued).

Parameter	Mean±SD		DKD (N=32)	*p* value
	CKD (N=32)	Control (N=64)		
Blood urea (mg/dL)	89.28±25.57*	28.38±6.64**	95.95±30.78*	<0.001
Creatinine (mg/dL)	6.20±2.26*	0.77±0.18**	6.33±1.47*	<0.001

Note: *The p values were calculated using one-way ANOVA for continuous variables and Chi-square test for categorical variables. Level of significance following Tukey's multiple comparisons test: *groups sharing the same letter do not differ significantly (p>0.05); **groups with different letters differ significantly (p<0.05).*

No significant difference in serum albumin concentrations was observed between the CKD and DKD groups (3.00±0.242 g/dL and 2.944±0.223 g/dL, respectively; *p*=0.7677). However, as illustrated in Figure 1, the control group exhibited significantly higher serum albumin levels (3.986±0.394 g/dL, *p*<0.0001) than those in both patient cohorts.

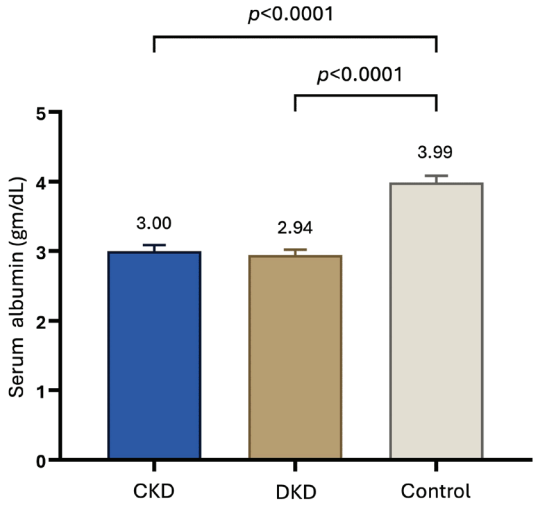


Figure 1. *A comparison of mean serum albumin concentrations among the chronic kidney disease, diabetic kidney disease, and control groups.*

As depicted in Figure 2, serum GAL-3 levels showed a significant, progressive increase across the study groups. The mean concentrations were lowest in the control group (210.04±34.65 ng/mL), intermediate in the CKD group (262.21±33.19 ng/mL), and highest in the DKD group (368.50±67.10 ng/mL). These differences were statistically significant (*p*<0.001, η^2=0.72, indicating a large effect size).

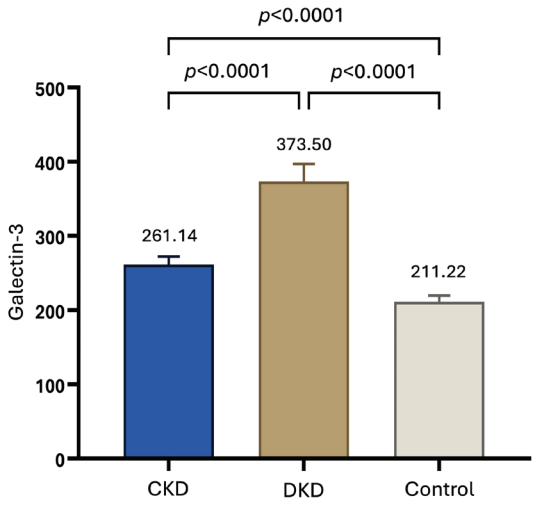


Figure 2. *A comparison of mean serum GAL-3 concentrations among the chronic kidney disease, diabetic kidney disease, and control groups.*

In the DKD group, the results differed again. GAL-3 was not significantly associated with renal, metabolic, or anthropometric parameters in this group.

For distinguishing between healthy controls and non-diabetic CKD, GAL-3 performed strongly, with an AUC of 0.852 (95% CI: 0.765-0.916; p<0.0001), sensitivity of 73.44%, and specificity of 90.62% at ≥229.199 ng/mL (Figure 3). In discriminating DKD from healthy controls, GAL-3 achieved very high diagnostic accuracy in this cohort. GAL-3 yielded an AUC of 1.00 (95% CI: 0.963-1.000, p<0.0001), with 100% sensitivity and 100% specificity at optimal cut-off values of ≥275.766 ng/mL (Figure 4). When directly comparing non-diabetic CKD to DKD, the biomarker maintained discriminatory performance. GAL-3 showed a similarly high AUC of 0.987 (95% CI: 0.905-0.999, p<0.0001), with 84.37% sensitivity and 100% specificity (Figure 5). When all patients with kidney disease (CKD and DKD combined) were compared to healthy controls, diagnostic performance remained excellent. GAL-3 yielded an AUC of 0.926 (95% CI: 0.866-0.965; p<0.0001), with 98.44% sensitivity and 73.44% specificity (Figure 6).

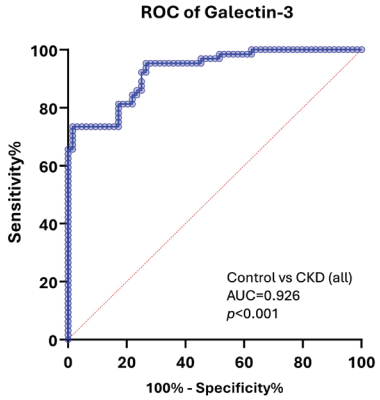


Figure 3. *Diagnostic performance of GAL-3 in differentiating non-diabetic CKD from healthy controls.*

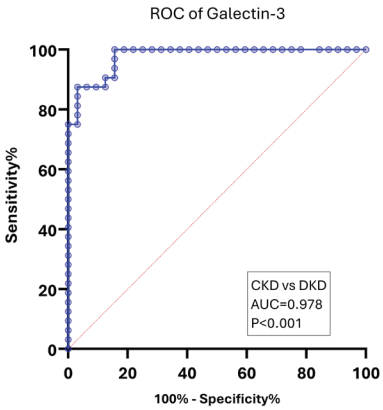


Figure 4. *Diagnostic performance of GAL-3 in differentiating DKD from healthy controls.*

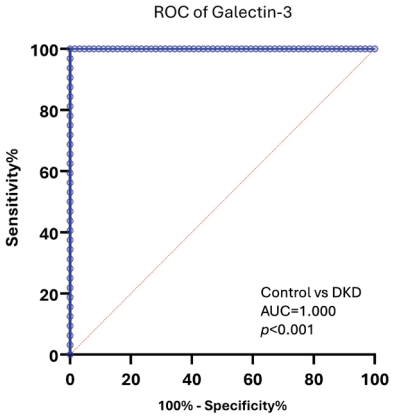


Figure 5. *Diagnostic performance of GAL-3 in differentiating DKD from non-diabetic CKD.*

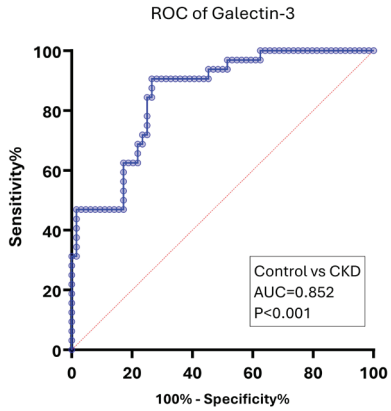


Figure 6. *Diagnostic performance of GAL-3 in differentiating kidney disease from healthy controls.*

Discussion

This study investigated serum GAL-3 as a diagnostic and discriminatory biomarker across three well-characterized cohorts: patients with DKD (all with type 2 diabetes mellitus), patients with non-diabetic CKD, and healthy controls. All patients in the CKD and DKD groups were classified as CKD stage 5 (ESRD) and were receiving maintenance hemodialysis, ensuring comparability between the disease groups with respect to the degree of renal impairment. The principal findings demonstrated a statistically significant and progressive elevation of serum GAL-3 concentrations from healthy controls through non-diabetic CKD to DKD, with the highest levels observed in the DKD group (368.50±67.10 ng/mL). The ROC analyses further confirmed the very high diagnostic accuracy of GAL-3 in distinguishing DKD from healthy controls (AUC=1.00), from non-diabetic CKD (AUC=0.987), and in differentiating all kidney disease patients from controls (AUC=0.926). These results are consistent with and extend a growing body of evidence positioning GAL-3 as a clinically relevant biomarker in the spectrum of kidney diseases.

The progressive increase in serum GAL-3 observed across the disease spectrum in this study closely aligns with findings from multiple independent investigations. A recent case-control study conducted in an Iraqi population by Mahdi *et al*. demonstrated that serum GAL-3 levels were significantly elevated in patients with CKD compared to healthy controls, with a progressive increase from mild to severe CKD stages (p<0.001). This elevation was further associated with metabolic comorbidities, including diabetes mellitus and hypertension.[12] These findings mirror the pattern observed in the present study, in which both the CKD and DKD groups exhibited markedly elevated GAL-3 levels compared with controls, with the diabetic subgroup showing the highest concentrations. This parallel is particularly noteworthy given the shared geographic and demographic context, as both studies were conducted in Iraqi clinical settings, lending regional validity to the biomarker's performance.

The mechanistic basis for GAL-3 elevation in kidney disease has been substantially elucidated in recent years. Wang et al. provided a comprehensive review of the roles of GAL-3 in both acute kidney injury (AKI) and chronic kidney disease (CKD), demonstrating that GAL-3 is a key mediator of inflammation and fibrosis through its interactions with toll-like receptor 4 (TLR4), activation of nuclear factor E-kappa B (NF-κB) signaling, and promotion of transforming growth factor-beta (TGF-β)-mediated tubulointerstitial fibrosis.[13] The pro-fibrotic role of GAL-3 was further confirmed mechanistically by Chen *et al.,* who demonstrated in a murine DKD model that macrophage-derived GAL-3 is the primary driver of renal fibrosis in DKD, operating through enhanced TGF-β signaling, and that GAL-3 expression in plasma and kidneys was positively correlated in DKD mice, positioning it as a potential therapeutic target.[14] These mechanistic insights provide a compelling biological rationale for the elevated GAL-3 levels observed in the DKD group in the present study, where the combined burden of hyperglycemia-driven metabolic stress, glomerular hypertension, and inflammatory activation is expected to maximally stimulate GAL-3 secretion.

A notable finding of this study is the potential diagnostic value of GAL-3 in this cohort. Traditional markers, such as serum creatinine and eGFR, are widely recognized to lack discriminative power in advanced CKD populations, where values are uniformly elevated.[7] Albuminuria, while more sensitive in some contexts, is confounded by exercise, infection, and cardiac failure, and may remain within normal limits in up to one-third of patients with histologically confirmed DKD.[15] The present study's ROC analysis demonstrated that GAL-3 achieved very high discrimination between DKD patients and healthy controls in this cohort (AUC=1.00, 95% CI, 0.963-1.000, sensitivity = 100%, specificity = 100%). However, an AUC of 1.00 warrants cautious interpretation. This finding likely reflects, at least in part, the extreme group separation inherent in our study design (ESRD patients on dialysis vs healthy controls), which creates

a wide biochemical gap between groups, a phenomenon known as spectrum bias. The diagnostic performance reported here should therefore not be extrapolated to populations with earlier stages of CKD or to general diabetic populations without kidney disease. Importantly, this study did not perform a formal head-to-head comparative diagnostic analysis between GAL-3 and established renal biomarkers (creatinine, eGFR, albuminuria) using methods such as DeLong's test for comparing AUCs. Therefore, the present findings suggest that GAL-3 showed potential diagnostic value and may help overcome some limitations of conventional kidney function tests, particularly in diabetic conditions, rather than demonstrating definitive superiority over conventional markers.

This finding is corroborated by the systematic review by Bellos *et al.*, which evaluated the prognostic role of GAL-3 in patients with CKD, including those on dialysis, and concluded that elevated serum GAL-3 levels are consistently associated with adverse outcomes, including reduced eGFR, increased albuminuria, and progression to dialysis or death.[16] Similarly, a prospective study by Hodeib *et al*. followed 300 patients with type 2 diabetes over three years and demonstrated that serum GAL-3 was a significant independent predictor of progression to microalbuminuria, macroalbuminuria, ESRD, and death, with levels significantly higher in patients with macroalbuminuria than in those with micro- or normoalbuminuria.[17] The present study extends these findings to a dialysis population, demonstrating that GAL-3 retains its discriminatory power even in end-stage disease, where traditional markers are uniformly elevated and therefore less informative for differential diagnosis.

Buliga-Finis *et al*.'s comprehensive review further reinforces the clinical utility of GAL-3, citing data from the Framingham Offspring Study (N=2,450) in which elevated GAL-3 was associated with a 50% increased risk of CKD events and a more rapid decline in kidney function over a 10-year follow-up period, independent of age, sex, diabetes, hypertension, proteinuria, and baseline eGFR.[18] Importantly, that analysis also indicated that GAL-3 specifically predicted tubulointerstitial fibrosis rather than glomerular injury, suggesting that its elevation reflects a distinct and clinically important pathological process that is not captured by conventional biomarkers.

One of the most clinically significant findings of the present study is GAL-3's ability to discriminate DKD from non-diabetic CKD with high accuracy (AUC=0.987, sensitivity = 84.37%, specificity = 100%). This differential diagnostic capacity addresses a critical clinical challenge, as both conditions share overlapping presentations, including elevated creatinine, reduced eGFR, and hypoalbuminemia, making their distinction on biochemical grounds alone difficult without renal biopsy. The present data suggest that GAL-3 may serve as a non-invasive adjunct for this distinction, potentially complementing invasive diagnostic procedures.

The biological basis for the differential elevation of GAL-3 in DKD relative to non-diabetic CKD likely reflects the additive pro-fibrotic and pro-inflammatory effects of hyperglycemia on the kidney.[19] In the diabetic milieu, advanced glycation end-products, oxidative stress, and activation of the renin-angiotensin-aldosterone system collectively amplify TGF-β signaling and macrophage activation, both of which are upstream drivers of GAL-3 secretion.[20] A review by Sinha and Nicholas specifically highlighted these interconnected pathomechanisms in DKD, noting that glomerular hypertension, metabolic disturbances, and hemodynamic irregularities collectively activate transcription factors and molecular pathways that culminate in structural and functional renal changes.[3] The finding of the present study that DKD patients had significantly higher HbA1c (7.14±0.64%) and fasting blood glucose (156.34±30.47 mg/dL) levels than non-diabetic CKD patients, alongside their higher GAL-3 levels, supports the hypothesis that glycemic dysregulation is an independent contributor to GAL-3 elevation beyond the effect of kidney dysfunction alone.

An important consideration when interpreting the present findings concerns the type of diabetes included in the DKD group. All patients in this group had T2DM, which is characterized by insulin resistance, chronic low-grade inflammation, and features of metabolic syndrome that may independently influence GAL-3 levels through mechanisms distinct from those operative in T1DM. T2DM is associated with greater adipose tissue inflammation, higher circulating levels of pro-inflammatory cytokines, and more pronounced metabolic derangements, all of which are known to upregulate GAL-3 expression.[18,20] Whether similar GAL-3 elevations and diagnostic performance would be observed in patients with T1DM-associated DKD remains to be determined, as the pathophysiology of DKD in T1DM may involve different inflammatory and fibrotic pathways. This represents an important area for future investigation, and the present findings should be interpreted as applicable specifically to T2DM-associated DKD.

Limitations

Several limitations of the present study should be acknowledged. Firstly, the case-control design with extreme group separation (ESRD patients on hemodialysis vs. healthy controls) introduces spectrum bias, which likely inflates the observed diagnostic accuracy. The AUC of 1.00 for DKD vs healthy controls should be interpreted in this context; these results cannot be directly extrapolated to early CKD populations or to general diabetic populations without kidney disease. Secondly, the relatively small sample size (N=32 per disease group) limits statistical power, particularly for correlation analyses, and increases the risk of overfitting in ROC analyses. Thirdly, GAL-3 is influenced by several confounding factors not fully addressed in this study, including systemic

inflammation, cardiovascular disease, dialysis status, and hepatic fibrosis. The hemodialysis procedure itself may affect GAL-3 levels through inflammatory activation and clearance dynamics. Fourthly, this study did not include a direct head-to-head ROC comparison between GAL-3 and conventional markers (creatinine, eGFR, albuminuria); therefore, claims of GAL-3 superiority over these markers should be interpreted with caution. Fifthly, all patients in both the CKD and DKD groups were classified as CKD stage 5 (ESRD) on maintenance hemodialysis; therefore, the findings cannot be generalized to patients with earlier CKD stages (stages 1-4), where GAL-3 levels and diagnostic performance may differ. The inability to match CKD stages between groups was mitigated by enrolling only stage 5 patients in both disease groups, ensuring comparability; however, this limits the generalizability of the findings. Sixth, the DKD group included exclusively patients with type 2 diabetes mellitus; therefore, the applicability of these findings to patients with type 1 diabetes-associated DKD remains unknown and represents an area for future research. Finally, all cutoff values were derived from the same dataset and require external validation in independent, prospectively recruited cohorts before clinical application can be recommended.

Conclusion

In conclusion, the present exploratory study provides preliminary evidence that serum GAL-3 showed potential diagnostic value for discriminating DKD from non-diabetic CKD and healthy controls in a cohort of ESRD patients (all with type 2 diabetes mellitus) on hemodialysis. The progressive elevation of GAL-3 across the CKD-DKD spectrum, its strong ROC performance, and its biological plausibility as a mediator of renal fibrosis and inflammation collectively warrant further investigation of its potential role in clinical diagnostic algorithms for DKD. These findings suggest that GAL-3 may help overcome some limitations of conventional kidney function tests, particularly in diabetic conditions; however, formal comparative diagnostic studies against established biomarkers are needed to confirm any added clinical value. Given the limitations inherent in the case-control design, small sample size, and spectrum bias, larger prospective multicenter studies with independent validation cohorts including patients with early-stage CKD and both type 1 and type 2 diabetes are essential to confirm these findings, establish standardized reference ranges, and evaluate the utility of GAL-3 as a therapeutic target and treatment response biomarker in this high-risk population.

Ethical approval

An agreement to conduct this study was signed prior to the start of sample collection. This was done in collaboration with the Department of Biochemistry at the College of Medicine, Tikrit University. The research committee approved the study (code MIDTUH2 on January 5, 2026) in accordance with the Declaration of Helsinki.

Funding

None

Competing Interests

The authors declare no competing interests.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Asmaa. H. Nasser: conceptualization, methodology, investigation, data curation, writing: original draft, review and edit; visualization, formal analysis, software, validation; **Entedhar Rifaat Sarhat**: supervision, project administration, resources, conceptualization, writing; review and edit.

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